TARGETS IN HETEROCYCLIC SYSTEMS

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VERSATILE NITROBUTADIENIC BUILDING-BLOCKS FROM THE RING-OPENING OF 2- AND 3-NITROTHIOPHENES

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Dedicated to the memory of Carlo Dell'Erba, Angelo Mugnoli and Marino Novi: teachers, colleagues and friends, without whose contribution this review would have never been written.

Abstract. *A number of variously substituted α- and β-nitrothiophenes undergoes ring opening by treatment with secondary amines in mild conditions. Anyway, at variance with 3,4-dinitrothiophene, all of the other derivatives break just one C-S bond, leading to asymmetrically functionalized nitrobutadienes which can be isolated in good yields after alkylation at sulfur. Such appealing building-blocks have been successfully employed in a number of synthetic procedures mainly targeted to the preparation of heterocycles of various nature (nitrogen, oxygen or sulfur heterocycles) within an overall ring-opening/ring-closing protocol. Furthermore, some of the nitrobutadienes produced by the ring-opening have revealed, after proper modification of the existing functionalities, interesting pharmacological activities.*

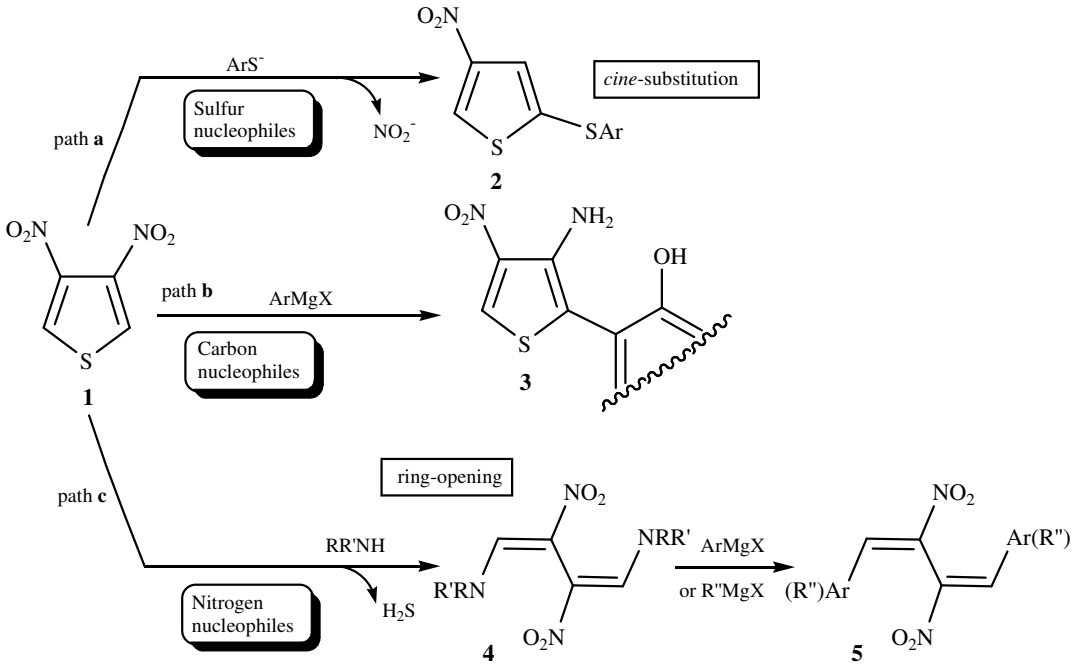
Contents

1. Introduction

The chemistry of nitrothiophenes and in particular their reactivity with nucleophiles has been one of our main research fields since 1968.[1] Actually, a *series* of peculiar behaviours has been evidenced along way for such interesting derivatives, essentially stemming from the relatively low aromaticity degree of the thiophene ring,[2] with respect to, *e.g.*, benzene.[3]

Thus, for instance, it was found that 3,4-dinitrothiophene (**1**) undergoes *cine*-substitution in the reaction with sulfur nucleophiles (Scheme 1, path **a**),[4] while 2,5-dialkyl-3,4-dinitrothiophenes undergo, with the same nucleophiles, a *tele*-substitution[5] process. More recently, C-nucleophiles like Grignard reagents have been shown to lead to the aminonitroderivatives **3**, as the result of a rather complex process characterized by a pivotal Claisen-like rearrangement (Scheme 1, path **b**).[6]

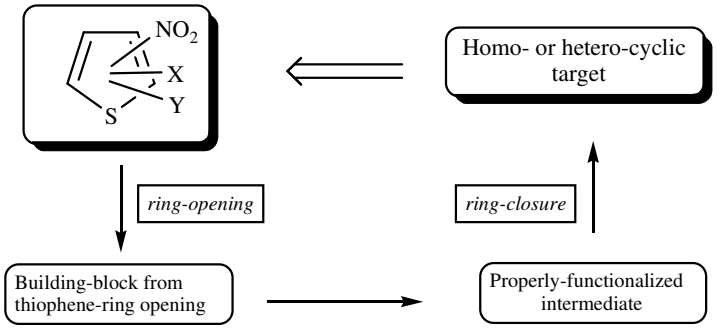
Anyway, the most intriguing and fruitful result from 3,4-dinitrothiophene is surely represented by the ring-opening observed in its reactions with *N*-nucleophiles like primary or secondary amines:[1] a process leading to dinitrobutadienes [**4** and **5** therefrom[7] (Scheme 1, path **c**)], which have proven to be extremely effective building-blocks for the synthesis of both linear and homo- or hetero-cyclic targets (Scheme 2). Our research in this field has been recently reviewed.[7]



Scheme 1. Examples of the non-benzenoid behaviour of 3,4-dinitrothiophene towards nucleophiles of different nature.

The extension of the reaction with amines to other nitrothiophene derivatives such as 2-nitro- (**6**)[8] or 3-nitrothiophenes (**7**)[9] other than 3,4-dinitrothiophene has interestingly enlightened an only partial parallelism in the behaviour of mononitrothiophenes with respect to 3,4-dinitrothiophene itself. The main

results in this field are reported hereinafter, with particular attention paid to the application of the building-blocks from the ring-opening of **6** and **7** in organic synthesis (Scheme 2) and in pharmacology.



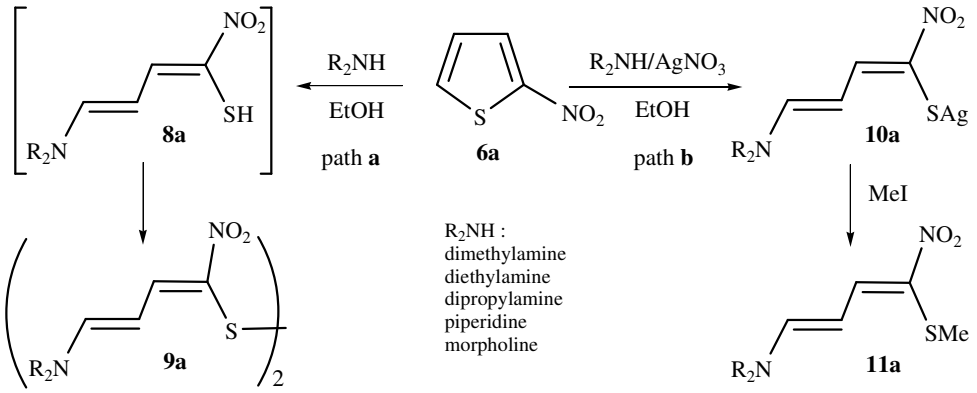
Scheme 2. Ring-opening/ring-closure protocol from nitrothiophenes.

2. The behaviour of 2-nitrothiophenes towards secondary amines

2.1. Ring-opening of 2-nitrothiophene to 1-amino-4-nitro-1,3-butadienes

In 1974, the treatment of 2-nitrothiophene (**6a**) with secondary amines resulted in a ring-opening process that, at variance with what observed with 3,4-dinitrothiophene, does not induce sulfur extrusion.[8a] The reaction (Scheme 3) proceeds through the breakage of only one carbon-sulfur bond generating, as the final product (path **a**), the nitrobutadienedisulfide **9a** instead of the expected, never isolated thiol **8a**, which evidently undergoes a fast oxidation in the experimental conditions employed.

If the reaction is performed in the presence of silver nitrate (path **b**), the butadienethiol intermediate can be isolated as a silver thiolate (**10a**) which furnishes the corresponding methylthio derivative **11a** by treatment with excess MeI.[8a] It has also been verified that the silver thiolate can be conveniently trapped with MeI with no need for isolation.



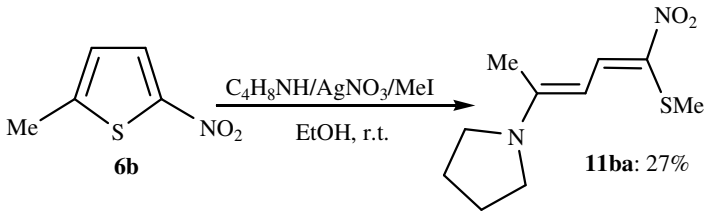
Scheme 3

More recently, in the perspective of an investigation of the chemical behaviour of the nitrobutadienes **11**, and also on the grounds of the experience acquired with the ring-opening of 3,4-dinitrothiophene, we have optimized the preparative procedure for a selected aminonitrobutadiene which could represent the best compromise between synthesis and further reactivity. In this respect, **11aa** (in **11a**, R_2N = pyrrolidinyl) proved to be most suited and its synthesis, performed "one-pot" (*i.e.* without isolation of **10a**) following path **b** of Scheme 3, allowed to raise the yield to a more than satisfactory 80% by means of a proper choice of the

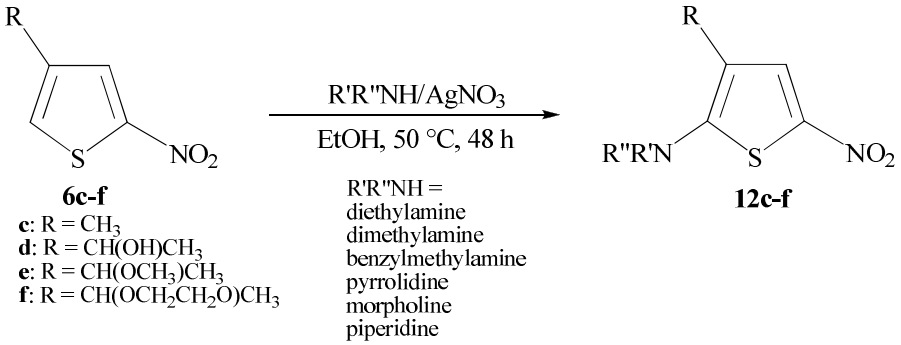
reaction conditions.[8b] As previously reported,[8a] the ring-opening resulted to be completely diastereoselective and **11aa** was always obtained exclusively in the 1*E*,3*Z* configuration shown in the Scheme.

2.2. Ring-opening *vs.* oxidative nucleophilic substitution of hydrogen on alkyl-2-nitrothiophenes

The introduction of an alkyl substituent on the 2-nitrothiophene ring led to interesting, somehow unexpected results. Actually, while 5-methyl-2-nitrothiophene (**6b**) provides ring-opening, although in considerably lower yields (27%) (Scheme 4),[10] it has been more recently found[11] that the reaction of the isomeric 4-methyl-2-nitrothiophene (**6c**) with a variety of secondary amines in otherwise similar reaction conditions furnishes only the ring-substitution products **12** in good yields, with no trace of the expected ring-opening (Scheme 5).



Scheme 4



Scheme 5

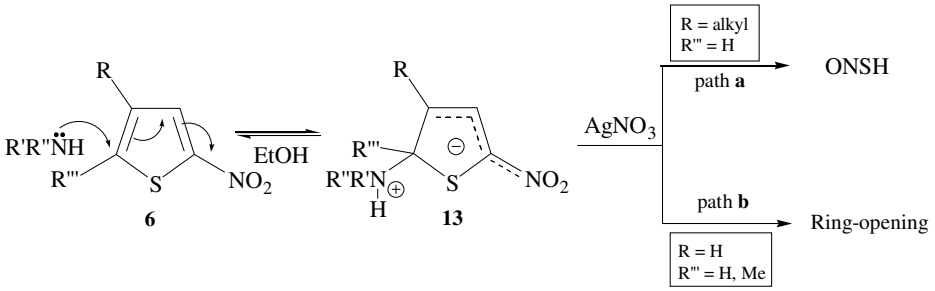
The reaction is always regioselective, occurring exclusively at the quasi-*para* position with respect to the nitro group. The same kind of reactivity is also shown by substrates bearing at C(4) slightly modified alkyl substituents [R = 1-hydroxyethyl (**6d**), 1-methoxyethyl (**6e**), 2-methyl-1,3-dioxolan-2-yl (**6f**)[10]]. With the exception of the reactions with dimethylamine (10–15%), yields are generally from acceptable to good (20, 30–55, 75%), and in every case a significant amount (5–10%) of unreacted substrate is recovered.

The behaviour of compounds **6c–f** represents an example of Oxidative Nucleophilic Substitution of Hydrogen (ONSH)[12] where $AgNO_3$ acts as an external oxidant; a similar outcome has been observed for 2-nitrobenzo[*b*]thiophene in reactions with primary amines in the presence of cerium ammonium nitrate (CAN).[12d]

The two kinds of process (ring-opening and nucleophilic substitution) share the initial addition of the nucleophile to the electron-poor nitro-substituted thiophene ring; the anionic σ^H-adduct **13** is then a common intermediate, whose evolution to a final product may occur in different ways (Scheme 6).

Interestingly enough, Ag^+ conceivably plays a different role in the two pathways, acting as an oxidant in path **a** (thus allowing the outcoming of "hydride" from the intermediate σ-adduct **13**) and as an effective scavenger of the resulting thiolate in path **b** [thus preventing oxidation to the disulfide **9** (see Scheme 3)],

possibly also concurring to facilitate the C-S bond breakage through coordination at sulfur (cf. Scheme 8 below).

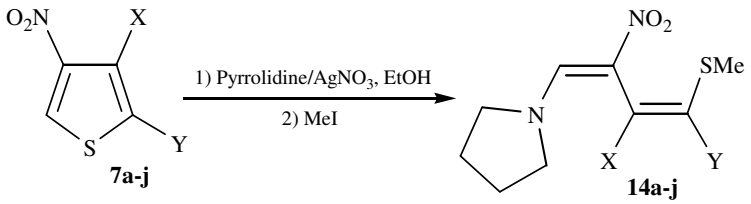


Scheme 6

The dichotomic behaviour[10,11] of Scheme 6 has been explained on the grounds of steric effects and/or of a stabilizing effect of the 4-alkyl group on the σ-intermediate. Thus, the longer lifetime of the adduct deriving from the 4-alkyl derivatives seems to be crucial to allow the attack of the oxidizing agent and direct the process towards the ONSH. Interestingly enough, this finding also brings support to the belief that alkyl groups may "modulate" their overall electronic effects, not always disfavouring nucleophilic substitution as it occurs in benzene derivatives.

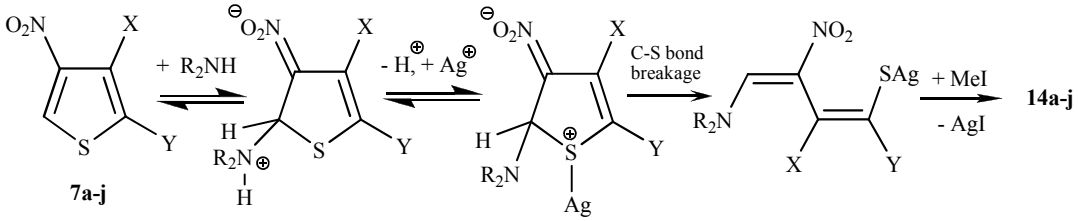
3. The reaction of 3-nitrothiophene derivatives other than 3,4-dinitrothiophene with secondary amines: synthesis of variously functionalized 1-amino-2-nitro-1,3-butadienes

In 1997 it was reported that the same experimental conditions employed by our group in 1974 for the ring opening of 2-nitrothiophene[8a] could also be applied, although with only moderate success, to 3-nitrothiophene[13] and 3-nitrobenzo[*b*]thiophene.[12d] A few years later, we reported optimized conditions for the ring-opening of 3-nitrothiophene with pyrrolidine, successfully extending the process also to a number of variously 2- and/or 3-substituted 4-nitrothiophenes, among which 3-nitrobenzo[*b*]thiophene itself (Scheme 7, Table 1).[9]



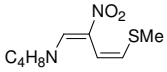
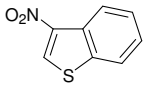
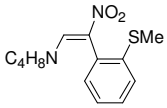
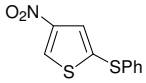
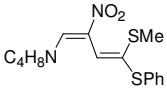
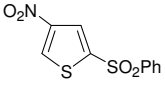
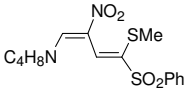
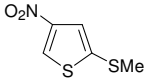
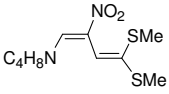
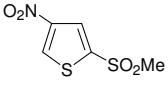
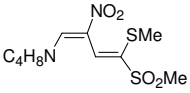
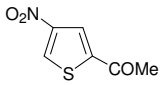
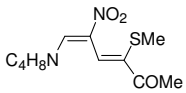
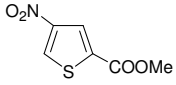
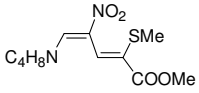
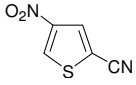
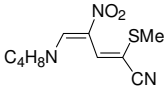
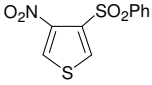
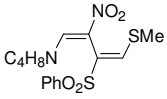
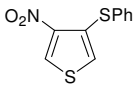
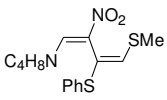
Scheme 7

In a typical procedure, the β-nitrothiophene and silver nitrate (2 mol equiv) are dissolved under argon in absolute ethanol, and pyrrolidine (2.2 equiv) is added; after 30' of sonication, the reaction mixture is left overnight at room temperature in the dark. Excess MeI is then added to the mixture, leading directly to the recovery of the methylthioderivative **14**. Yields are always from good to satisfactory (see Table 1); in each case, variable amounts of substrate (6–49%) are recovered. Much as proposed for the ring-opening of 2-nitrothiophene (see above), the process can be envisaged as a reversible, nucleophilic addition of amine to a ring carbon conjugated with the nitrogroup to give a σ-adduct, which undergoes an Ag^+-assisted ring-opening (Scheme 8).



Scheme 8

Table 1. Yields[a] of the ring-opening products **14a–k** from the reaction of β-nitrothiophenes **7a–k** with pyrrolidine and silver nitrate, followed by MeI quenching.[9]

Substrate		Product			Unreacted **7**
7a		**14a**		64%	11%
7b		**14b**		62%	21%
7c		**14c**		59%	25%
7d		**14d**		79%	10%
7e		**14e**		52%	26%
7f		**14f**		54%	39%
7g		**14g**		45%	49%
7h		**14h**		48%	46%
7i		**14i**		58%	13%
7j		**14j**[b]		87%	6%
7k		**14k**[c]		70%	22%

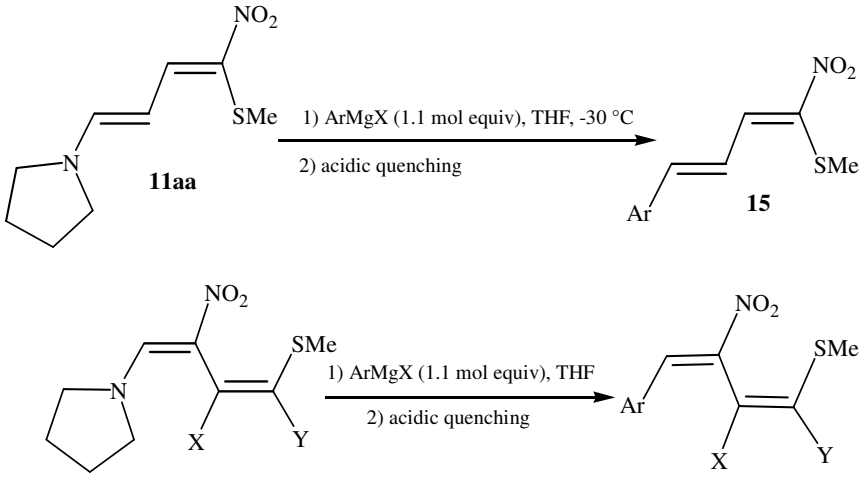
[a]Yields of isolated, pure compounds. [b]Ref. 18. [c]Unpublished result.

At variance with 2-nitrothiophene, the coordination of Ag^+ to sulfur is herein necessary for the success of the reaction, as no ring-opening can be detected in the absence of $AgNO_3$.

4. Synthetic exploitation of nitrobutadienic building-blocks

The most relevant common feature of the unsaturated butadienic building-blocks deriving from the ring-opening of 2-nitrothiophenes **6a,b** and 3-nitrothiophenes **7a–k** (*i.e.* **11a,b** and **14a–k**, respectively) is the presence of a *tert*-nitroenamine moiety whose well-known reactivity[14] guarantees wide synthetic potentialities. The following sections will deal with a number of synthetic protocols specially targeted to either homocyclic or heterocyclic derivatives through a proper preliminary modification of the functionalities of such appealing intermediates.

As a matter of fact, in all of the protocols to be reported below, the initial step is represented by the treatment of the substrate with an aryl Grignard reagent, followed by acidic quenching. On both **11**[8b] and **14**[9,15–18] the reaction performs a nitrodienylation of the aryl moiety *via* replacement of the amino group of the substrate with the aryl itself (Scheme 9). Although such a result was expected on the grounds both of the well-known reactivity of nitroenamines[14] and of our recent experience on the behaviour of the bis(nitroenamines) **4**,[7] it is noteworthy that the reaction proceeds in every case with complete chemo- and stereo-selectivity: the exclusive replacement of the pyrrolidino group being accompanied by the retention of configuration at both double bonds.



14a	X = Y = H	**16**
14b	X, Y : CH=CH-CH=CH	**17**
14e	X = H, Y = SMe	**18**
14j	X = SO_2Ph, Y = H	**19**

Scheme 9. Nitrodienylation of aryls with nitrodienamines (see Table 2).

The results collected in Table 2 are relevant to the reactions of some selected nitrobutadienes with a series of aryl Grignard reagents. Anyway, in order to ascertain the generality of the method, we verified the reactivity of each 1-pyrrolidino-2-nitrobutadiene **14** of Table 1 with *p*-tolylmagnesium bromide (1.1 mol equiv) at –78 °C in THF, obtaining the expected substitution product generally with yields from good to high (57–94%), with the only exception of the reaction on **14g** (X = COMe, Y = H, yield: 39%).[9]

Table 2. Yields[a] of compounds **15–19** from the reactions of 1-pyrrolidinonitrobutadienes **11aa** and **14a,b,e,j** with aryl Grignard reagents, according to Scheme 9.

	Ar	**15**: Y%[b]	**16**: Y%[c]	**17**: Y%[d]	**18**: Y%[e]	**19**: Y%[f]
a	Ph	**15a**: 84	**16a**: 90	**17a**: 99	**18a**: 65	**19a**: 90
b	2-MeC_6H_4		**16b**: 95	**17b**: 95		**19b**: 98
c	3-MeC_6H_4		**16c**: 88	**17c**: 87		**19c**: 95
d	4-MeC_6H_4	**15d**: 91	**16d**: 98	**17d**: 94	**18d**: 88	**19d**: 90
e	3-$MeOC_6H_4$		**16e**: 87		**18e**: 97	
f	4-$MeOC_6H_4$	**15f**: 92			**18f**: 89	**19f**: 89
g	3-ClC_6H_4				**18g**: 77	
h	4-ClC_6H_4	**15h**: 78		**17h**: 99	**18h**: 91	
i	1-Naphthyl	**15i**: 85	**16i**: 91	**17i**: 99	**18i**: 93	**19i**: 98
j	2-Naphthyl		**16j**: 89		**18j**: 89	**19j**: 98
k	2-Thienyl	**15k**: 69	**16k**: 76	**17k**: 99	**18k**: 98	**19k**: 98
l	3-Thienyl		**16l**: 78			**19l**: 77

[a]Yields of isolated, pure compounds. [b]Ref. 8b. [c]Ref. 15. [d]Ref. 16. [e]Ref. 17. [f]Ref. 18.

The so obtained 1-aryl-4-nitro-1,3-butadienes **15** and 1-aryl-2-nitro-1,3-butadienes **16–19** represent a valuable pool of poly-substituted building blocks endowed with different sets of functionalities: among the others, ketene S,S- and S,SO_2-acetals, or captodative vinyl systems like α-methyltio-α,β-unsaturated ketones, esters and nitriles seem particularly promising as synthetic intermediates.

As a further functional modification, some of these compounds have been exploited by us in synthetic protocols which include as the first step the convenient oxidation of the methylthio group to a methylsulfonyl group, in order to increase their stability and/or improve or modify their electronic features.

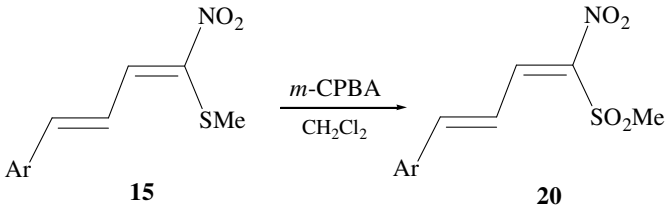
4.1. The reaction of 1-aryl-4-methylthio- or 1-aryl-4-methylsulfonyl-4-nitrobutadienes with diazomethane: an interesting dichotomic behaviour

Following the above mentioned, high-yielding preparation of sulfides **15a,d,f,h,i,k** (Scheme 9, Table 2), the easy oxidation of the methylthio group of the latter with *m*-CPBA in dichloromethane[8b] furnishes the corresponding sulfones **20** in high, when not quantitative, yields (Scheme 10, Table 3).

Actually, these two very simple, high-yielding reactions allow to obtain, *via* successive modification of the functionalities of **11aa**, two *series* of derivatives (**15** and **20**) which are identical but for the oxidation level of the sulfur atom, a feature which significantly influences their electronic requirements.

Among the various possibilities offered by their expectedly wide synthetic potentialities, the treatment with diazomethane seemed an appealing breakthrough: as a matter of fact, the cycloaddition reaction of electron-deficient alkenes with diazomethane represents a useful access to a number of interesting targets

(like pyrazolines and pyrazoles and/or cyclopropanes therefrom), as the literature clearly acknowledges with a continuous interest on the subject.[19] Nitroalkenes are particularly suited at this regard because the resulting nitrocyclopropanes can in turn be considered important building-blocks thanks to the presence of the versatile nitro group.[20]



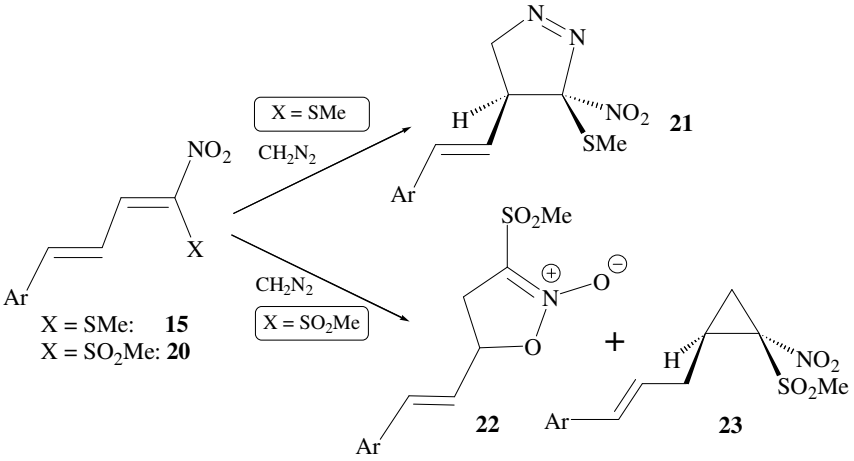
Scheme 10

Table 3. Synthesis of sulfones **20a,d,f,h,i,k** according to Scheme 10.

Ar	**20**: Yield %[a]
Ph	**20a**: 95
4-MeC_6H_4	**20d**: 96
4-$MeOC_6H_4$	**20f**: 95
4-ClC_6H_4	**20h**: 88
1-Naphthyl	**20i**: 99
2-Thienyl	**20k**: 78

[a]Yield of isolated, pure compounds.

When added with diazomethane (2 mol equiv) in THF at 0 °C,[8b] nitrosulfides **15** gave in any instance a single product, *i.e.* the diastereomerically-pure racemic 3-methylsulfanyl-3-nitro-4-styryl-4,5-dihydro-3*H*-pyrazole **21** (Scheme 11), as determined by NMR analyses and by a single-crystal X-ray analysis on the model **21a** (see the relevant ORTEP in Figure 1). Yields of **21**, reported in Table 4, were always more than satisfactory.



Scheme 11

As a matter of fact, the formation of isolable pyrazolines as the result of a 1,3-dipolar cycloaddition is well in agreement with literature data.[19b] The reaction is, as expected, completely stereospecific because the

original *cis*/*trans* relationship of the substituents in **15** is maintained in **21** and, accordingly, **21a–f** are diastereomerically-pure racemic mixtures.

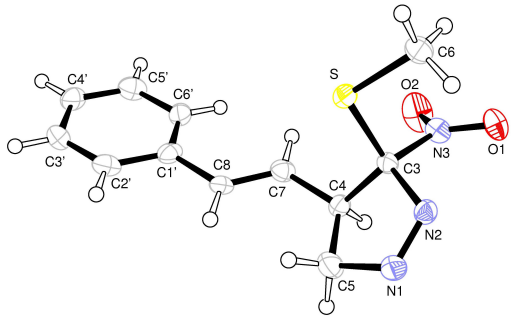


Figure 1. ORTEP drawing of pyrazoline **21a**.

Table 4. Yields of pyrazolines **21** from sulfides **15**, and of isoxazoline *N*-oxides **22** and cyclopropanes **23** from sulfones **20** (Scheme 11).[a,b]

Ar	**21**: Yield %[c]	**22**: Yield %	**23**: Yield %[c]
Ph	**21a**: 80	**22a**: 44	**23a**: 31
4-MeC_6H_4	**21d**: 83	**22d**: 65	**23d**: 25
4-$MeOC_6H_4$	**21f**: 76	**22f**: 50	**23f**: 34
4-ClC_6H_4	**21h**: 71	**22h**: 54	**23h**: 20
1-Naphthyl	**21i**: 73	**22i**: 64	**23i**: 24
2-Thienyl	**21k**: 82	**22k**: 64	**23k**: 27

[a]CH_2N_2 2 mol equiv, THF, 0 °C to rt, 15 h. [b]Yields of isolated, pure compounds. [c]Isolated as single racemic diastereoisomers.

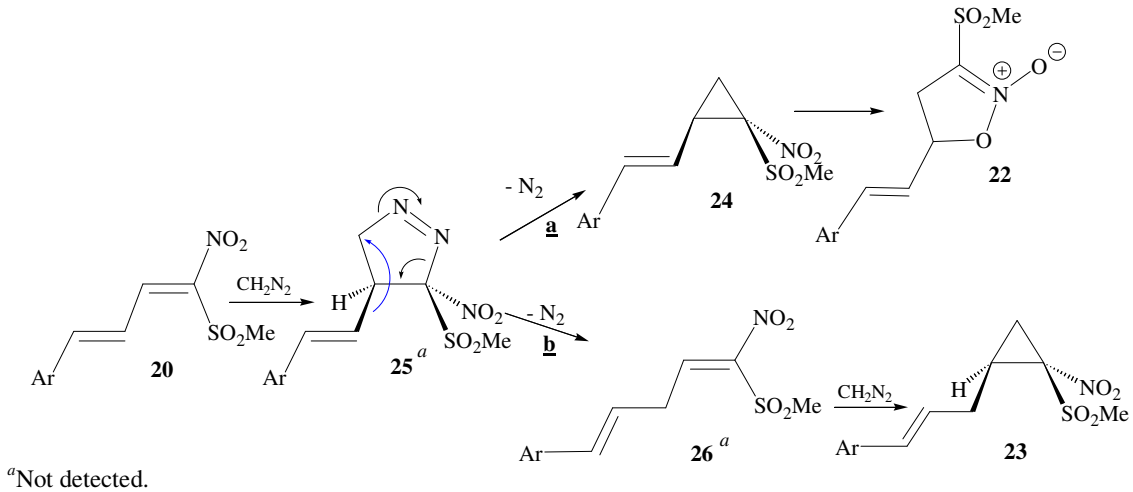
When the same reaction conditions were applied to nitrosulfones **20** the main products were the isoxazoline *N*-oxides **22** (Scheme 11) always accompanied by minor, but significant quantities of the cyclopropane derivatives **23**, according to the data reported in Table 4.[8b]

The formation of the isoxazolines **22** has been explained (Scheme 12, path **a**)[8b] on the grounds of the well-known nitrocyclopropane to five-member cyclic nitronate isomerization,[21] which proceeds through the selective breakage of the most substituted bond of the cyclopropane ring. The 1-methylsulfonyl-1-nitro-2-styrylcyclopropane precursor **24** could be isolated only in one occasion (Ar = 4-ClC_6H_4), as the contemporaneous presence of two strongly electron-withdrawing groups at C(1) of the cyclopropyl ring favours a fast **24** to **22** isomerization thanks to a strong polarization of the C(1)-C(2) bond and to an effective delocalization of the negative charge developing on the C(1) carbon. Concomitantly, the incipient positive charge on the allylic C(2) carbon would be in turn stabilized by the conjugative effect exerted by the styrene moiety. The cyclopropyl derivatives **24** are most likely the products of nitrogen extrusion from the unstable, never observed pyrazolines **25**, generated by a 1,3-dipolar cycloaddition of diazomethane on sulfones **20**.

The structure of the unexpected homologous cyclopropyl derivatives **23** was deduced on the grounds of ^1H and ^{13}C NMR analysis and NOE experiments. It should be noted that the cyclopropyl ring of **23** does

not spontaneously isomerize into the corresponding isoxazoline *N*-oxide, in agreement with the fact that the breakage of the C(1)-C(2) cyclopropane bond would develope a positive charge on a carbon atom in a non-conjugated position.

On the grounds of the experimental evidence, it is reasonable to assume that **23** derives from the reaction of diazomethane with the transient nitroalkene precursor **26** (Scheme 12), whose formation can be justified by means of nitrogen extrusion (Scheme 12, black arrows) from **25** coupled with migration of a styrene moiety from C(4) to C(5) of the pyrazoline nucleus (blue arrows: path **b**): a process which bears tight analogies with previous reports in the literature[22–25] and which can be rationalized on conformational grounds.[22,23]



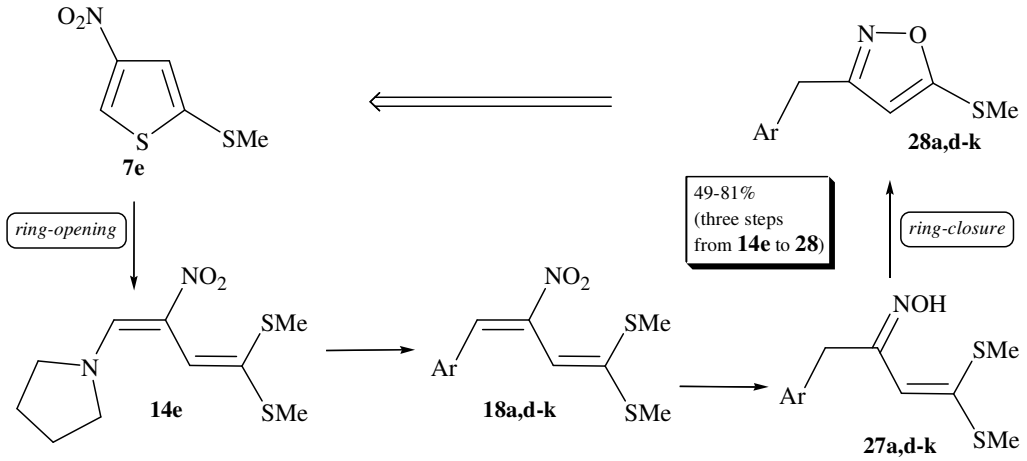
[a]Not detected.

Scheme 12

Thus, the final outcome of the reaction dramatically depends on the stability, in the reaction conditions, of the alleged primarily formed pyrazolines (**21** and **25** from **15** and **20**, respectively) and, hence on the nature of the substituents present on the butadiene system, the oxidation level of the sulfur atom geminal to the nitro group playing a decisive role. In this line, it should be remarked that 2-nitrothiophene is quite peculiar in providing, *via* ring opening and successive transformations, a 1,3-butadiene moiety possessing two geminal strongly electron-withdrawing groups such as NO_2 and SO_2Me: a structural feature which is surely bound to characterize the chemical behaviour of building-blocks such as **20**.

4.2. Synthesis of 5-(methylthio)isoxazoles from 2-methylthio-4-nitrothiophene

Among the numerous heterocyclic moieties of biological interest, the isoxazole ring is characterized by a well acknowledged multi-faceted activity, strongly dependent on the presence of proper ring substituents.[26] An easy three step synthesis[17] of 3-arylmethyl-5-methylthioisoxazoles has been obtained starting from 1,1-bis(methylthio)-3-nitro-4-pyrrolidino-1,3-butadiene (**14e**), that is the ring-opening product of 2-methylthio-4-nitrothiophene (**7e**), by the initial replacement of the pyrrolidino group with an aryl group (see Scheme 8, Table 2), followed by reduction of the nitrovinyl moiety to give the benzyl vinyl oximes **27a,d–k**; the treatment in acetonitrile at reflux with an acidic ion-exchange resin (amberlyst 15®) of these compounds, which possess two geminal methylthio substituents, finally allows the cyclization to the isoxazole derivatives **28a,d–k** (Scheme 13, Table 5).



Scheme 13

Table 5. Yields[a] of oximes **27** and isoxazoles **28** (according to Scheme 13).[17]

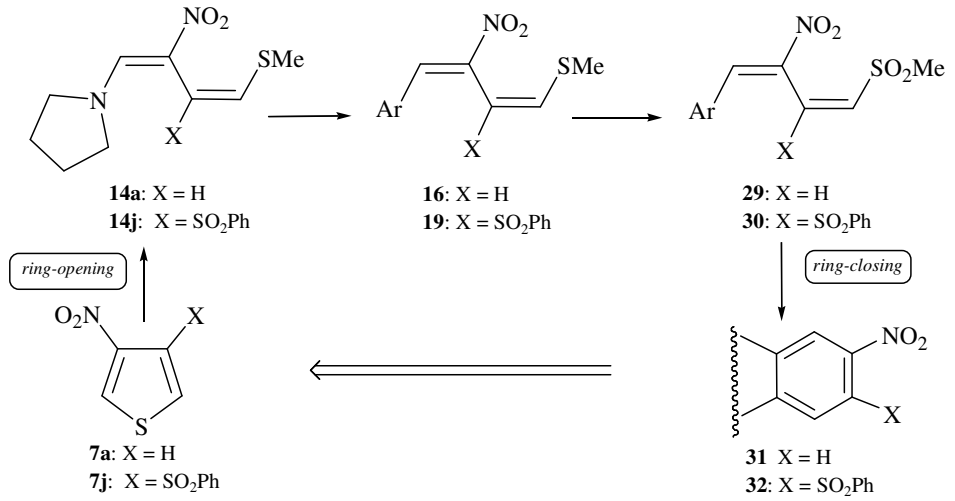
Ar	**27**: Yield %	**28**: Yield %
Ph	**27a**:88	**28a**: 94
4-MeC_6H_4	**27d**: 82	**28d**: 86
3-$MeOC_6H_4$	**27e**: 90	**28e**: 93
4-$MeOC_6H_4$	**27f**: 92	**28f**: 91
3-ClC_6H_4	**27g**: 80	**28g**: 80
4-ClC_6H_4	**27h**: 81	**28h**: 95
1-Naphthyl	**27i**: 95	**28i**: 88
2-Naphthyl	**27j**: 84	**28j**: 98
2-Thienyl	**27k**: 83	**28k**: 87

[a]Yields of isolated, pure compounds.

4.3. Thermal cyclization of products deriving from the ring-opening of 3-nitrothiophene and 3-nitro-4-(phenylsulfonyl)thiophene

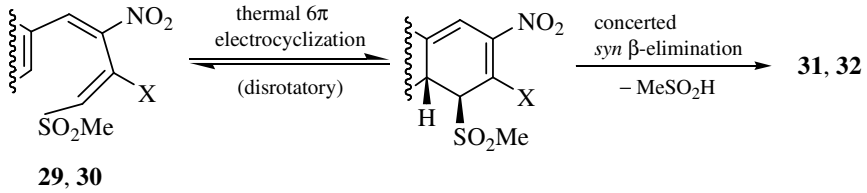
Other interesting results to be framed within an overall ring-opening/ring-closing protocol have been obtained from nitrobutadienic fragments deriving from 3-nitrothiophene and 3-nitro-4-(phenylsulfonyl)thiophene. Actually, the nitroenamines **14a** and **14j** (see Table 1 and Scheme 14) are the start-point to synthesize the two *series* of 1-aryl-2-nitro-4-methylthiobutadienes (**16a–e,i–l**) and 1-aryl-2-nitro-3-phenylsulfonyl-4-methylthiobutadienes (**19a–d,f,i–l**), thanks to the usual reaction with aryl Grignard reagent (Scheme 14). With the aim of improving the electronic features of our building-blocks, we chose to oxidize the methylthio function to the methylsulfonyl group of compounds **29** and **30** respectively (Scheme 14, Table 6). The so-obtained building-blocks were then subjected to thermal cyclization by reflux in dry xilene for the requested time (1–96 h for **29**, 1–48 h for **30**).[15,18]

The thermal cyclization shown in Scheme 14 leads to the benzocondensed derivatives **31** and **32** in more than satisfactory yields (Table 6), representing then an appealing synthetic route to compounds (substituted naphthalenes, phenanthrenes and benzothiophenes) which are generally not easy to prepare *via* more conventional methods.



Scheme 14

The mechanism of this reaction involves a disrotatory thermal 6π-electrocyclization followed by a fast *syn* β-elimination of methanesulfinic acid (Scheme 15). The efficiency of the final aromatization step is conceivably responsible for the reaction conditions, which are exceptionally mild with respect to electrocyclic processes where electrons of aromatic systems are involved.[27]



Scheme 15

Table 6. Yields[a] of sulfones **29** and **30**, and of products from thermal cyclization (*p*-xylene at reflux) of the latter (**31** and **32** respectively).[15,18]

	X = H		**X = SO_2Ph**	
Ar	**29**: Y%	**31**: Y%	**30**: Y%	**32**: Y%
Ph	**29a**: 92	**31a**: 86	**30a**: 95	**32a**: 96
2-MeC_6H_4	**29b**: 94	**31b**: 90	**30b**: 98	**32b**: 98
3-MeC_6H_4	**29c**: 93	**31c**: 79[b]	**30c**: 98	**32c**: 93[b]
4-MeC_6H_4	**29d**: 98	**31d**: 84	**30d**: 92	**32d**: 90
3-MeOC_6H_4	**29e**: 96	**31e**: 92[b]		
4-MeOC_6H_4			**30f**: 98	**32f**: 81
1-Naphthyl	**29i**: 98	**31i**: 77	**30i**: 99	**32g**: 88
2-Naphthyl	**29j**: 98	**31j**: 75	**30j**: 99	**32h**: 98
2-Thienyl	**29k**: 93	**31k**: 90	**30k**: 99	**32i**: 90
3-Thienyl	**29l**: 98	**31l**: 72	**30l**: 98	**32j**: 98

[a]Yields of isolated, pure compounds. [b]Mixture of isomers.

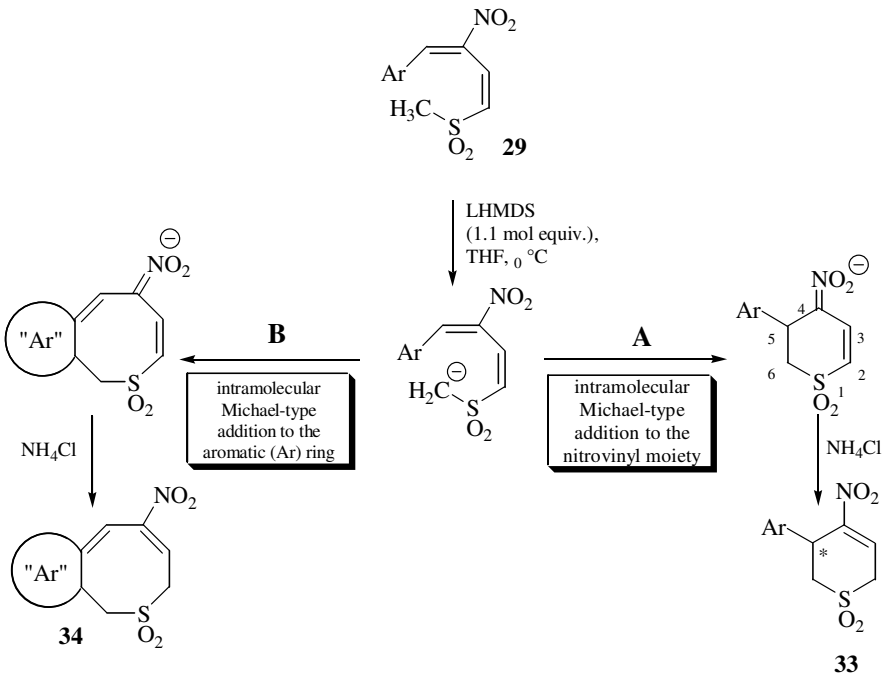
The slight differences observed in the behaviour (yields and reaction time) of **29** and **30**, which differ only for the presence of the phenylsulfonyl group in the 3-position of the butadienic chain, testify for the 6π-electrocyclic nature of this process, while the involvement of a pathway of ionic nature could be excluded thanks to appropriate experimental tests, including use of solvents of different polarity and/or introduction in the aryl moiety of groups of very different electronic properties.[15]

4.4. Base induced cyclization of ring-opened products from 3-nitrothiophene

When basic conditions are applied (LHMDS in THF at 0 °C), the nitrobutadienes **29** have been found to undergo a completely different kind of cyclization, which allows, after acidic quenching, to isolate thiopyran *S,S*-dioxides **33** as single racemic mixtures in satisfactory yields (**A** in Scheme 16).[28]

The neat result of such base-induced cyclization is therefore an enlargement of the starting thiophene ring *via* deprotonation and Michael-type cyclization onto the nitrovinyl moiety, followed by selective protonation of the carbon adjacent to the sulfonyl group.

Within this context, an interesting unexpected competitive process (**B** in Scheme 16) has been evidenced, depending on the nature of the aryl moiety (Ar) in **29**. Actually, when the aryl is a less aromatic naphthyl or thienyl group, the unusual derivatives **34**, containing a 8-atom heterocycle *ortho*-condensed to the original aryl, can be isolated. Such a surprising reactivity, whose details are still under investigation, is justifiable with the involvement of an aromatic electronic couple within the intramolecular Michael-type addition.[28]



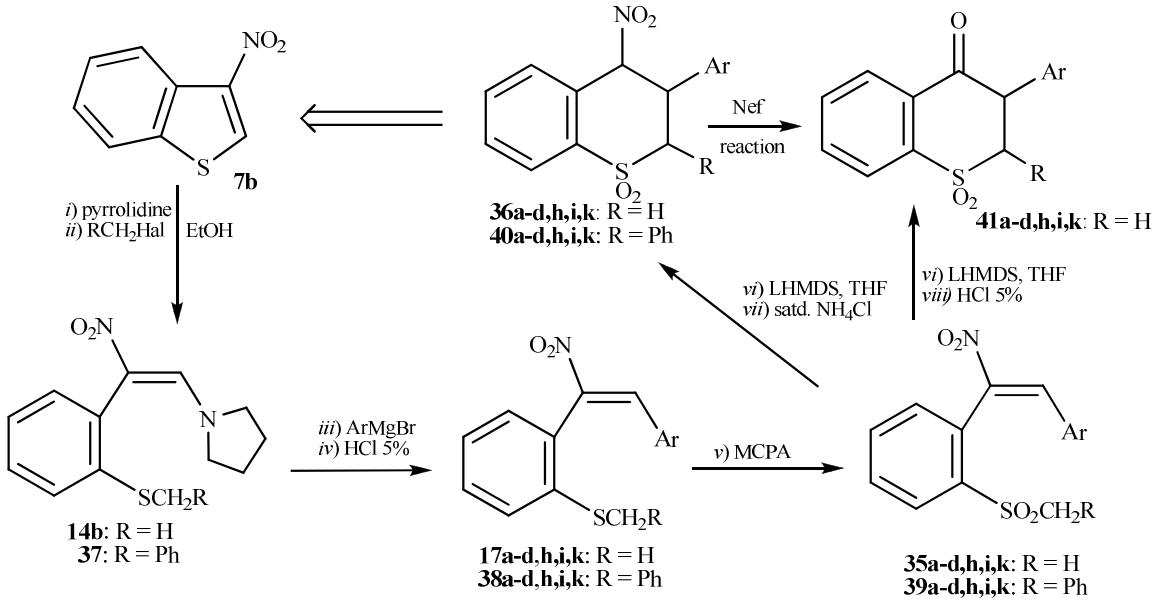
Scheme 16

It is interesting to note that nitrobutadienes **30**, structurally similar to **29** but for the presence of the phenylsulfonyl group at C-3 and able to give (like **29**) thermal 6π-electrocyclization, failed to undergo the base-induced process as no significant evidence for the formation of the corresponding cyclized product was detected after treatment in analogous reaction conditions.

4.5. Base induced cyclization of ring-opening products from 3-nitrobenzo[*b*]thiophene

As already mentioned, the condensed heterocycle 3-nitrobenzo[*b*]thiophene **7b** undergoes, as much as simple β-nitrothiophenes, ring opening when reacted with pyrrolidine and silver nitrate (Scheme 7); after methylation of the non-isolated silver thiolate it is possible to recover in high yields (Table 1) a peculiar "butadiene" system in which one double bond is part of a phenyl ring (**14b**).[9] Following the high-yielding replacement of the pyrrolidino group with the aryl group of a Grignard reagent, the styryl derivatives **17a–d**,**h**,**i**,**k** (Scheme 17 and Table 7) can be oxidized to the corresponding sulfones **35a–d,h,i,k**, endowed with a sulfonyl-activated methyl group. Similarly to the nitrobutadienes **29**, when treated with LHMDS at 0 °C followed by acidic quenching, compounds **35** underwent a cyclization reaction, being eventually converted into the thiochroman *S,S*-dioxides **36a–d,h,i,k** (Scheme 17, R = H).[16] This definitely represents a synthetically useful outcome, given the renewed interest attached to such sulfur heterocycles.[29]

The cyclization step generally furnishes excellent yields. The process can again be explained as an intramolecular Michael-type addition of the initially formed sulfonyl-stabilized anion to the nitrovinyl moiety; stereochemical aspects should be considered as the reaction generates two stereocenters. Actually, two diastereomeric racemic mixtures are isolated throughout, with rather low stereoselectivity, corresponding to the *cis* and *trans* configurations at the C(3)-C(4) bond, with a slight preference for the *cis*-racemate.



Scheme 17

Similar sulfides (**38**) and sulfones (**39**) have been synthesized from **37**, obtained by quenching the ring opening reaction with benzyl bromide rather than MeI (Scheme 17) and the cyclization reaction of sulfones **39** proceeds with satisfactory yields. As far as stereochemistry is concerned, in this case the system is complicated by the occurrence that three stereocenters are contemporaneously generated in the final thiochromans **40**: from a speculative point of view, the reaction promises to be rather intriguing because only three of the four possible diastereoisomers are present in each case in the final mixture and the relative ratios strictly depend on the reaction temperature. The matter is presently under investigation.[28]

Another interesting facet of this intramolecular cyclization is that different derivatives are produced

depending on the nature of the acidic quenching: the nitrothiochromans **36** and **40** are obtained when ammonium chloride is used as the acid, while the corresponding thiochromanones **41** are obtained, although in less satisfactory yields, with 5% hydrochloric acid (Scheme 17). Thiochromanones **41** can alternatively be synthesized from the isolated nitroderivatives **36** by the Nef reaction.[30]

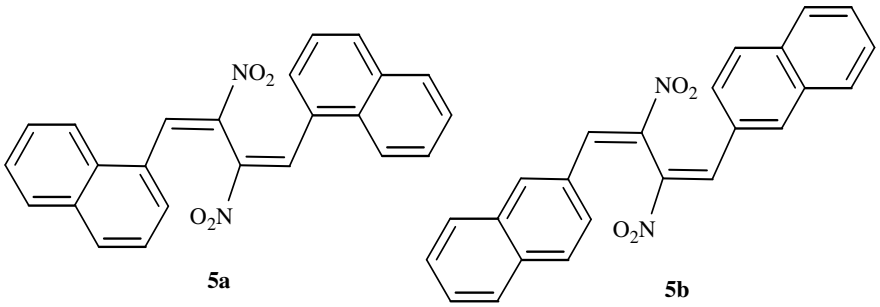
Table 7. Yields[a] of sulfones **35** and thiochroman *S,S*-dioxides **36** from the initial ring opening of 3-nitro-benzo[*b*]thiophene **7b** (Scheme 17).[16]

Ar	**35**: Yield %	**36**: Yield %
Ph	**35a**: 99	**36a**: 78
2-MeC_6H_4	**35b**: 97	**36b**: 80
3-MeC_6H_4	**35c**: 99	**36c**: 80
4-MeC_6H_4	**35d**: 94	**36d**: 88
4-ClC_6H_4	**35h**: 99	**36h**: 78
1-Naphthyl	**35i**: 99	**36i**: 99
2-Thienyl	**35k**: 99	**36k**: 70

[a]Yields of isolated, pure compounds.

5. Pharmacological activity of some nitrobutadienes

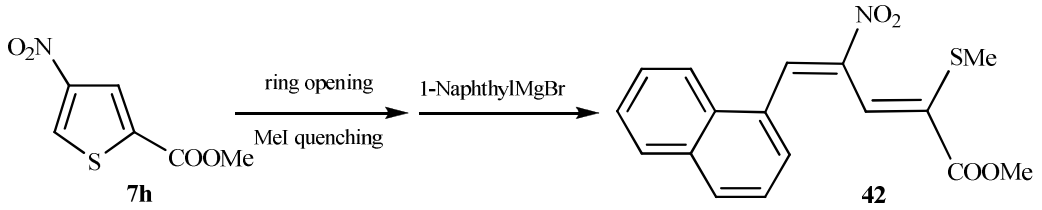
Recently, following a preliminary screening of a number of 1,4-diaryl-2,3-dinitrobutadienes **5**, the 1,4-bis(1-naphthyl) derivative **5a** (Figure 2) has revealed significant pharmacological properties against tumour cell lines characterized by different mechanisms of resistance towards the most common anticancer drugs.[31–35] The encouraging results obtained both *in vitro*[31,32] and *in vivo*[33,34] as well as on its toxicological effects[35] have suggested **5a** as a potential lead compound for a new class of pharmacologically-active molecules. On this ground, more recently some new derivatives, characterized by a common nitrobutadienic array, have been designed, synthesized and subjected to pharmacological tests. Thus the 1,4-bis(2-naphthyl) derivative **5b** (Figure 2), a structural isomer of **5a** provided with a different spatial arrangement, has in turn revealed a remarkable *in vitro* activity, although with significant differences, with respect to the lead, against some cell lines.[36]



5a **5b**

Figure 2

More interestingly, an enhanced *in vitro* activity has been displayed by the non-symmetric nitrobutadiene **42** (Scheme 18) characterized by just one naphthylnitrovinyl moiety and designed as an application of the concepts of the molecular semplification strategy.[34,37]



Scheme 18

When **42** was analyzed *in vitro* for its inhibition of cell proliferation and apoptotic activity it showed a significant pharmacological activity at micromolar concentrations, with a significant improvement compared to the parent compound **5a**.[37] Furthermore, when considering the ability to induce apoptosis, **42** showed an activity that was in some cases better than that observed for **5a**, as evaluated by the morphological analysis of nuclear segmentation. Apoptotic activity was also confirmed by the staining with Annexin V and by the analysis in western blot of the upregulation of p53 oncosuppressor protein, classically involved in the activation of the apoptotic machinery in response to DNA damage. Moreover, the analysis of formation of interstrand cross-links demonstrates the binding of **42** to DNA, although it was lower than that observed with the parent compound **5a**.[37] This observation, together with the indication of partially different cutting sites, was confirmed by the analysis of the inhibition of restriction enzymes cutting activity in λ phage DNA treated with the compound.[38] Finally, the analysis of the cell-cycle phases showed that **42** was able to cause a dose-dependent block of cells in the G2/M phase of the cell cycle, with a concomitant decrease of cells in the S phase.[37]

On the basis of these interesting results, we oriented **42** toward *in vivo* studies with the aim to evaluate its toxicological and pharmacological behaviour. For this reason, we tested the antitumour activity of **42** in several murine tumour models derived from different tumour histotypes, namely the myelomonocytic P388, the Lewis lung carcinoma 3LL, the melanoma B16, the fibrosarcoma WEHI and, finally, the C51 colon cancer. The molecule was previously analyzed by means of toxicological experiments on mice, in order to determine the lethal (LD) and the maximal tolerated (MTD) doses applicable in antitumour activity studies together with the spectrum of histological alterations caused by its endovenous administration.[34,35]

The results obtained so far definitely show that the "simplification" of the original structure of **5a** has been rewarding, as it has led to the synthesis of a promising nitrobutadiene derivative characterized by a) negligible histological toxic effects, b) an antitumour activity which is in some cases even better than that showed by the parent compound and c) tumour selectivity significantly different from that of **5a**.[34]

Finally, it should be stressed that the possibility to introduce an alkoxycarbonyl (COOR) group at C(4) of the butadiene array can be exploited *e.g.* in order to improve the water solubility of the molecule and hence to reach a better administration of the active principle, *e.g.* introducing hydrophilic functionalities in R: this is, of course, just one of our ongoing research lines in the field.

6. Conclusions

Following a longstanding synthetic exploitation of the amine-induced ring-opening of 3,4-dinitro-thiophene, likewise interesting results have been collected in more recent years also from the manipulation of the asymmetrically-substituted nitrobutadienes deriving from the ring-opening of other nitrothiophenes. As a matter of fact, in systems like **11** or **14** the different functionalization of the 1,3-butadiene skeleton

allows selective transformations of the two conjugated vinyl moieties which are precluded to the symmetric dinitrobutadienes deriving from **1**: as a consequence, the pool of heterocycles obtainable from nitrothiophenes is significantly enriched, *e.g.* by isoxazoles such as **28** or cyclic nitronates such as **22** (of course, in turn amenable of further manipulation). The conservation of the original sulphur atom in the opened products is, in particular, surely profitable from the synthetic point of view, triggering new pathway eventually leading to interesting sulphur heterocycles such as **33**, **34**, **36** and **40** or derivatives therefrom.

Finally, the "diversity" endowed in butadienes such as **14** would hopefully play a role also from the pharmacological point of view: actually, the promising antitumor activity of the "symmetric" **5a**, somewhat enhanced in **42**, can gain further improvements from newly designed structural (functional and/or geometrical) modification (possibly regarding just "one half" of the molecular array) aimed to optimizing the mechanism of action of such a promising new class of potential drugs.

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SYNTHESIS AND PROPERTIES OF COVALENT COFACIAL BISPORPHYRINS

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Abstract. *Porphyrins are among the chromophores most widely used by Nature. Very simple and basic porphyrin derivatives are incorporated in sophisticated architectures by means of self-assembly or weak interactions with the protein environment. Many synthetic porphyrin structures are inspired by Nature, and face-to-face arrangements have received much attention due to their relevance to the "Special Pair" in the photosynthetic reaction center. This chapter provides an overview of the available synthetic strategies leading to preorganized cofacial porphyrin dimers. The prime importance of the spacer responsible for the controlled spatial arrangement of the chromophores is emphasized.*

Contents

1. Introduction

Porphyrins are chromophores named after their most common purple color (*porphura* in Greek), which belonged to a pigment extracted from shells in the ancient times. The porphyrin marocycle was isolated for the first time in 1884 by Nencki[1] who, in 1896, suggested a chemical structure based on the pyrrole motif. The correct structure was then proposed in 1912 by Kuster.[2] The Fischer synthesis of etioporphyrin[3] later confirmed the association of four pyrrole moieties *via* methane bridges. As shown in bold in the structure in Figure 1, 18 π-electrons contribute to the aromaticity of the porphyrin macrocycle. The aromatic character and the high density of π-electrons induce high stability, photoactivity and electroactivity for most porphyrin based structures.

Due to its stability, the porphyrin core is one of Nature's most versatile pigments. Although in modern coordination chemistry the on-demand tuning of porphyrin properties can be achieved, Nature uses only three major structures for which the reactivity is tuned by the surrounding polypeptide environment. Protoporphyrin IX derivatives are the main component of the active site in hemoproteins, chlorophyll derivatives are widely used in plant photosynthesis and bacteriochlorophyll derivatives are involved in

energy collection and conversion in bacterial photosynthesis. The involvement of bisporphyrin scaffolds in photo-induced charge separation in natural systems has stimulated the imagination of chemists during the last two decades. Numerous synthetic cofacial bisporphyrins have been prepared in which two porphyrins in parallel plans are nearly facing each other. Due to the close proximity of the two macrocycles, it is possible to combine the reactivity of two electroactive metals (iron, cobalt) or the reactivity of two chromophores when the central ions are redox inactive.

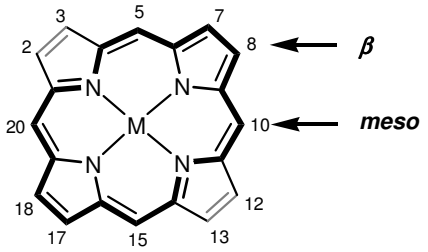


Figure 1. Porphyrin structure as initially proposed by Kuster and IUPAC numbering. Trivial names for common denominations of peripheral positions are also indicated.

This account provides an overview of covalent cofacial bisporphyrin scaffolds and their use in the fundamental understanding of chromophore interactions, or in the design of redox active species for catalysts or switches. Bisporphyrins without cofacial preorganization will be deliberately ignored and synthetic strategies will not be discussed in detail as far as the porphyrin ring formation is concerned.[4] For each compound, strategic key steps will be schematically highlighted together with the structure of the compounds. The influence of the spacer on the behavior of the scaffolds will also be discussed.

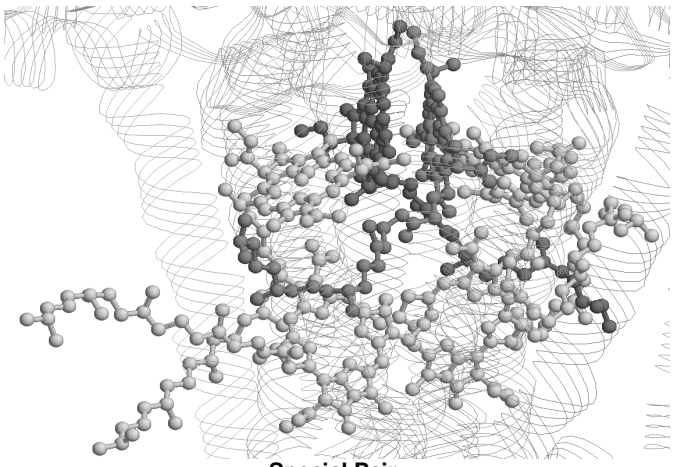
2. Cofacial bisporphyrins and photosynthesis

Photosynthesis transforms light energy into chemical energy in an efficient process that occurs in a highly organized molecular architecture. Among the chromophores chosen by Nature for this process, porphyrin derivatives play a central role. In the peripheral light harvesting antenna complexes, these tetrapyrrolic pigments absorb light and transfer it rapidly and efficiently to the complex's core, where a reaction center called the "special pair" initiates charge separation. This photo-induced electron transfer across the membrane ultimately leads to the release of chemical energy in the form of ATP.

In purple bacteria, the "special pair" is a bacteriochlorophyll (BChl) *a* dimer. The slipped, cofacial arrangement of the bacteriochlorophyll chromophores is one important feature of the special pair that was elucidated by the structural resolution of the reaction center of the purple bacteria Rhodopseudomonas Viridis. In 1982, H. Michel first succeeded in crystallizing a transmembrane protein responsible for photoinduced charge separation in this purple bacterium.[5] During the next three years, in collaboration with J. Deisenhofer and R. Huber, the atomic structure was resolved by X-ray diffraction (Figure 2).[6] These three scientists were awarded the Nobel Prize in Chemistry in 1988 for this work.

Although the first reports of cofacial bisporphyrins like Kagan's "strati-bisporphyrin" **1** (Figure 3) appeared in 1977,[7–9] the recognition of Michel, Deisenhofer and Huber's work rapidly led to the synthesis of a large number of diverse cofacial porphyrin structures aimed at modeling the special pair. Many of these bisporphyrins were synthesized in hopes of obtaining a better mechanistic understanding of photo-induced biological processes.[10] Others were designed for their electrocatalytic properties or four electron reduction of

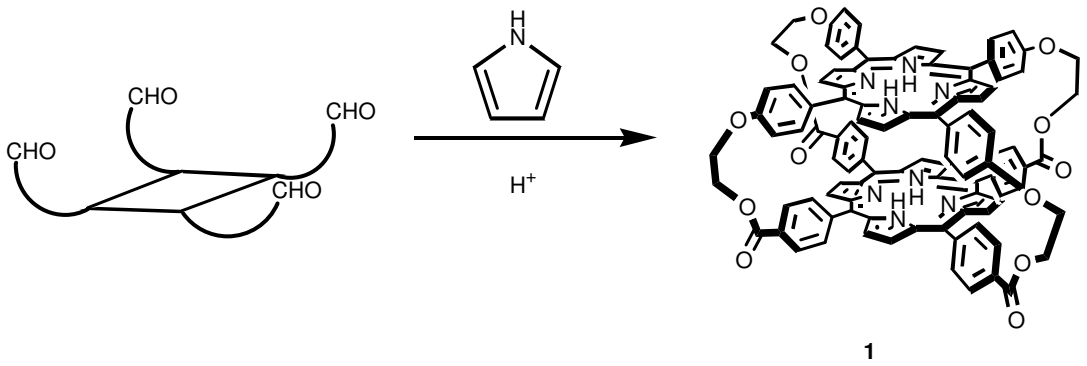
oxygen.[11] As we will see, face-to-face porphyrin assemblies have recently attracted attention in supramolecular recognition, for example as allosteric hosts, gas sensors and catalysts.



Special Pair:

BChl **602** (dark grey) and **603** (medium grey), others (light grey).

Figure 2. Structure of the reaction center of Rhodopseudomonas Viridis.[1] *Generated with Rasmol 2.6 from PDB file 1PRC.*



1

Figure 3. Kagan's strati-bisporphyrin.

3. General spectral and redox properties of porphyrins

Among the properties of porphyrins, their photochemical and electrochemical activities are the most utilized. Porphyrins usually exhibit very intense absorptions ($10^5 < \varepsilon < 3 \times 10^5$) in the high energy region of the visible spectrum (Soret band ~390 to 450 nm). These absorptions correspond to the generation of S_2 excited states. Less intense ($2 \times 10^3 < \varepsilon < 2 \times 10^4$) absorption bands (Q bands) associated with vibrational levels of transitions generating S_1 excited states are generally observed at lower energies (500 to 700 nm). Without going into detail, the estimated HOMO LUMO gap in porphyrins is generally situated around 2.3 eV, which quite invariably gives a standard electrochemical behavior for simple porphyrin macrocycles, given that they do not contain electroactive metal ions.

In cofacial arrangements, the two porphyrins can either be stacked one directly above the other (H-aggregates) or in a slipped stacked arrangement where one porphyrin is off-center but above the other (J-aggregates). In both arrangements, the dipole moments of the porphyrins are coupled, resulting in UV-visible spectral changes. The distance separating the two chromophores is also a determining factor in the

strength of the excitonic coupling. For example, hypochromism, blue shifts, broadening and/or splitting of the Soret band (around 400 nm in a single porphyrin chromophore) are consequences of excitonic coupling in H-aggregates or cofacial bisporphyrins that are the focus of this update.[12] For example, Kagan's bisporphyrin **1** showed only a relative hypochromism, a small broadening and no blue shift for the Soret band. Instead, a small red-shift of the Q-bands was observed that supports a J-aggregate character permitted by the relative flexibility of the linkers.

Regarding electrochemical properties, the distance separating the two porphyrins in a cofacial arrangement will also determine the degree and the consequences of interactions between the two redox active species. Thus, most of the discussion throughout this chapter will be based on geometric considerations, and the flexibility or rigidity of the scaffolds will be the main parameter examined. Hereafter, cofacial porphyrins will be classified into two main families depending on the type of linker between the chromophores. Rigid assemblies will be distinguished from flexible assemblies. In general, rigid assemblies have a limited degree of freedom of movement compared to flexible scaffolds in which the bridge permits topographic changes within the scaffold.

4. Rigid assemblies

When two porphyrins are held in a face-to-face arrangement by rigid spacers, the inter-porphyrin distance is well defined. Dimers of this kind are often called "Pacman" porphyrins. The term Pacman stems from the description of small geometric longitudinal changes occurring, for example, in the presence of substrates in between the two macrocycles, while lateral degrees of freedom are limited.[11] The pinching motion suggested the Pacman name in relation with the munching characters of the pioneer video game. These compounds generally display optical properties different from those of the special pair in which the chromophores have a slipped (off center) cofacial orientation. Pacman porphyrins have been studied widely as catalysts for their electrocatalytic properties.

A family of Pacman porphyrins **2–5** (Figure 4) with anthracene or similar spacers has been developed by several groups. Synthesis of the first member of this family, the anthracene Pacman **3**, was reported by Chang[8] in 1977 and was later improved by Collman.[11] The initial interest in these compounds stemmed from the electrocatalytic properties of their cobalt complexes for four electron reduction of oxygen.[13] These species were obtained by stepwise bis-dipyrrylmethane formation on the chosen dialdehyde (spacer), followed by condensation with two dipyrrylmethane moieties, as depicted schematically in Figure 4.

Later, Nocera studied the influence of the porphyrin-porphyrin distance on the activation of small substrates.[14] Variation of both the dihedral angle and the interchromophore distance was accomplished with dimethylxanthene[15] and dibenzofuran[16] spacers in compounds **4** and **5**, respectively. Compared to the C_{meso}-C_{meso} distance of 4.94 Å in **3**, this C_{meso}-C_{meso} distance is smaller in **4** (4.32 Å) and larger in **5** (5.53 Å). Due to the Pacman effect and subtle geometric changes allowed by the structure, the interporphyrin distance and the electronic properties of the Pacman dimers built with etioporphyrins were modified by introducing a meso-aryl groups in porphyrins **6** and **7**[17,18] (Figure 5) or by replacing the etioporphyrins with triarylporphyrins.[19–21] The photoinduced oxidations of phosphines,[22] dimethylsulfite,[23] olefins[20] and hydrocarbons[21] were compared in the μ–oxo complexes of the iron(III) aryl-substituted porphyrin dimers **6** and **7**. The activation of the iron-oxygen bond was enhanced 1000–10,000 times in **7** compared to **6**. A broader range of substrates could also be oxidized by **7** because of its larger, more accessible cavity.

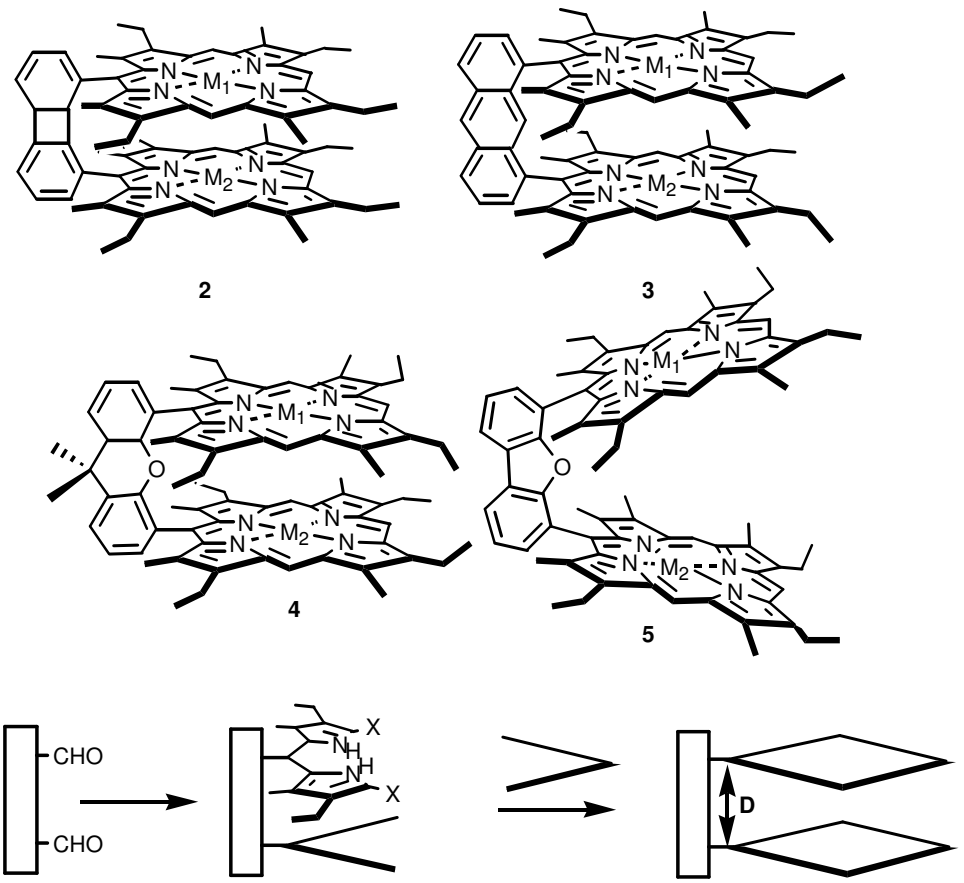
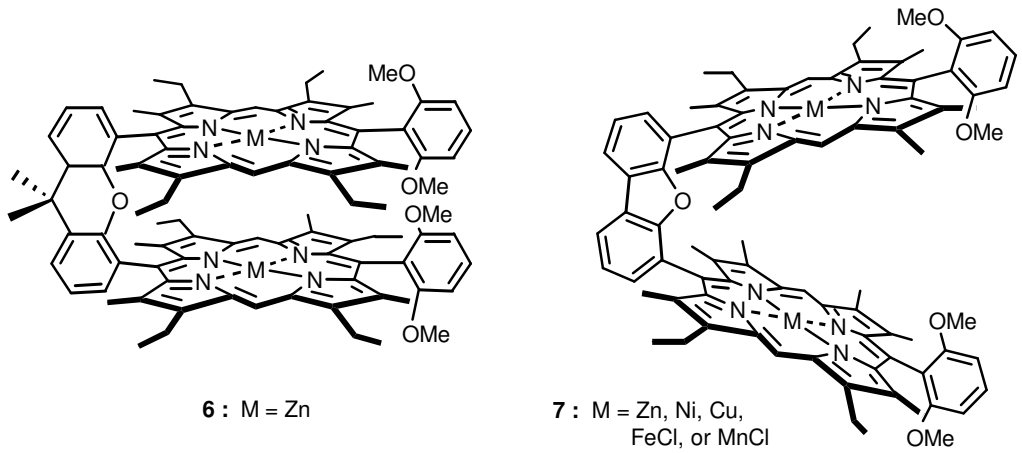


Figure 4. A series of rigid Pacman bisporphyrins covering a range of inter-chromophore distances from 3.80 Å to 5.53 Å, and schematic synthetic strategy used to produce the desired scaffold from dipyrrylmethane units. D = d (meso-meso).



6 : M = Zn

7 : M = Zn, Ni, Cu, FeCl, or MnCl

Figure 5. Subtle steric constraints introduce longitudinal distortion in Pacman architectures built on dimethylxanthene and dibenzofuran spacers.

Whereas initially the reduction of oxygen was the main focus of attention, in particular the characterization of the μ-peroxo adduct between two cobalt octaethylporphyrins,[24] the reduction of dinitrogen[25] and the activation of H_2[26] using ruthenium Pacman bisporphyrins with biphenylene spacers drew much attention in the beginning of the 90s. Because of the electrocatalytic properties of their cobalt derivatives and their potential interest in fuel-cell applications for the reduction of oxygen, architectures **8–10**, were prepared according to the strategy[27] depicted in Figure 6 and grafted on graphite electrodes.[28]

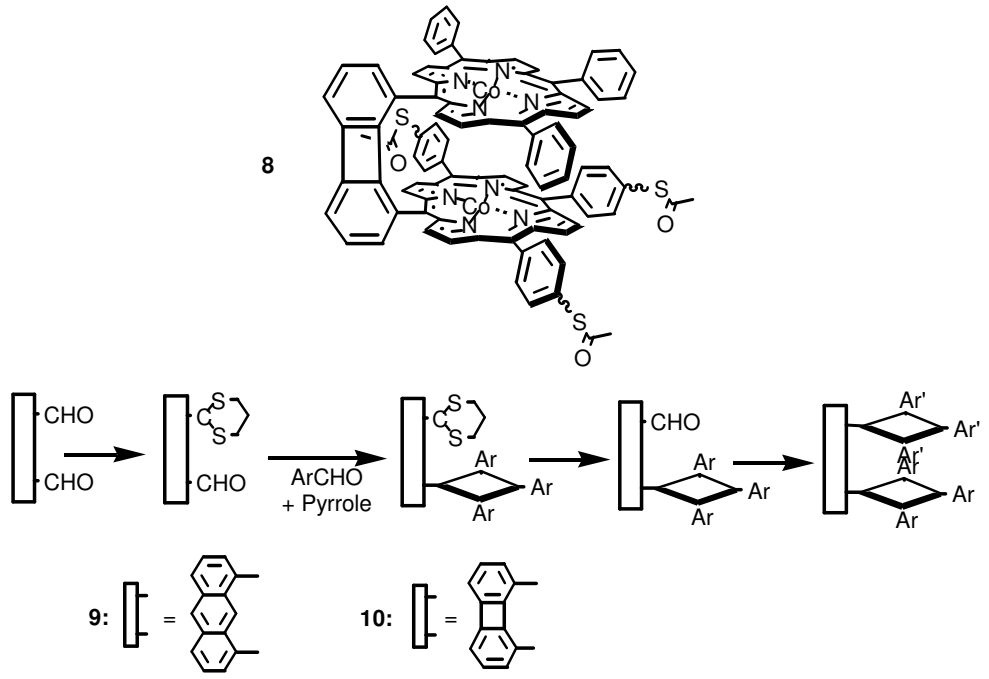


Figure 6. Unsymmetrical Pacman bis-tetraarylporphyrins: synthesis and example.

These studies showed that the electrocatalytic properties of the grafted Pacman were dependent on the electrode substrate (surface), confirming that mechanistic insights were still needed, especially when the porphyrin units of the Pacman contain metal ions that require external ligands (outside the Pacman mouth). Stepwise, four electron reduction in solution using ferrocene as one electron donor was recently reported for scaffolds **2-5** (M_1 = M_2 = cobalt) by Guilard and Fukuzumi.[29] The properties of Pacman **2** and **3** in which a cobalt porphyrin was associated with a porphyrin containing a cation with a strong Lewis acid character were investigated.[30] Lutetium (III) and scandium (III) derivatives did catalyze the tetraelectronic reduction of oxygen.

The distance separating the two porphyrin macrocycles plays a crucial role and influences the ease of cooperation of the two redox active metal centers or the strength of interactions between the chromophores. For photochemical interactions, the main properties of hollow Pacman will be examined first.

Using the dibenzothiophene analog **11** (not shown) of compound **5**, singlet-singlet energy transfer was studied for the zinc/free base and gallium/free base Pacman compounds.[31] The C_{meso}-C_{meso} distance in **11** is the longest in this series of compounds, reaching 6.30 Å. The blue shifts of the absorption bands were indicative of ground state interactions. In the excited state, interchromophore interactions increase as the distance decreases, as shown by the variation of the fluorescence quantum yields and lifetimes. Whether Förster or Dexter mechanisms of energy transfer operate in these dimers is governed by the interporphyrin distance. For example, Förster energy transfer occurs from the zinc donor to the non metallated (or free base) acceptor in dyads (Zn-H_2)**11** and (Zn-H_2)**5**, whereas the Dexter mechanism occurs in (Zn-H_2)**2–4**. Harvey and Guilard determined that the Dexter mechanism is inoperative above the critical distance of 5–6 Å.[31,32] This observation was later confirmed by analyzing the distance dependence of triplet-triplet energy transfer in Pd-Zn and Pd-H_2 porphyrin Pacman (Pd-H_2)**3** and (Pd-H_2)**3**-(O_2)-(1-*t*-butyl-5-phenylimidazole) complexes.[33] With the aim of developing oxygen sensors, the luminescence of the (Pd_2)**3** was studied.[34] The

interaction with dioxygen quenched the excited states of the Pd-porphyrin moieties. Quenching was weaker in (Pd_2)**3**[34] than in the (Pd_2)**4** counterparts.[35]

Nocera also demonstrated Pacman effects for **12** (Figure 7) in which the initial Zn-Zn distance of 7.78 Å[16] could be shortened to 6.68 Å in the presence of a 2-aminopyrimidine bidentate bound to both zinc atoms.[36] The emission lifetime of the Pacman bisporphyrin in the presence of the guest increased by more than an order of magnitude compared to the free Pacman due to the rigidification of the scaffold. Vibrational deactivation processes can thus be significantly reduced in Pacman species.

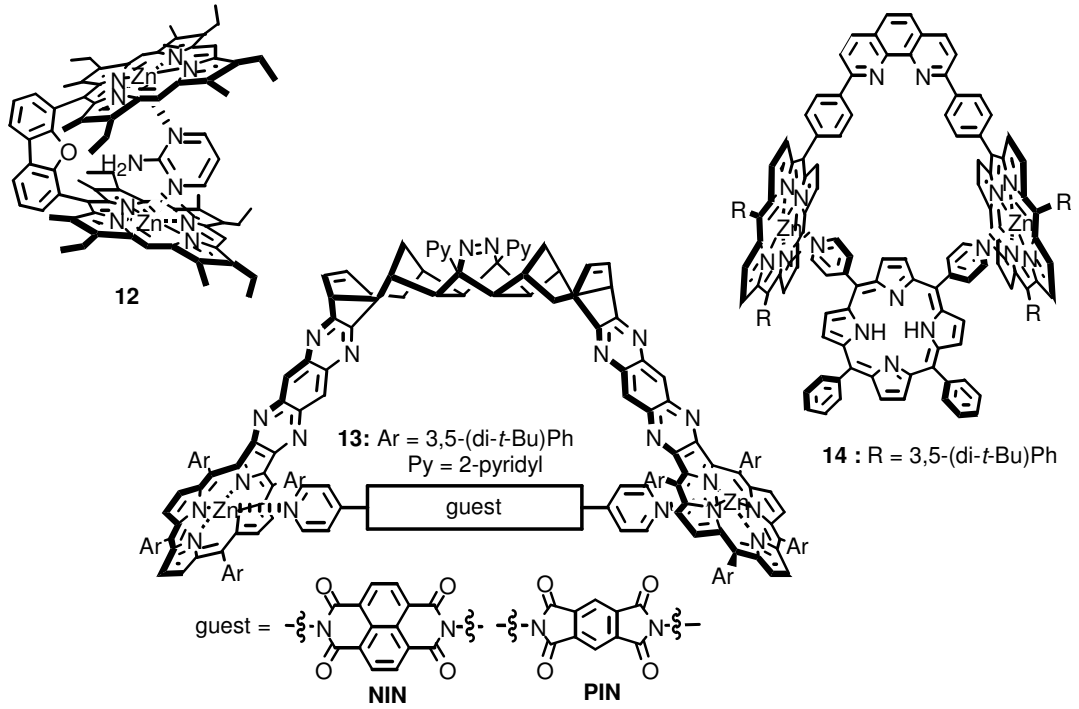


Figure 7. Inclusion of guests into geometrically well-defined Pacman.

The insertion of guests is not restricted to architectural purposes and their consequences. Due to the rather well defined geometric properties of species organized around rigid spacers, specific binding can be used as a tool for the precise positioning of photochemical partners. In that case, the structuring guest also plays a role in the photoinduced processes that are observed. This strategy has been widely used in two distinct approaches by Johnston and Sauvage. As shown in compound **13** (Figure 7), coordination of a diimide derivative of an appropriate length provides a tool for the assembly of two photo- and electro-active moieties.[37] Johnston and Flamigni showed that in the presence of a naphthalene diimide derivative (NIN), bound within **13** with an association constant in the 10^8 M^{-1} range, excitation of the zinc porphyrin donors lead to a very fast electron transfer to the diimide in 1.2 x 10^{10} s^{-1}. Similar association constants were reported for the porphyrin supramolecular assembly **14** in Figure 7.[38] Energy transfer from the zinc porphyrin to the free base porphyrin was also fast (2 x 10^{10} s^{-1}) in this host-guest assembly.

Significant innovative synthetic progress was made by the use of [2+2+2] cycloadditions. Therien elegantly used the reactivity of triple bonds at the periphery of porphyrins to prepare various scaffolds such as **15**.[39] The influences of the linker as well as the position of the anchoring point of the spacer on each porphyrin ring were explored. The strategy depicted in Figure 8 can be applied to the synthesis of Pacman species, superstructured single porphyrins[40] and also to face-to-face multiporphyrin arrays.[41]

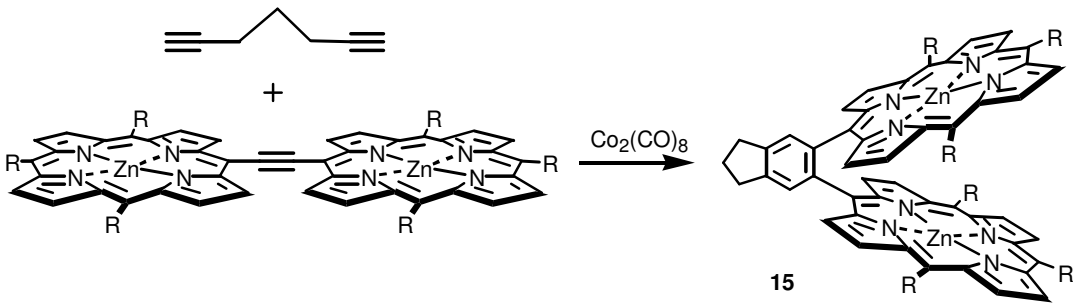


Figure 8. A [2+2+2] cyclization strategy for the preparation of Pacman species.

Similar scaffolds were prepared by Smith using McMurry coupling in the presence of titanium catalysts.[42] More recently, the same author investigated the use of porphyrin monomers bearing a fused cyclopentadienyl derivative **16** to organize face-to-face species *via* dimerization or formation of a ferrocenyl bridge as depicted in **17** (Figure 9).[43]

In bisporphyrin **17**, only the Q bands were red shifted relative to those of the monomer precursor as a result of the slipped cofacial arrangement of the two porphyrins. An X-ray structure confirmed this arrangement. The porphyrin planes were 4.2 Å apart and nearly parallel, with a dihedral angle of 4.1(5)°. The distance between copper centers was 5.290(4) Å.

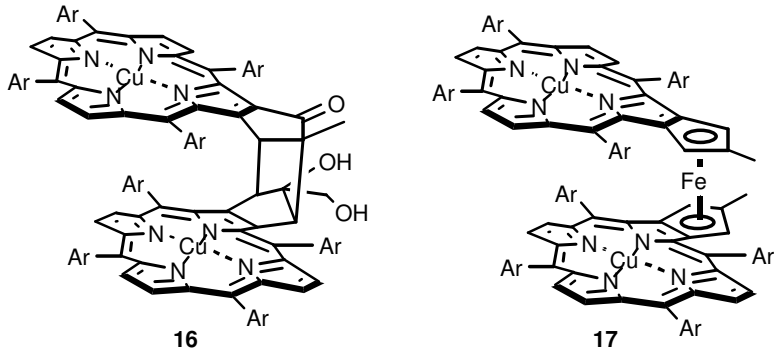


Figure 9. Pacman bisporphyrins based on cyclopentadienyl substituted precursors.

Cofacial bisporphyrins in which the distance modulation is extremely limited have been reported as well. The synthesis of the bisporphyrin-quinone scaffold **18** in Figure 10 can be seen as a combination of dipyrrylmethane formation and stepwise condensation with a masked dialdehyde.[44]

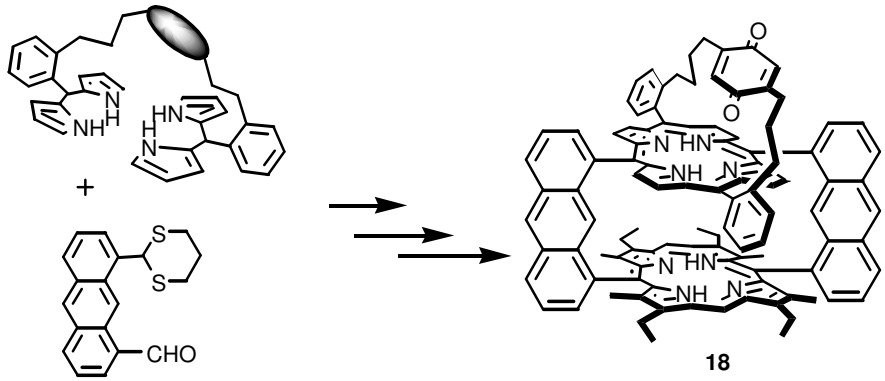
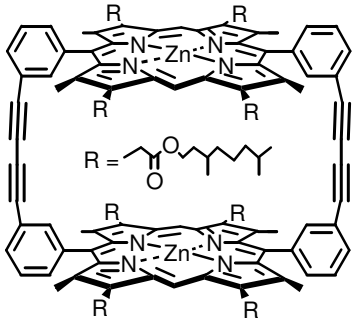


Figure 10. Quinone capped mixed cofacial architecture.

In such a structure, the rigidity of the scaffold is of utmost importance, as it ensures the stepwise electron transfer from the bottom porphyrin to the quinone. For this reason, this structure is more relevant to the class of cyclophanes than to the Pacman family.

The bisporphyrin **19** (Figure 11) described by Sanders also belongs to the cyclophane family.[45] This cage compound displays interesting preferential binding properties inside the cavity on the basis of entropic stabilization. It is also very important, as we will see later on, to consider the butadiyne linkers as precursors of flexible linkers that can be generated upon hydrogenation of the unsaturated bonds.



19

Figure 11. A cofacial bisporphyrin cyclophane with butadiyne linkers.

5. Flexible assemblies

In this section bisporphyrins in which the two chromophores are joined by flexible spacers will be discussed. The term flexible implies that some degree of movement is possible within the system. Hence, contrary to the rigid assemblies presented above, the interporphyrin distance is not necessarily fixed in the flexible systems. In some cases, substrate binding or some other stimulus is required to obtain a face-to-face arrangement of the porphyrins. In other examples, the two porphyrins are preorganized in a cofacial arrangement. Each type of assembly will be discussed as a subsection.

5.1. Flexible scaffolds requiring a stimulus for cofacial arrangement

Flexible scaffolds in which a cofacial arrangement is not initially present are generally linear molecules with ether, polyether or other non rigid bridges between the two porphyrins. The porphyrins adopt a cofacial arrangement when an external stimulus, such as a binding event, induces a topographic rearrangement. Large reorganization energies are often required to obtain the cofacial bisporphyrin. Consequently, the resulting host-guest complexes have lower association constants than in rigid assemblies. The advantage of these flexible systems is their relatively simple synthesis and their ability to adjust to the size of the substrate.

Using simple, high yielding reactions such as the Williamson coupling, Monti and co-workers prepared linear bisporphyrins bridged by polyether chains[46] (Figure 12). In the presence of alkaline or alkaline earth cations (Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) the polyether chain wraps around the cation, creating a cofacial porphyrin arrangement. Despite low binding constants, interchromophore interactions were observed by UV-visible and NMR spectroscopies. The porphyrin-porphyrin distance was controlled by the choice of the cation and by the length of the ether chain. A similar compound, in which one 5,10,15-triphenylporphyrin was replaced by an octaethylporphyrin (OEP), was also reported; however, cation complexation had little effect on the efficiency of energy transfer.[47]

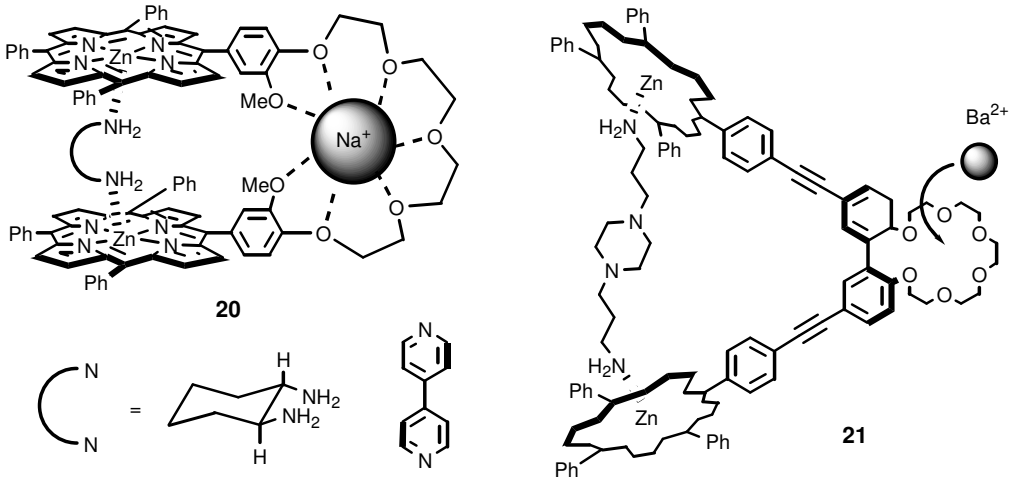


Figure 12. Allosteric receptors.

To improve the efficiency of cation detection, Monti developed an allosteric approach in which the binding affinity for bidentate nitrogen ligands by the zinc porphyrins in **20** (Figure 12) is modified by the complexation of a sodium cation within the ether chain.[48] This allosteric effect decreases the host's affinity for 4,4'-bipyridine but increases its affinity for 1,2-diaminocyclohexane.

An interesting example of an allosteric effect was reported by Kubo for the compound **21** in Figure 12.[49] The biphenyl groups are linked by a pseudo-crown ether that is a binding site for Ba^{2+}. In the absence of barium, this bisporphyrin has a high affinity for a diamine. However, the diamine is progressively released in the presence of increasing amounts of barium perchlorate.

Another important property often associated with allostery is chiral induction caused by the binding of a chiral guest within a bisporphyrin host. Such binding events can be followed by circular dichroism (CD).[50] Kubo showed that the complexation of potassium within a macrocyclic spacer assists the rise of induced CD during the complexation of chiral diamines by receptor **22** (Figure 13).[51] This allosteric effect of potassium provides a means of determining the chirality of potassium carbonate salts such as camphorates and mandelates using a bi-phasic extraction method.

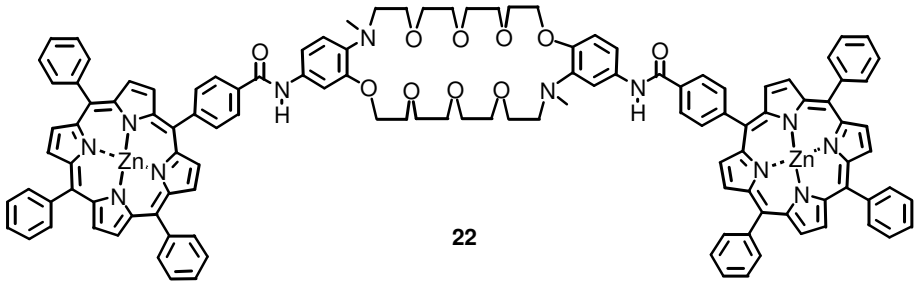


Figure 13. An allosteric receptor for chiral induction.

Chiral binaphthyl bis(zinc porphyrin) receptors were used as chiral sensors by Ogoshi and Hayashi for the amplification or induction of CD signals in the presence of substrates.[52] In a chiral host, the CD signal was amplified upon binding dialkylamines. The degree of amplification was a function of the diamine length and the binding constant. The absolute configuration of a lysine derivative was determined thanks to the enantioselectivity of the bisporphyrin cavity.

Bisporphyrins with flexible, linear bridges also act as chiral sensors. Bis(tetraaryl-porphyrin) **23** bearing diester bridges (Figure 14) were developed to study chiral induction or the origins of CD signal amplification upon substrate binding. Nakanishi and Berova have shown that the amplitude of induced CD spectra is directly related to the steric bulk of the substrate's largest substituent.[53] Furthermore, the sign of the CD signal depends on the absolute configuration of the substrate.[54]

Inoue, Borovkov and collaborators studied supramolecular chirogenesis for **24** with the ethane-bridged zinc octaethylporphyrins (ZnOEP) in Figure 14.[55] At room temperature, a cofacial *syn* conformation is preferred. This *syn* arrangement is favored over the extended *anti* form due to strong π-π interactions. Conformational switching from the achiral, *syn* conformation to the chiral, *anti* conformation was both temperature dependent and ligand assisted.[56] The chirality of the *anti* conformation could be induced by a chiral guest[57] and, in one case, tuned by increasing the guest's concentration.[58]

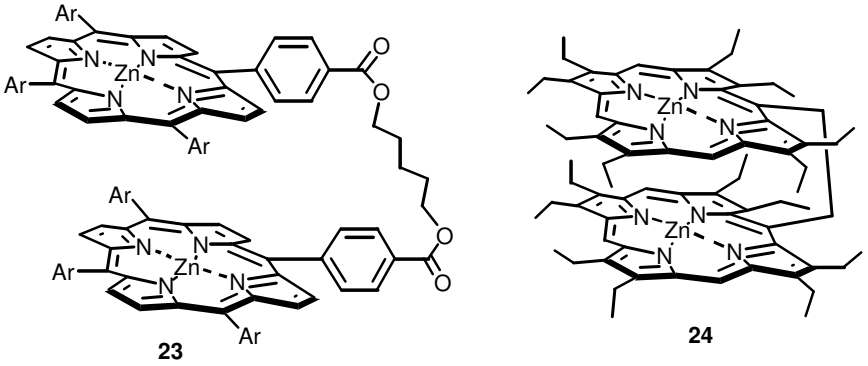


Figure 14. Chirality sensors based on CD spectra induction by chiral bidentate.

Flexible species in which the cofacial geometry can be induced by substrate complexation were reported by Flamigni and Solladié.[59,60] At first glance, the porphyrin dimer **25** (Figure 15), prepared by sequences of Sonogashira coupling with acetylene and anthracene spacers, might seem to have little flexibility. However, rotations around single bonds between the acetylene and anthracene provide a variety of possible conformations. The porphyrin-porphyrin distance can vary from 5 to 20 Å and topography can be adjusted by substrate binding. With a diazabicyclooctane (DABCO) guest, the porphyrins could be held approximately 5 Å apart. Dipyridyl free base porphyrins or 4,4'-bipyridine guests force the porphyrins further apart. Association constants in toluene were one order of magnitude higher for the bipyridine complex (3.8×10^7 M^{-1}) than for the 5,10-dipyridylporphyrin complex, probably due to more a more cofacial, less strained arrangement of the porphyrins in the presence of the 4,4'-bipyridine guest.

Similar "induced-fit" behavior[61] or template effect[62,63] was previously observed by Ballester and Hunter in **26** and **27**, represented in Figure 15. The ability of each scaffold to form face-to-face arrangements upon complexation of DABCO,[61] dipyridyl ligands[63] or a bis(4,4'-bipyridine)Pt wedge[62] is mostly controlled by the positioning of the amide nitrogen on the porphyrin moieties. *Ortho* and *meta* substituted species **26a** and **26b** form face-to-face complexes offering various distances between the chromophores, whereas *para* substituted species **26c** afford higher degrees of supramolecular arrangements. Haino and Fukazawa reported free base analogs of **26b** that dimerize through π-π interactions.[64] Bisporphyrins similar to **26c**, but with chiral ester linkages instead of amide bridges, were shown to be chiral NMR shift reagents.[65] The enantiomeric purity of chiral diamines, aziridine and isoxazoline was determined using micromolar concentrations of the bisporphyrin.

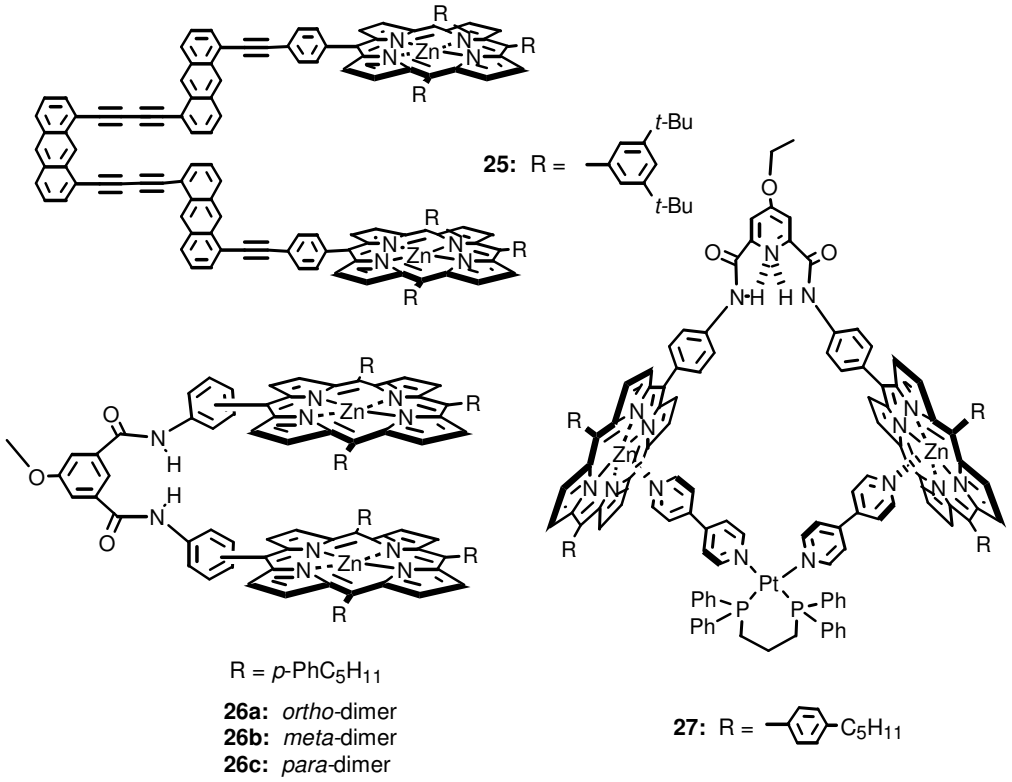


Figure 15. Flexible bisporphyrins that organize in cofacial geometry upon binding of a bidentate guest.

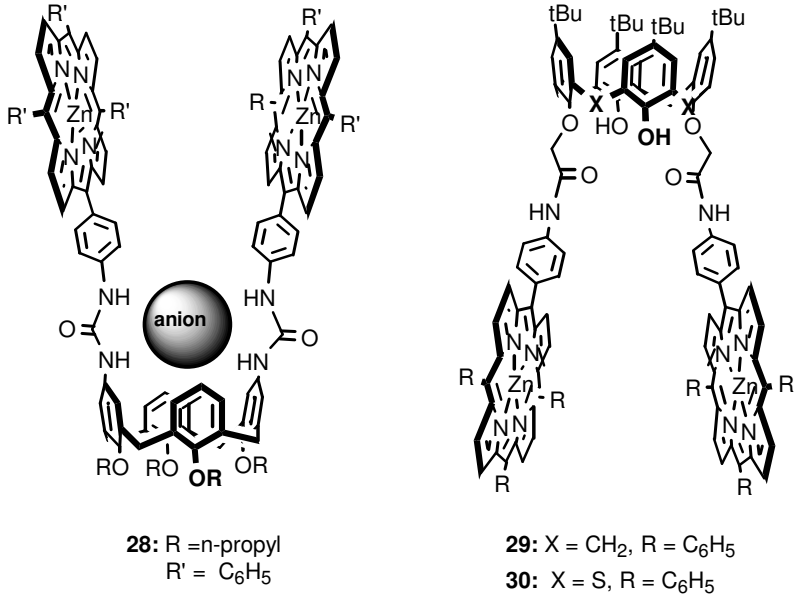


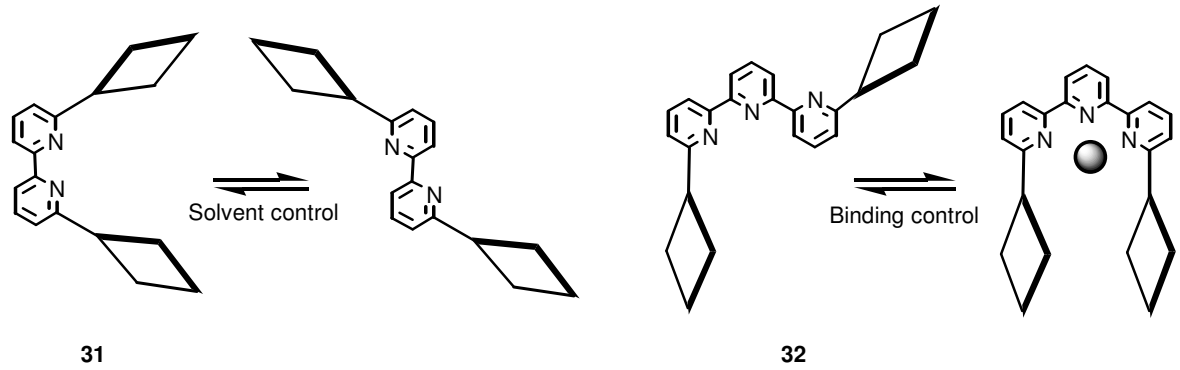
Figure 16. Highly flexible calixarene-porphyrin scaffolds.

Several bisporphyrin species in which the positioning of the two chromophores on the same side of the spacer is secured by the use of calix[4]arene spacers have been reported.[66–68] In scaffolds **28–30** represented in Figure 16, the cofacial arrangement is only obtained upon binding of a linear bidentate such as DABCO, pyrazine, or 4,4'-bipyridine, due to the flexibility of the bridge between the chromophore and the calixarene platform.

The choice of the rim of the calixarene (**29**) or thia-calixarene (**30**) spacer used has little influence on the weak preorganization, but will influence the selectivity of the geometric rearrangements upon substrate

binding in the case of anions,[66] cations[67] or bidentates.[64] Similar observations were reported by Ballester and Hunter in receptors for which the stoichiometry of the guest binding influences the size and shape of self-assembled cavities comprising more than one calixarene moiety.[69] To avoid the flexibility of amide, ester or ether linkages, direct attachment of the porphyrin framework to the wide rim of the calixarene platforms has led to more rigid species that will be examined in the last section of this chapter.

Other guests have been used to force the face-to-face arrangement of bisporphyrins for which coordination to the central core of the porphyrin is not required. For example, bipyridine[70] and terpyridine[71] platforms **31** and **32**, respectively, which exhibit conformational changes that can be controlled either by solvation or metal complexation, can be used as platforms for the preorganization of chromophores (Figure 17). In this case, the main advantage is that hetero-dimetallic porphyrins or non metallated species can be used to detect the guest binding *via* modification of their photophysical properties. This advantage also stands for guests bound by π-π stacking interactions between the flat surfaces of the two porphyrins.



31 **32**

Figure 17. Flexible bisporphyrins with solvent or cation binding control over the cofacial preorganization.

5.2. Flexible species with two links: cyclophanes

The introduction of a second link in the framework provides better control of the cofacial organization of the two tetrapyrrolic macrocycles. Of course, the overall flexibility of the linkers used will be responsible for defects in the cofacial arrangement, like in the original porphyrin-based macrocycles **34–38**[72,73] (Figure 18) that are far more flexible than the first bisporphyrin (**33**) described by Collman.[74] Again, in the species described by Sanders, cofacial geometry can be attained not only by DABCO binding between the two porphyrins and also by spontaneous π-π stacking interactions.[72,73]

In synthesizing flexible species, classical cyclization approaches are usually involved in the low yield preparation of the final macrocyclic species. However, an interesting approach was based on the initial formation of a rigidly bridged bisporphyrin of the butadiyne type (*e.g.* Figure 11), followed by the hydrogenation of the rigid linker in **39** into a floppy saturated alkyl chain in **40** (Figure 19).[75] In the flexible host **40**, high association constants (10^8 M^{-1}) were observed for the C_{60} guests,[75,76] especially when Rh porphyrins were used,[77] whereas the rigid analogs did not afford such stable host-guest complexes.[75]

5.3. Flexible preorganized cofacial arrangements

Among the preorganizing spacers used for controlling cofacial geometries, the diurea scaffold was employed very early, in the beginning of the 1980s, by Reed and coworkers in the preparation of bis-(iron tetraarylporphyrins) **41** as models for cytochrome c oxidase (Figure 20).[78] To fully preorganize the cofacial

arrangement of the two macrocycles in the final Pacman architecture, the group of Yagi more recently introduced two urea spacers instead of one in scaffold **42** (Figure 20).[79] In **42**, the subtle difference of affinity for guests bound *via* π-π interactions and *via* axial zinc binding resulted in the formation of host-guest photoswitches in which photoinduced electron transfer (PeT) was turned off in the presence of DABCO. The switching action is based on π-π interactions between the porphyrins (separated by 7 Å) and hexylviologen (HV), and on the receptors' affinity for DABCO. In the presence of HV, the fluorescence of the host is quenched by an electron transfer process (PeT on). Fluorescence can be turned on by adding DABCO, which forms more stable complexes, thus ejecting the HV.

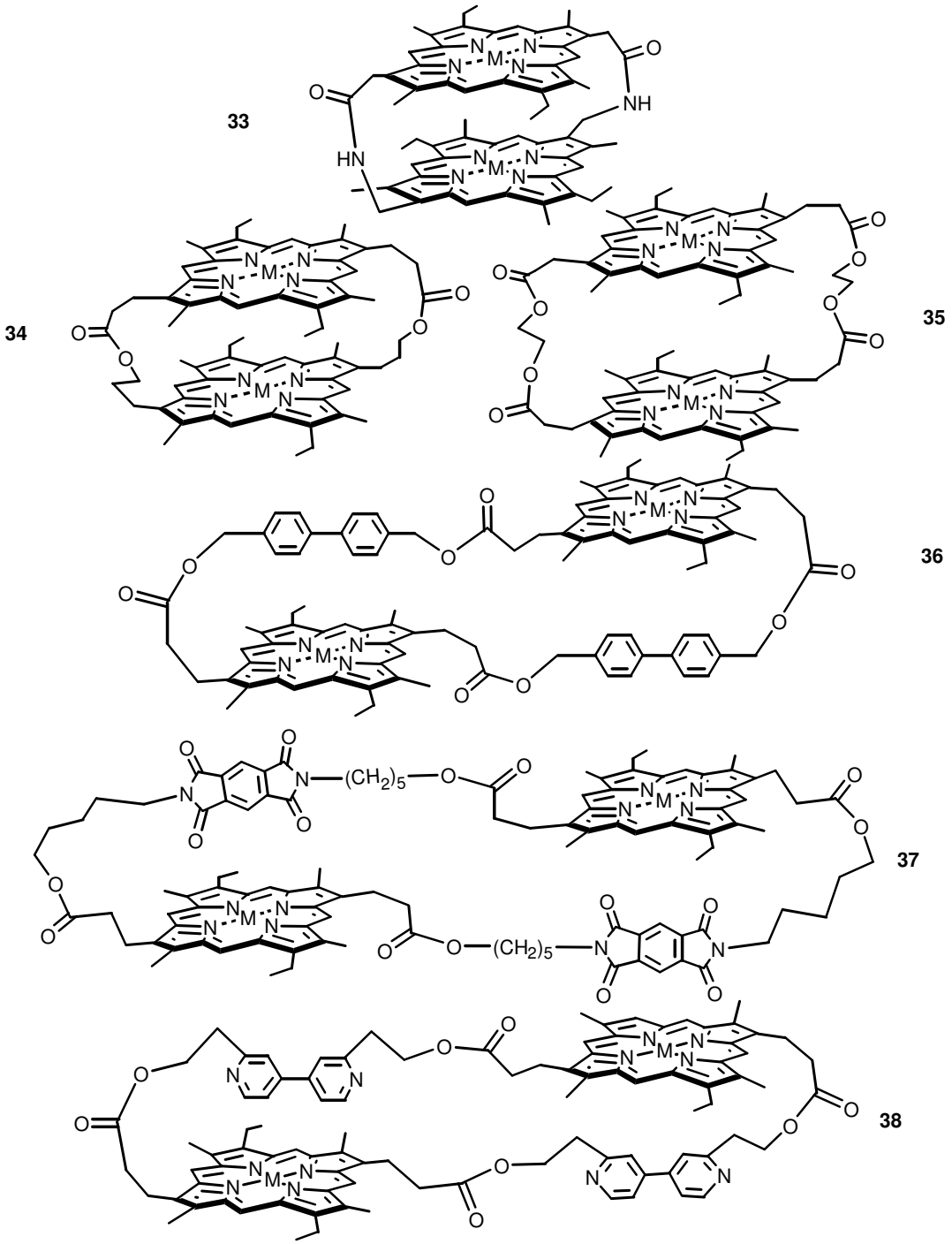


Figure 18. Flexible bisporphyrins.

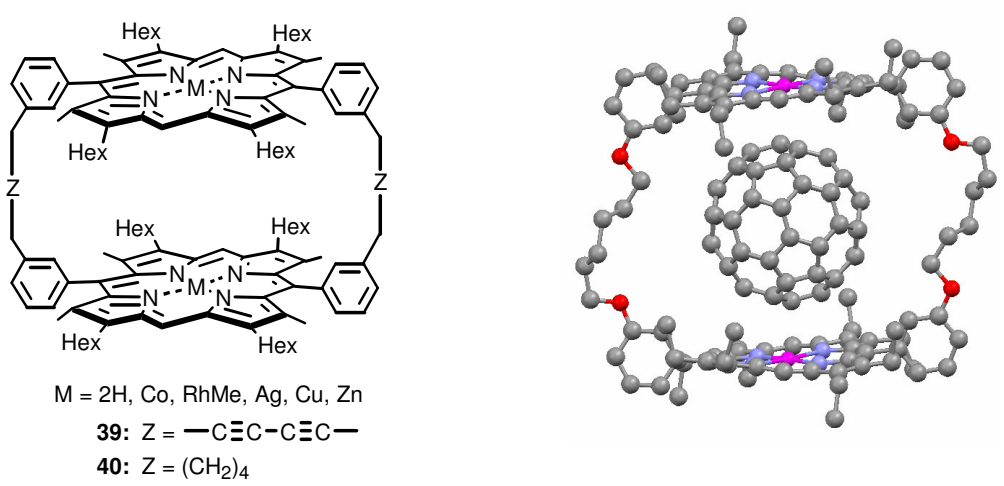


Figure 19. A flexible host and its C_{60} inclusion complex **40(C_{60})** in a bis-(zinc porphyrin) obtained from a rigid precursor. Representation of the solid state structure based on ref. 75 using Ortep-3 for Windows by: Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565.

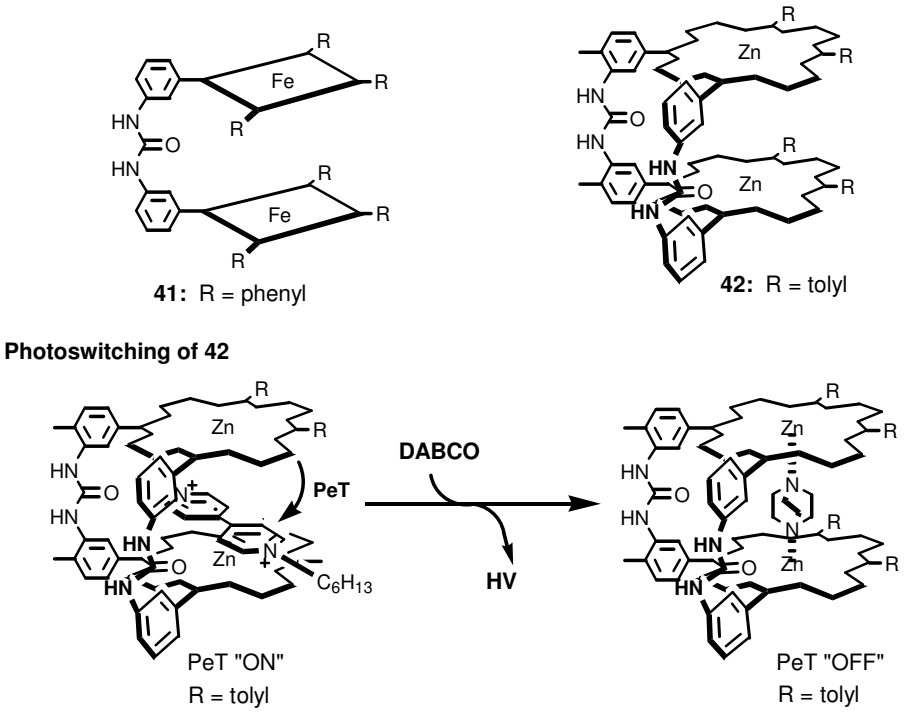


Figure 20. Pacman structures preorganized around urea linkers.

A recent evolution in the preorganization of cofacial bisporphyrins utilizes the formation of transition metal complexes as spacers. This approach is intermediate between dynamic self-assembled species organized by weak interactions (not reviewed in this chapter) and covalently assembled scaffolds. This strategy implies the functionalization of porphyrin monomers by side arms bearing binding sites for transition metals. These binding side arms may incorporate just one heteroatom, like species **43** and **44** described by Hupp[80] or chelating units **45–46** reported by Mirkin[81] (Figure 21).

The methodology developed by Mirkin has been identified as the weak link approach (WLA)[82] and is based on the use of hemilabile bond formation with the transition metal template. The WLA seems very general and has been applied to the formation of many square boxes with catalytic properties. Both

approaches have produced box-like cofacial porphyrins with interesting catalytic properties.[83] In the WLA, recent results demonstrate that chelation can be controlled by changing the nature of the heteroatom X.[84] Such changes introduce modularity to the approach.

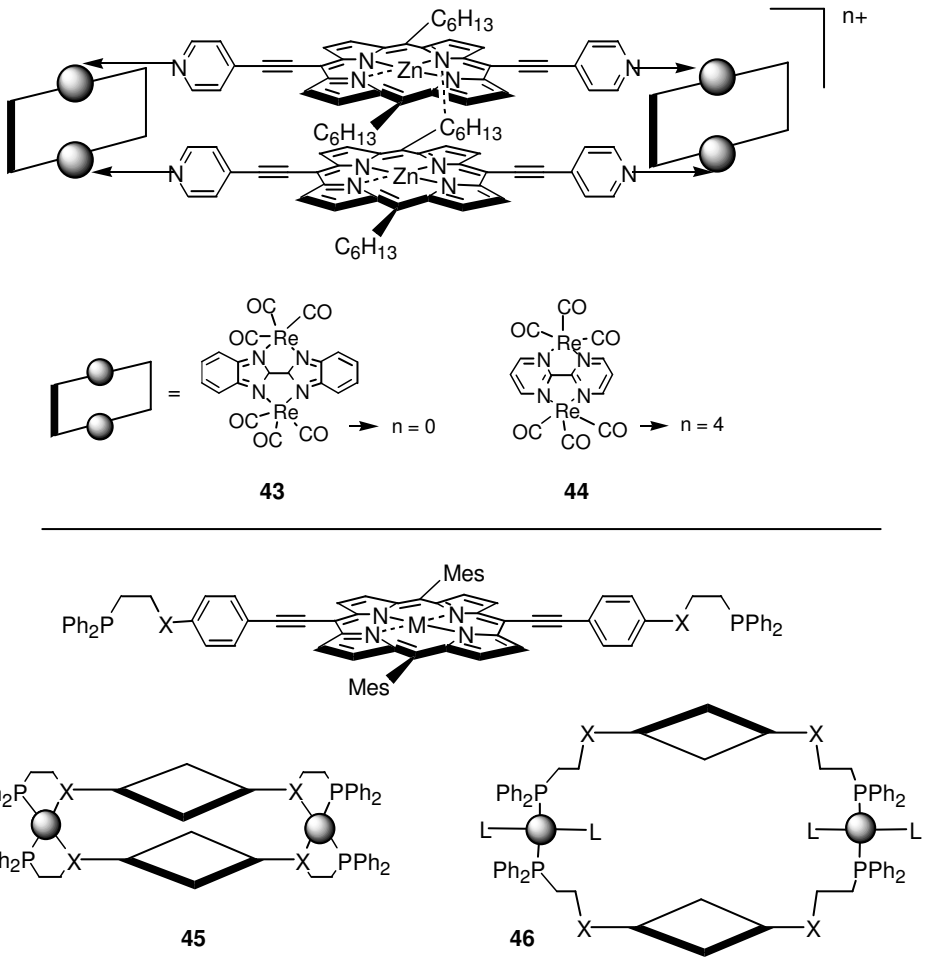


Figure 21. Cofacial bisporphyrins organized by transition metal templates.

As demonstrated for the receptors **28–30** in Figure 16, the presence of a flexible amide or ester bridge between the porphyrins and the calixarene renders the recognition properties less selective. Indeed, to utilize the conformational properties of the calixarene support, the motions and geometric changes in the calixarene moiety must be mechanically transmitted to the porphyrin macrocycle. The direct linkage of the porphyrin macrocycle was envisioned by the incorporation of one of the porphyrin's meso phenyl groups into the calixarene's structure. This approach led to the preparation of sterically constrained species that were highly preorganized in geometries which cannot be cofacial owing to the ca. 60° dihedral angle usually observed between the plane of the porphyrin macrocycle and any meso-aryl group.[85] This classical orientation can be observed by X-ray diffraction in the case of tetra-porphyrin calixarene assemblies reported by Smith. Even when steric compression is absent, the disruption of planarity between the calixarene platform and the porphyrin plane was observed. In Figure 22, the X-ray structure of the bisporphyrin **47** built on an oxa-calixarene platform reported by Vicente illustrates the impossibility of obtaining a face-to-face orientation in the scaffold.[86] The meso-phenyl/porphyrin dihedral angle also explains why dimer **48**, obtained according to the strategy depicted in Figure 4, affords a slipped conformation typical of J-aggregates.[87]

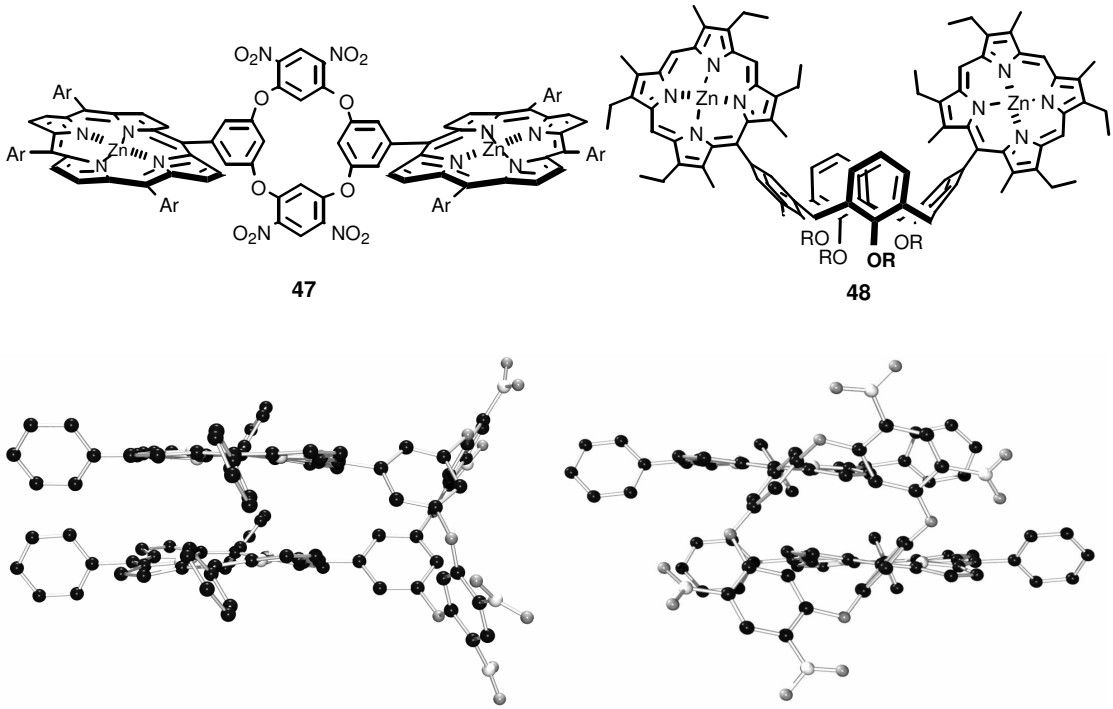


Figure 22. Direct connection of porphyrins on platforms of the calixarene type and impact of the aryl-porphyrin dihedral angle on the global geometry of the bisporphyrin scaffold. X-Ray representation of **47** from SI of ref. 86 using Ortep-3 for Windows.

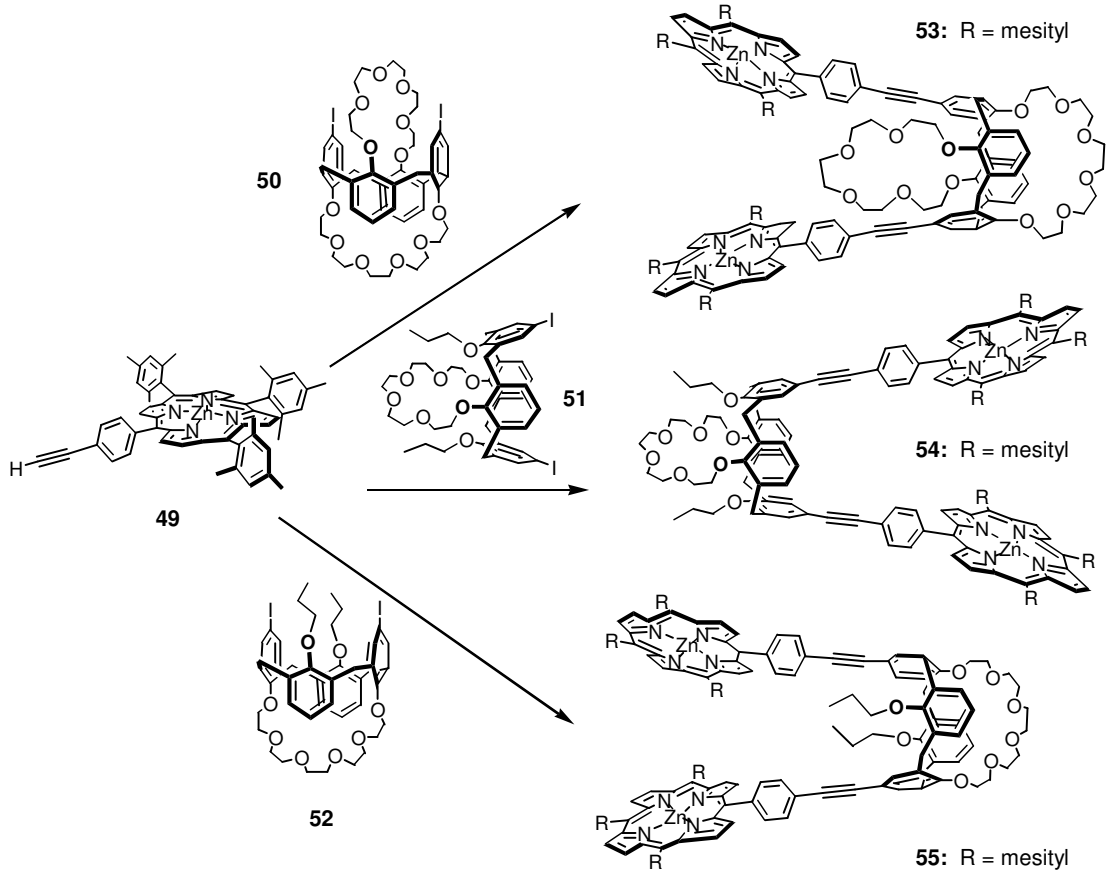


Figure 23. Versatile strategy for the preparation of calixarene supported bisporphyrin scaffolds.

This problem was anticipated during the design of the calixarene-based Pacman structures **53–55** (Figure 23) and an additional degree of freedom was introduced between the calixarene platform and each porphyrin. The synthetic strategy[88] used for the preparation of these Pacman type bisporphyrins is both simple and versatile and is based on the preparation of *p*-iodo calixarene derivatives **50–52**.[89] The acetylene derivative **49** of tetra-aryl porphyrin can be prepared by statistic methods from mixtures of aldehydes and pyrrole,[90] combined with Sonogashira coupling[91] of trimethylsilyl-protected acetylene. In this first family of Pacman receptors **53–55**, only weak interactions between the two porphyrin rings were observed.[92] Only the use of a calixarene in the cone conformation resulted in a large broadening of the Soret band concomitant to a small blue shift. The X-ray structure of the bis-crown derivative **53** in Figure 24 shows the large distance between the two chromophores (Zn-Zn ~ 20.5 Å). This distance explains the poor efficiency of through space inter-porphyrin communication. However, this large separation also demonstrates that the ethynyl link between the porphyrin macrocycle and the calixarene is efficient in decoupling the respective orientations of the meso-aryl porphyrin and the calixarene.

Thus, in this first series of hosts, the introduction of a guest was necessary to improve the communication between the chromophores.[88,92] Contrary to previously mentioned scaffolds, the binding of a guest does not imply major geometric rearrangements and thus is energetically almost costless, leading to high stability constants. In the most flexible cone conformation, electrochemically induced motions were observed in the presence of DABCO.

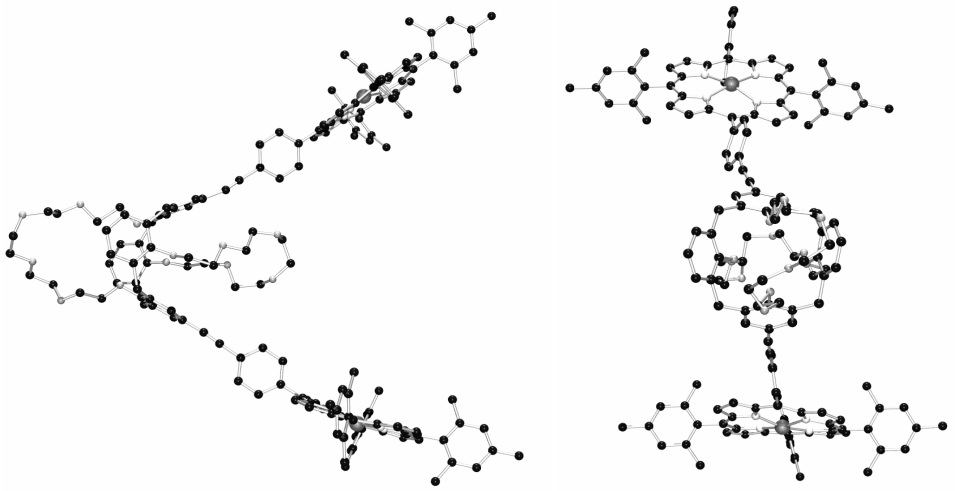
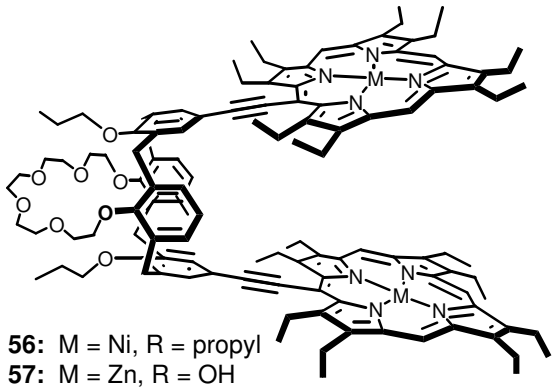


Figure 24. X-ray structure of the first calixarene based Pacman bisporphyrin **53**.

In the search for scaffolds offering maximum interactions between the two porphyrin chromophores, a new approach was designed in which the length of the connection between the wide rim of the calixarene and the porphyrin was reduced.[93] The option of removing the meso-aryl group on the porphyrin ring was chosen, especially when less hindered porphyrin cores could be used. Thus, the use of octa-β-ethyl porphyrins afforded more compact bisporphyrins, such as the bis-nickel derivative **56** represented in Figure 25. In the solid state, the distance between the mean planes of the porphyrin is now 3.6 Å and the shortest interatomic distance between the two rings is 3.27 Å.



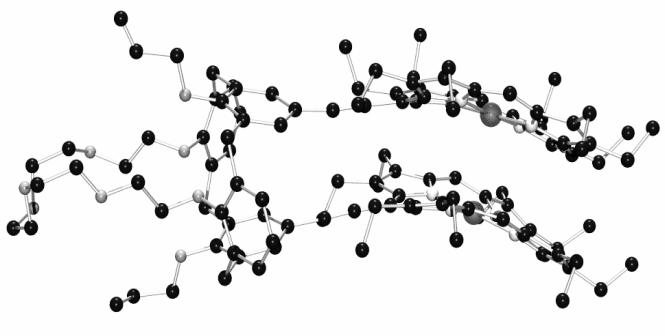


Figure 25. Representation and solid state structure of the first compact Pacman bisporphyrin.

In the compact scaffolds **56** and **58**, the huge broadening of the Soret band and the respective shielding of ^{1}H NMR signals corresponding to porphyrin protons confirms the close proximity of the two chromophores in solution. The strong interaction of the two macrocycles can now be observed by electrochemistry without the artificial connection by a guest substrate. The two nickel porphyrins cannot be oxidized simultaneously, but must be oxidized stepwise in clearly separated redox processes. Once the two di-radical cations are generated, the calixarene opens up under the electrostatic repulsion of the two positive charges, and the motion leads to an open state in which the two porphyrins behave independently, as depicted schematically in Figure 26.

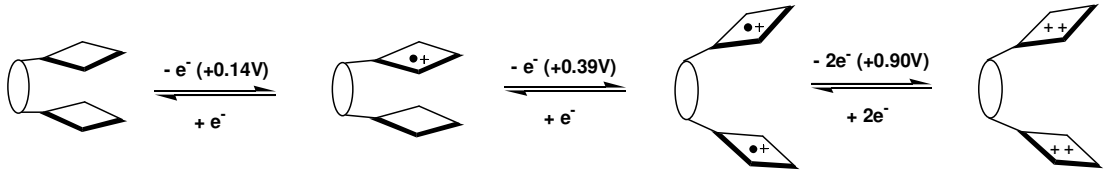


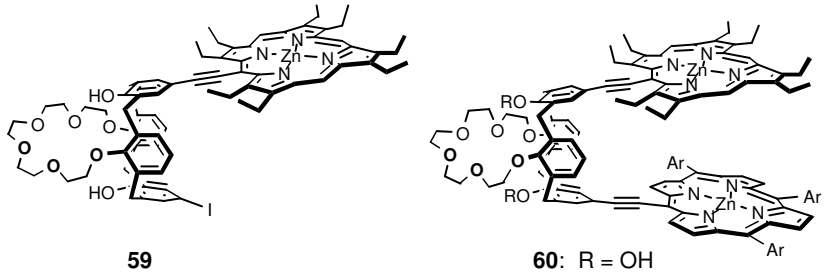
Figure 26. Electrochemically triggered opening and closing motion in compact Pacman bisporphyrin **56**.

After the validation of the calixarene Pacman concept, synthetic adjustments were necessary to generalize the approach to more versatile scaffolds. In particular, the preparation of hetero bisporphyrins was sought to provide access to photoinduced energy or electron transfer dyads. Differentiation of the porphyrins can occur as a function of the central metal, or as a function of the porphyrin's organic skeleton. Both approaches have been explored.

Due to the harsh conditions required for the removal of nickel compared to the mild conditions to remove zinc, the reported methodology for the preparation of 5-ethynyl nickel OEP was modified to obtain zinc derivatives.[94] 5-Ethynyl-ZnOEP can be used for coupling with diiodo calixarene intermediates using Sonogashira[91] or Negishi[95] conditions. Removal of zinc produces the corresponding free base into which other metal ions can be inserted.

Whereas Sonogashira coupling always afford bis-coupling products **57–58**, the use of equimolar amounts of 5-ethynyl ZnOEP and diiodo-calixarene yields rather selectively the monoporphyrin derivative **59** (Figure 27). This monoporphyrin derivative is an ideal starting material for the preparation of heteroporphyrin scaffolds **60–61** in which the porphyrin frameworks are different, such as the mixed OEP - triarylporphyrin in Figure 27. This non symmetrical derivative **61** allowed the observation of interporphyrin

interactions by 2D NMR and also photo-induced energy transfer from the octatalkyl donor to the triaryl acceptor.[96] Due to the different rates of metallation of meso-aryl and octaethyl porphyrins, this particular compound can be considered to be a good precursor for a large variety of hetero bisporphyrins of the Pacman type.



59 **60**: R = OH
61: R = propyl

Figure 27. A monoporphyrin calixarirene serves as a starting point for hetero bisporphyrin Pacman.

6. Conclusion

During the past 30 years, the focus of interest for cofacial arrangements in bisporphyrin systems has slowly shifted from modeling the special pair with rigid species towards catalysis and recognition properties requiring cooperation between two metals. Along the way, the development of flexible species that still offer the face-to-face preorganization has emerged as an attractive option, for which innovative design needed to be validated. The use of a calixarene platform with a rigid, linear link between its wide rim and the porphyrin macrocycles offers the opportunity for an efficient chromophore/spacer mechanical communication. The design opens the access to new molecular switches or new sensors upon proper functionalization of the calixarene, and can be conceptually extended to platforms other than calixarenes[97] and other electro- or photoactive species.[98–100]

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PYRAZOLOPYRIMIDINES: OLD MOLECULES, NEW TARGETS

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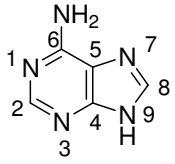
Abstract. *The synthetic strategies so far developed to build the pyrazolo[3,4-d]pyrimidine ring system and to generate highly functionalized analogues, with a particular emphasis on the 4-amino derivatives, has been reviewed. The evolution of this versatile scaffold, starting from the pioneering work of Robins up to the recent preparation of selective inhibitors (active against EGFR, Src, adenosine receptor etc.) has been discussed in terms of synthetic methodologies applied to the generation of more selective inhibitors. Being the literature on pyrazolo[3,4-d]pyrimidines particularly rich, the focus of this review deals with the construction of this ring system from pyrazoles only.*

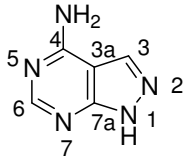
Contents

1. Introduction

The 4-aminosubstituted pyrazolo[3,4-*d*]pyrimidine ring represents a very interesting scaffold for the synthesis of molecules potentially endowed with different biological activities. This structure is in fact isoster with that of the purine derivative adenine (Figure 1), present in ATP that is fundamental for every aspect of cell life, and as constituent of DNA and RNA.



Adenine
(9*H*-purin-6-amine)

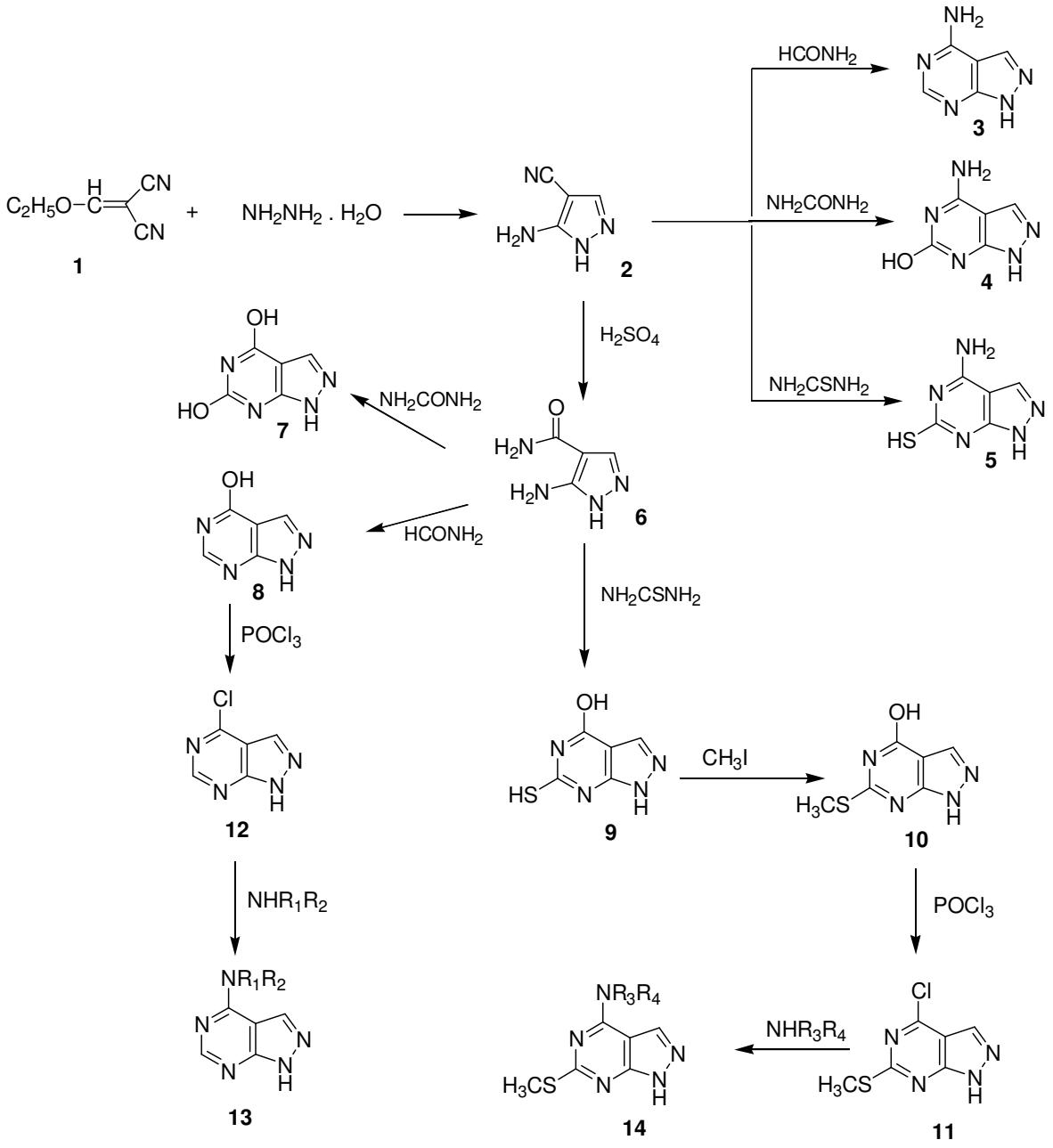


1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

Figure 1

The chemical synthesis of these molecules can be performed starting from both the pyrimidine and the pyrazole nucleus. In this article, the second type of synthetic approach will be reviewed, being also the most used for the preparation of the many biologically active analogues recently appeared in the scientific literature. The attention of this review has been focused on the non-nucleoside analogues of the pyrazolopyrimidines since the corresponding nucleoside derivatives, bearing a sugar moiety on the N1 atom, have been the subject of many reviews and articles.[1–3]

Among the many pyrazolo[3,4-*d*]pyrimidine derivatives present in literature, attention has been focused on the 4-amino analogues due to the great interest of medicinal chemists on this class of compounds.



R_1 = H, CH_3, C_2H_5
R_2 = CH_3, C_2H_5, *n*-C_4H_9, $CH(CH_3)_2$, C_6H_5, $CH_2C_6H_5$

R_3 = H, CH_3
R_4 = H, CH_3, C_2H_5, NH_2, $(CH_2)_2NEt_2$

Scheme 1

2. Preparation of pyrazolo[3,4-*d*]pyrimidines

In the mid 50ths, Ronald Robins reported the synthesis of differently substituted pyrazolo[3,4-*d*]pyrimidine systems and started the study of their biological activity, in particular, as anti-tumor agents.

In fact, the synthesis of this ring system was undertaken to provide new compounds isomeric with various biologically active purines in the hope to discover new purine antagonists endowed with anti-cancer activity. Reaction of (ethoxymethylene)malononitrile **1** and hydrazine monohydrate in refluxing ethanol gave the 5-amino-1*H*-pyrazole-4-carbonitrile **2**, that was in turn treated with formamide, urea and thiourea to obtain the adenine isoster 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine **3** (called 4-APP), the 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ol **4** and the 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-thiol **5**, respectively (Scheme 1). $POCl_3$ chlorination of **8** and **10** gave **11** and **12**, respectively, which were finally transformed into the 4-aminosubstituted derivatives **13** and **14**, by nucleophylic displacement of the chlorine atom with primary or secondary amines in refluxing alcoholic or benzene solution (Scheme 1).[4]

The antiproliferative activity exerted by **3** and its N1 methyl derivative[5] on adenocarcinoma and leukemia cell lines (as well as on other culture tissues)[6] prompted Robins and Cheng to synthesize and investigate a wide family of analogues (generic structure **15**, Figure 2) bearing different N1 substituents, and a variety of amino group on C4. Compounds **15** have been obtained from the corresponding 1-alkyl or 1-aryl-5-amino-4-cyanopyrazole, in turn synthesized by reaction of (ethoxymethylene)malononitrile **1** with the appropriate alkyl or aryl hydrazine, following the synthetic approach previously shown for the synthesis of **13**.[7]

To obtain the C4 *N*-substituted or *N,N*-disubstituted amino derivatives, the pyrazolecarbonitrile **2** was hydrolized with concentrated sulphuric acid to the corresponding amide **6**, in turn treated with urea, formamide and thiourea to give the corresponding 4-hydroxy derivatives **7**, **8** and **9**. Reaction of the latter compound with methyl iodide led to the 6-methylthio derivative **10**.

15

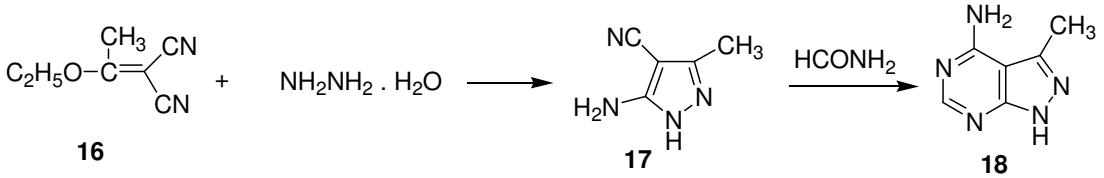
R_1 = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9

R_2 = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, $CH(CH_3)_2$, C_6H_5, *o*Cl-C_6H_4, *o*Me-C_6H_4, *m*Cl-C_6H_4,

R_3 = CH_3, C_6H_5, *p*Cl-C_6H_4, p*B*r-C_6H_4, *pN*O_2-C_6H_4, CH_2CH_2OH

Figure 2

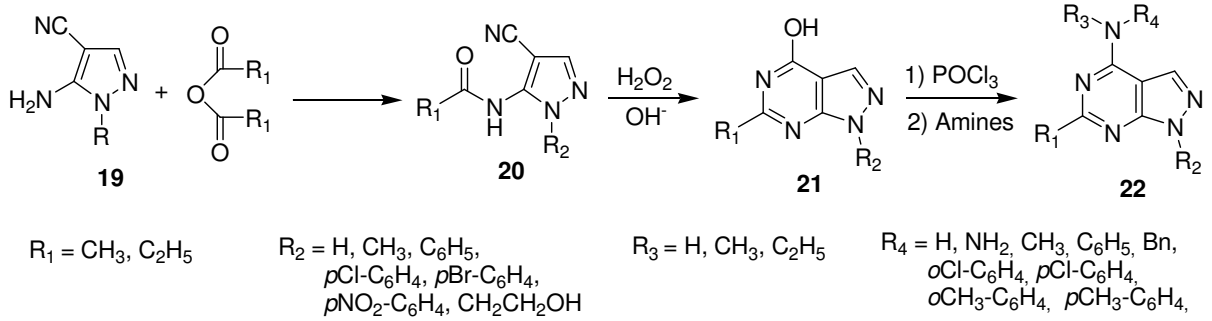
In the same article, the Authors also reported the synthesis of 3-methyl-4-aminopyrazolo [3,4-*d*]pyrimidine **18**, by reaction of methylethoxymethylene malononitrile **16** and hydrazine monohydrate, followed by treatment of the corresponding cyanopyrazole **17** with boiling formamide in high yield (Scheme 2).



16 **17** **18**

Scheme 2

Successively, a series of 4-amino-6-alkylsubstituted (in particular 6-methyl or 6-ethyl) pyrazolo[3,4-*d*]pyrimidines (generic structure **22**, Scheme 3) have been synthesized by the same Authors.[8] The 5-amino-4-cyanopyrazoles **19** were acylated either by acetic or propionic anhydride to give the corresponding 5-acylamino-4-cyanopyrazoles **20**, which were then treated with an alkaline solution of hydrogen peroxide, following a procedure already reported for the synthesis of hydroxyquinazolines,[9] to give the 6-alkyl-4-hydroxypyrazolopyrimidines **21**. Finally, C4 chlorination of **21** with phosphorus oxychloride and subsequent nucleophilic displacement with primary and secondary amines gave the desired compounds **22** (Scheme 3).

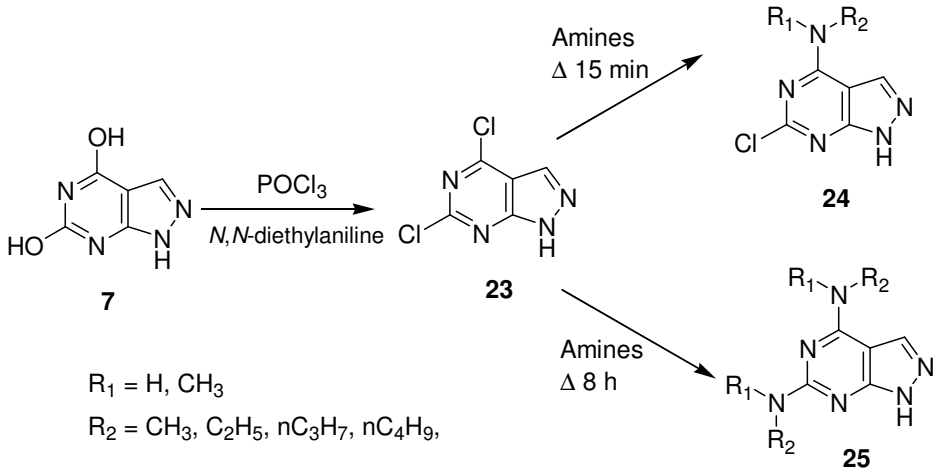


Scheme 3

Subsequent biological studies on 4-aminopyrazolo[3,4-*d*]pyrimidines showed that these new compounds possessed inhibitory activity toward *Neurospora Crassa*, an ascomycete, used at that time for genetic studies and for investigation of enzymes and precursors involved in the metabolism of purines and pyrimidines.[10] Moreover, some derivatives demonstrated to be inhibitors of xanthine oxidase[11] and it was also postulated that the antitumor activity of previously reported pyrazolopyrimidine derivatives could be connected with this enzymatic inhibition. A parallel study reported that a number of 4-aminopyrazolo[3,4-*d*]pyrimidines possessed the ability to inhibit the growth of adenocarcinoma and leukemia cells in mice,[12] confirming the previously observed anti-tumor activity of this family of compounds.

Pushed by the interesting biological data shown, chemical studies on the synthesis of new differently substituted 4-aminopyrazolo[3,4-*d*]pyrimidine derivatives started in the late 50ies.

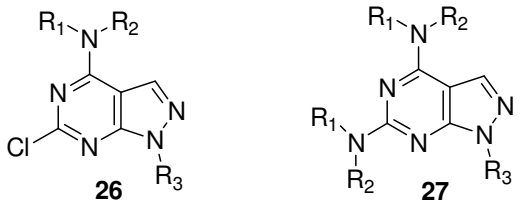
Chlorination of **7**, unsuccessful with a number of chlorinating agents, was finally performed with $POCl_3$ and *N*,*N*-diethylaniline, affording the 4,6-dichloropyrazolo[3,4-*d*]pyrimidine **23** in good yield (Scheme 4).



Scheme 4

The selective replacement of the chlorine atoms with amines under carefully controlled conditions gave a variety of 4-amino- and 4,6-diaminosubstituted derivatives. Generally, treatment of **23** with aqueous or ethanolic solutions of primary or secondary amines by steam bath heating for 10 to 30 min afforded the corresponding 4-amino-6-chloro derivatives **24**, while longer reaction times in the presence of a large excess of amines usually led to the disubstituted derivatives **25**.[13]

Analogously 1-alkyl or 1-aryl-4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines **26** and **27** have been synthesized by the same Authors (Figure 3).[14]

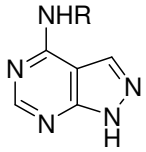


26 **27**

R_1 = H, CH_3, C_2H_5
R_2 = NH_2, CH_3, C_6H_5, $NHCH_3$, NHC_6H_5
R_3 = CH_3, C_6H_5, *p*Cl-C_6H_4

Figure 3

In ten years, Robins and colleagues prepared a large (for that time) library comprising approximately 1300 compounds, especially purines and pyrazolopyrimidines, that have also been tested against different induced rodent tumors. In particular, adenocarcinoma 755 appeared particularly useful for SAR studies of 4-aminosubstituted pyrazolo[3,4-*d*]pyrimidines, reported in detail by the Authors. Interestingly some derivatives exhibited also significant inhibition of Leukemia 5178 and myeloblastic leukemia cell growth, and were active against mammary adenocarcinoma and the Ehrlich ascites carcinoma.[15] Twenty years later, Chheda and colleagues found that some 4-aminosubstituted derivatives (general structure **28**, Figure 4) prepared following the Robins's synthetic approach, possessed a very good activity against cultured L1210 leukemia and 6410 human leukemic myeloblasts,[16] confirming the previously reported data.

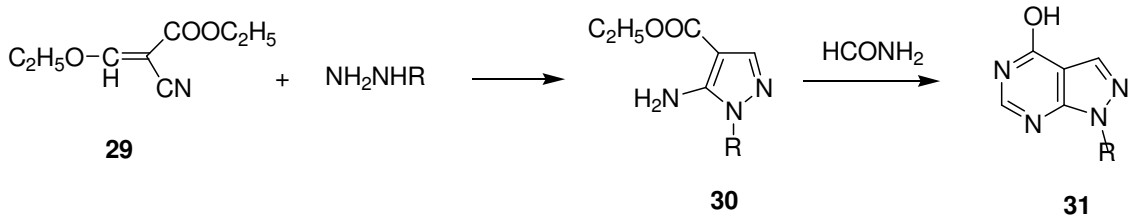


28

R = $CH_2CH{=}CH_2$, $CH_2CH_2CH(CH_3)_2$, $CH_2C_6H_5$

Figure 4

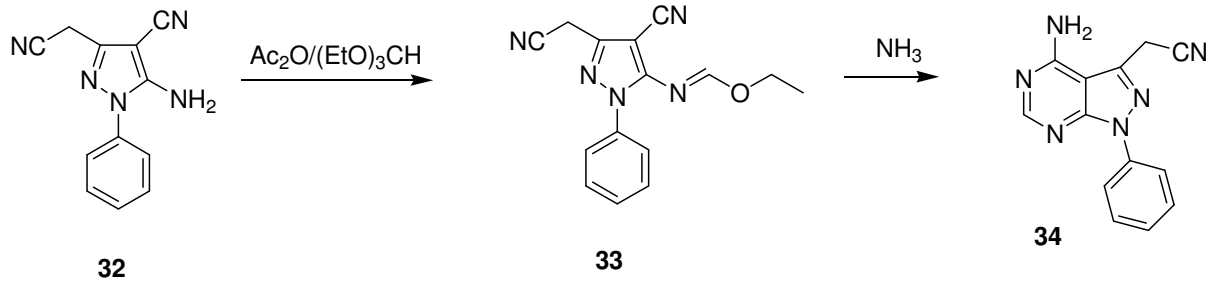
Following a similar synthetic approach, Schmidt and Druey reported in 1956 the synthesis of several pyrazolo[3,4-*d*]pyrimidines, starting from 3-aminopyrazole-4-carboxylates **30**, in turn obtained from ethyl(ethoxymethylene)cyanoacetate **29** and the appropriate hydrazine. The 4-hydroxy derivatives **31** (the N1-substituted analogue of **8**) was then directly obtained by reacting compound **30** with formamide (Scheme 5). The replacement of the C4 cyano group with an ester moiety within the pyrazole structure allowed to avoid the sometimes tricky hydrolysis step;[17] this one step shortening is particularly useful when a NH_2 in C4 is not needed.



29 **30** **31**

Scheme 5

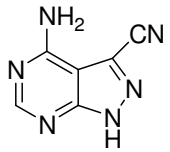
Taylor and colleagues prepared a number of new aminopyrazolo[3,4-*d*]pyrimidines, starting from 5-amino-3-(cyanomethyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile **32**, in turn obtained by reaction of malononitrile or malononitrile dimer with phenylhydrazine. As an example, compound **34** was obtained by reacting **32** with acetic anhydride and ethyl orthoformate leading to the intermediate **33**, which was finally cyclized with ammonia (Scheme 6).[18,19]



32 **33** **34**

Scheme 6

Using a similar procedure, the synthesis of the 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine **35** was also subsequently performed (Figure 5).[20]



35

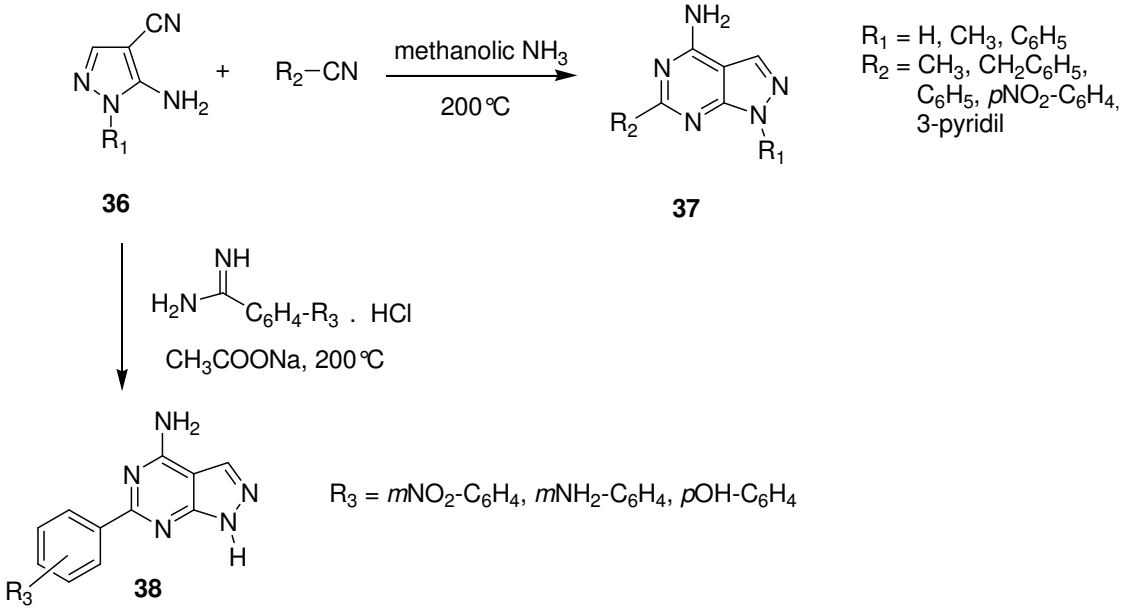
Figure 5

The same research group, during a study on the base-catalyzed condensation of aromatic and heterocyclic *o*-aminonitriles with nitriles, synthesized a series of 4-aminopyrazolo[3,4-*d*]pyrimidines **37** bearing a substituent at C6. Starting from the 3-amino-4-cyano-pyrazoles **36**, reaction with different nitriles in methanolic ammonia at 200 °C for 20 hours, in a steel hydrogenation bomb gave the desired C6-substituted analogues (Scheme 7).[21]

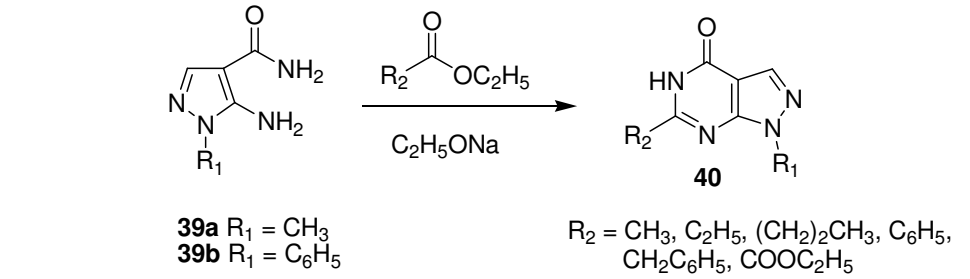
Successively, Baker and Kozma synthesized similar derivatives (generic structure **38**, Scheme 7) by reaction of **36** heated at 200 °C with substituted benzamidine hydrochlorides and sodium acetate, without solvent.[22]

An alternative methodology to obtain 6-alkyl- or 6-arylsubstituted derivatives (generic structure **40**, Scheme 8) was represented by the easy reaction of the 1-phenyl- or 1-methyl-1*H*-pyrazole-4-carboxamides **39a** and **39b** with different esters in the presence of sodium ethoxyde in ethanol. The resulting derivatives **40**

could in turn be chlorinated with $POCl_3$ and reacted with amines, as previously reported, to give the 4-amino derivatives.[23]

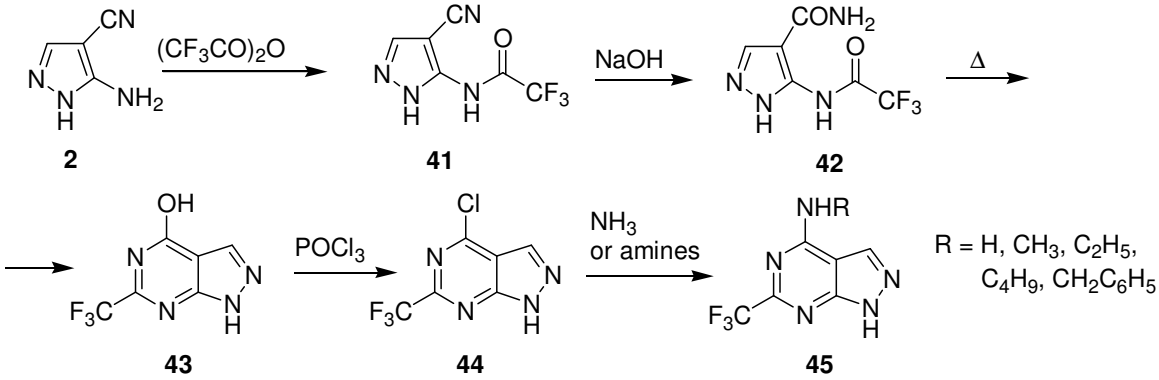


Scheme 7



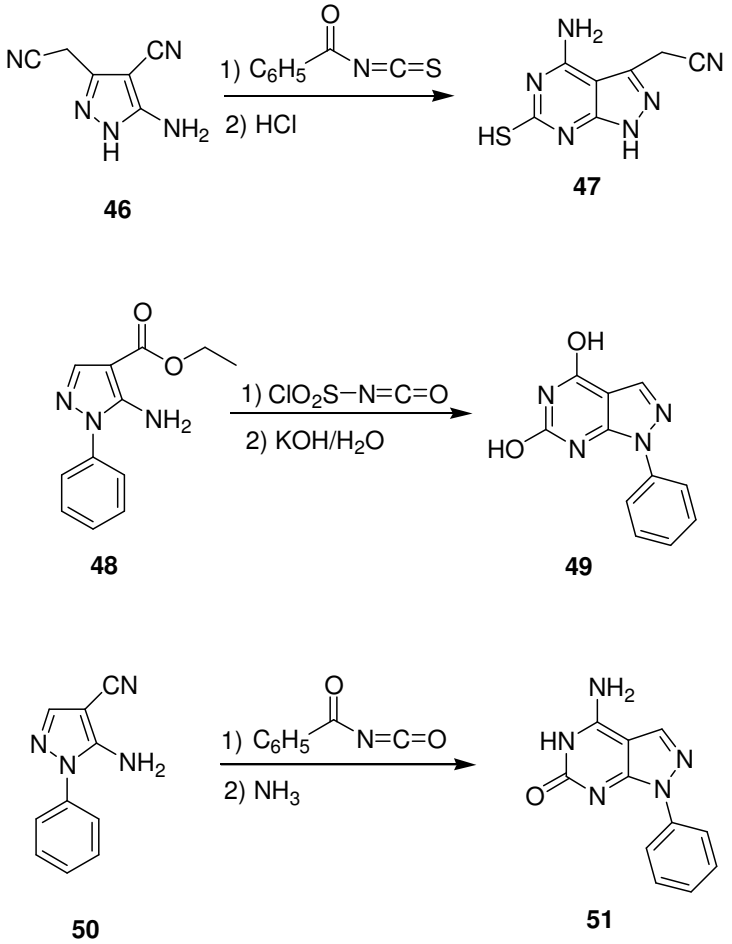
Scheme 8

Interestingly, 6-trifluoromethyl derivatives **45** were synthesized by other Authors using a similar procedure. The Robins' cyanopyrazole **2** was reacted with trifluoroacetic anhydride, to give the intermediate **41**, which was hydrolyzed to the corresponding amide **42**. The latter compound was cyclized by heating at 200 °C to give the pyrazolopyrimidine **43** which was first chlorinated and finally submitted to nucleophilic substitution with different amines (Scheme 9).[24]



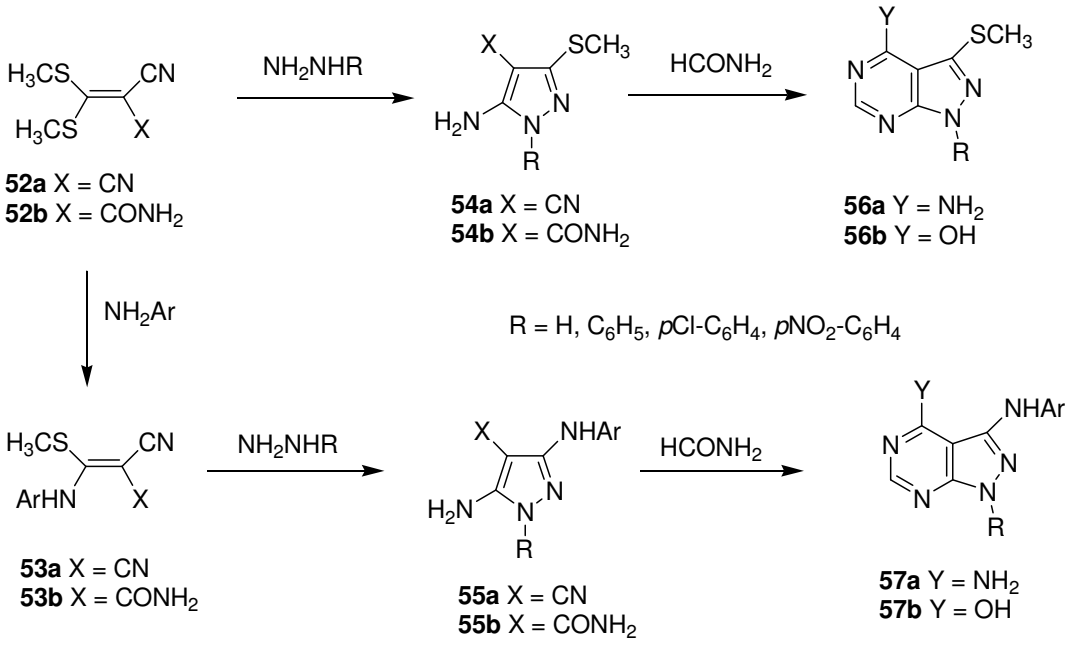
Scheme 9

The pyrazolo[3,4-*d*]pyrimidine ring can also be constructed by reaction of pyrazole derivatives with isocyanates or isothiocyanates, that react in a similar way as other cyclic enaminonitriles and *o*-amino-nitriles.[25] The 4-amino-6-thiopyrazolopyrimidine **47** has been synthesized by reacting the pyrazole **46** with benzoyl isothiocyanate, followed by acidification (Scheme 10).[26] Reaction of ethyl 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylate **48** with chlorosulphonyl isocyanate and following treatment with aqueous KOH, afforded derivative **49**,[27] already prepared in different ways by other Authors (Scheme 10).[14,17] 4-Amino-1-phenyl-5*H*-pyrazolo[3,4-*d*]pyrimidin-6-one **51** (the N1-substituted analogue of **4**) has been synthesized by Quinn and colleagues in a one pot reaction involving the condensation of 5-amino-1-phenylpyrazole-4-carbonitrile **50** with benzoyl isocyanate followed by annulation with ammonia, in 68% yield (Scheme 10).[28]



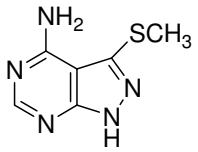
Scheme 10

Tominaga and colleagues synthesized a variety of pyrazolo[3,4-*d*]pyrimidines starting from ketene dithioacetals, in particular from bis(methylthio)methylene malononitrile **52a** and bis(methylthio)methylene cyanoacetamide **52b** or from anilino(methylthio)methylene malononitriles **53a** and the corresponding amides **53b**. The last two were prepared reacting **52a** and **52b** with the suitable arylamines. Reaction of **52–53a,b** with substituted hydrazines at 100 °C for 3–4 h gave the corresponding 5-aminopyrazoles **54–55a,b** that were in turn treated with formamide at 180 °C for two hours leading to the corresponding pyrazolo[3,4-*d*]pyrimidine-3-substituted derivatives **56–57a,b**. Starting from 3-cyanopyrazoles, the 4-aminopyrazolo-pyrimidines were obtained, while the 4-hydroxypyrazolopyrimidines were obtained starting from pyrazole-3-carboxamide derivatives (Scheme 11).[29]



Scheme 11

Notably Gompper had previously reported the synthesis of the 4-amino-3-methylthiopyrazolo[3,4-*d*]pyrimidine **58** (Figure 6) by the condensation of 5-amino-3-(methylthio)-1*H*-pyrazole-4-carbonitrile with ortho-formate, followed by cyclization with ammonia.[30]



58

Figure 6

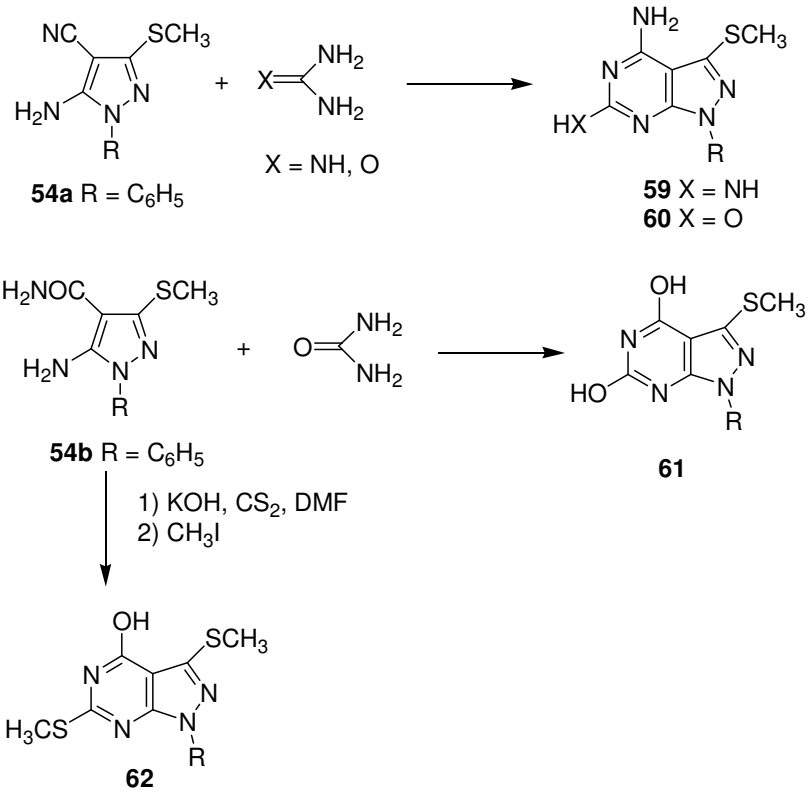
Tominaga in the same article reported also the synthesis of other substituted derivatives, starting from the cyanopyrazole of the **54a** series bearing a N1 phenyl substituent. Reacting **54a** with guanidine carbonate or with urea, the N1 phenyl pyrazolopyrimidines **59** and **60** were respectively prepared. Similarly, starting from the pyrazolocarboxamide of the **54b** series, the 2,4-dihydroxy derivatives **61** were synthesized, in more than 90% yield.

Moreover the reaction of *o*-aminocarboxamides **54b** with carbon disulfide in presence of potassium hydroxide, already reported for the preparation of different heterocycles,[31] gave derivatives **62** in reasonable yield (Scheme 12).[29]

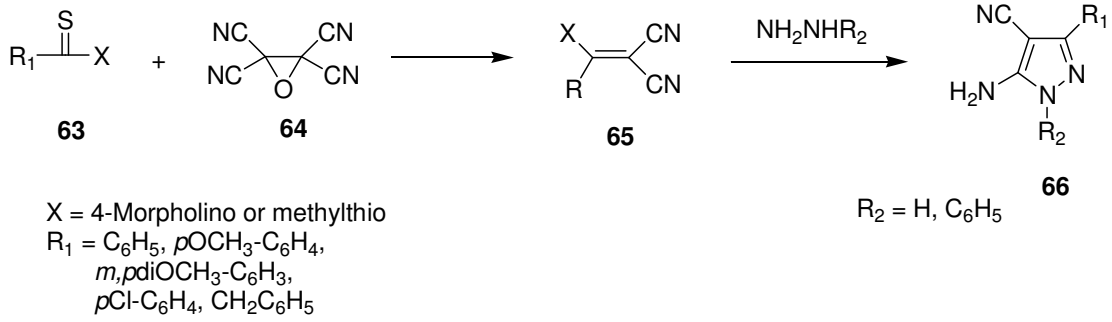
Treatment of the 4-hydroxy derivatives above reported with phosphorous oxychloride gave access to the 4-chloropyrazolo[3,4-*d*]pyrimidines which represent the key intermediates for the synthesis of the 4-aminosubstituted derivatives.

In a different article from the same Authors, the synthesis of different polarized ethylenes and their application to the preparation of pyrazolo[3,4-*d*]pyrimidines has been reported.[32] As an example, reaction of **63** with tetracyanoethylene oxide **64** at room temperature in benzene gave the corresponding dicyanoethylene compounds **65**, which was in turn reacted with hydrazine or phenyl hydrazine to obtain the

5-aminopyrazoles-4-carbonitriles **66** (Scheme 13). The latter compound was then cyclized with formamide to give the pyrazolo[3,4-*d*]pyrimidine ring, following the previously described procedure.

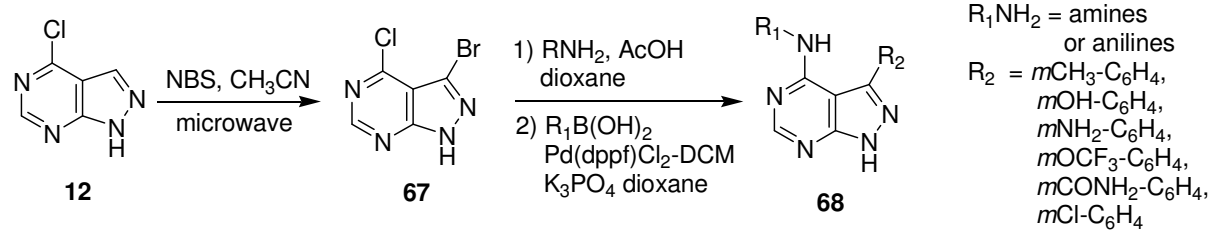


Scheme 12



Scheme 13

A different approach to obtain C3 substituted pyrazolo[3,4-*d*]pyrimidines has been recently reported by Schultz and Ding starting from the 3-bromo derivative **67**, in turn obtained from the Robin's derivative **12** by treatment with *N*-bromosuccinimide in acetonitrile at 100 °C under microwave irradiation. The application of microwave irradiation led to high yields (more than 95%), low side products formation and shorter reaction time. Compound **67** was reacted in a one pot two step process that involves a sequential S_NAr displacement of the C4 chloro substituent with different amines in mild acidic condition (acetic acid), followed by a Suzuki coupling reaction with different boronic acids, that afforded the C3 substituted derivatives **68** (Scheme 14). Interestingly, the mild conditions of this reaction allowed the tolerance of relatively reactive functional groups, such as amine, amide, alcohol, that should have been protected under the strong acid or basic conditions used by the previously reported procedures.[33]

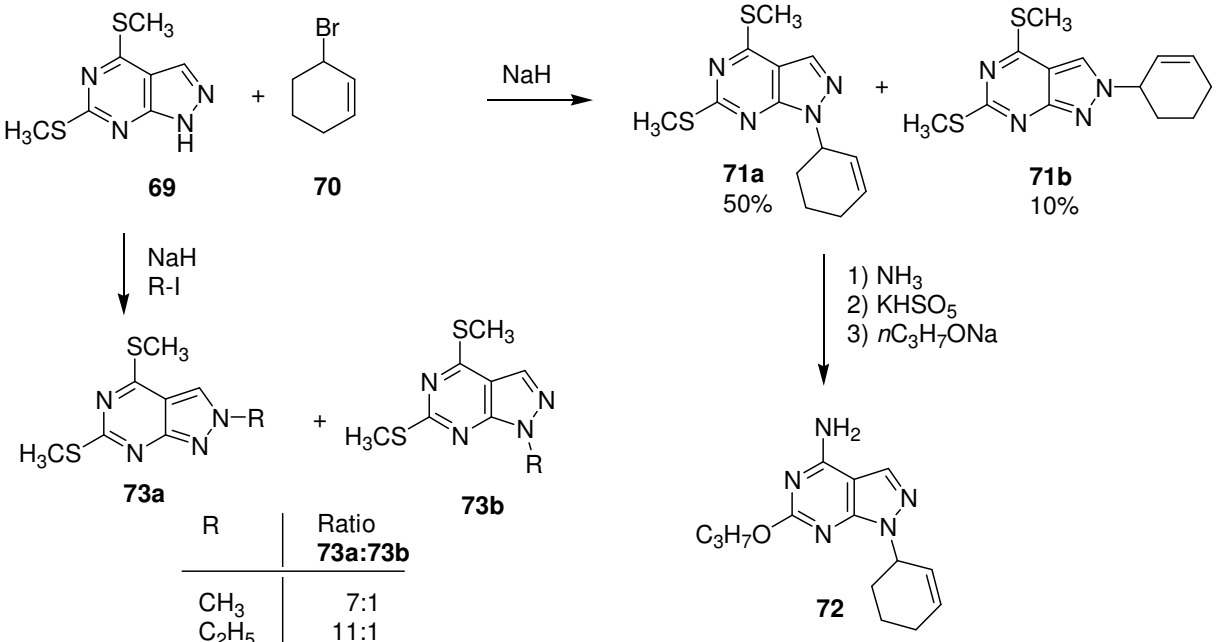


Scheme 14

Recently, other Authors reported the synthesis of pyrazolo[3,4-*d*]pyrimidines (already prepared by Robins) using Keggins heteropolyacids, such as phosphotungstic acid ($H_3PW_{12}O_{40}$) or molybdophosphoric acid ($H_3PMo_{12}O_{40}$) under classical heating and microwave irradiation, starting from the usual 5-amino-4-cyanopyrazoles and formamide.[34]

3. Selective N1-substitution of pyrazolo[3,4-*d*]pyrimidines

Even if most of the procedures leading to N1 substituted derivatives start from the corresponding substituted hydrazines, the direct N1 substitution of the pyrazolo[3,4-*d*]pyrimidine ring is sometimes possible, especially for short chain alkylation. Usually, a concurrent N2 substitution occurs but, in particular reaction conditions, the N1 substitution product predominates and can be isolated *via* standard cromatographic procedures. The N1/N2 substitution ratio usually depends on the base used to form the salt and is also related to the halide used in the nucleophilic substitution. Being this topic a very wide field of research, only a few significant examples will be herein reported.



R	Ratio **73a:73b**
CH_3	7:1
C_2H_5	11:1
C_3H_7	16:1
C_5H_{11}	20:1
CH_2Ph	14:1

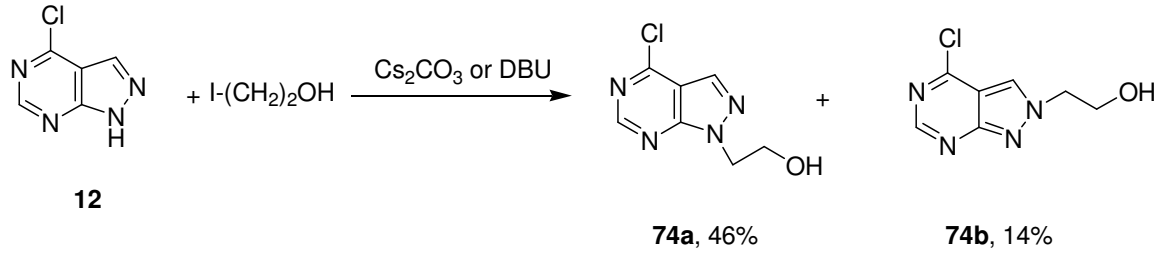
Scheme 15

Bhakuni and colleagues synthesized a number of pyrazolo[3,4-*d*]pyrimidines, such as **71**, starting from the Taylor's pyrazolopyrimidinethiones **69**,[35] by treatment with sodium hydride and 3-bromo-1-cyclohexene

70. The reaction led to the N1 and N2 substituted product **71a** and **71b** in 50 and 10% yield, respectively. Compound **71a**, purified on a silica gel column, was successively treated with ammonia, $KHSO_5$ and sodium propoxide to give the desired compound **72** (Scheme 15).[36]

Reacting **69** with different alkyl iodide in the presence of sodium hydride, the N2 substituted derivatives **73a** were obtained as major products, giving in this case an example of regioselective N2-alkylation (Scheme 15).[37]

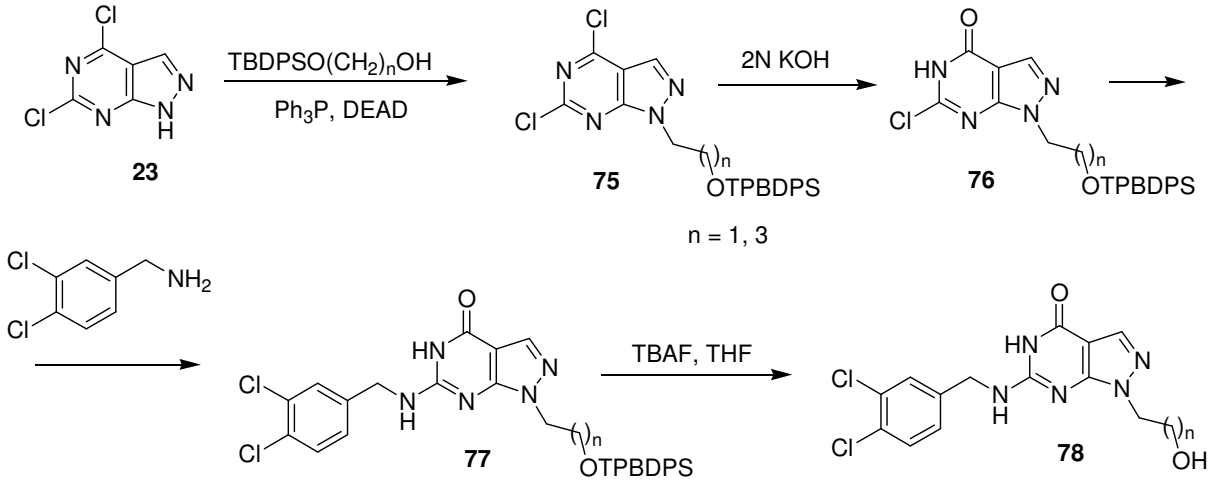
Zacharie and coworkers reported the alkylation of **12** with 2-iodoethanol (and protected or similar derivatives) in the presence of cesium carbonate or DBU in dry DMF at 0 °C leading to the N1 isomer **74a** in about 50% yield and N2 isomer **74b** in 15–20% yield. The same reaction, performed with the sodium salt of **12** (prepared with sodium hydride) and using the same alkylating agent in acetonitrile, gave only traces of the N1 isomer (Scheme 16).[38]



12 **74a**, 46% **74b**, 14%

Scheme 16

An interesting example of N1 substituted pyrazolopyrimidines was reported by Merck researchers, in the synthesis of the *N*-hydroxyalkylsubstituted derivatives **78**, endowed with inhibitory activity on *Staphylococcus Aureus* DNA polymerase III. The 4,6-dichloropyrazolo[3,4-*d*]pyrimidine **23** underwent Mitsunobu reaction with protected hydroxyalkyl derivatives, Ph_3P, DEAD in THF at room temperature to give intermediates **75**. Selective hydrolysis with 2N KOH afforded the 6-chloropyrazolo[3,4-*d*]pyrimidin-4-ones **76**, which was in turn reacted with 3,4-dichlorobenzylamine yielding the derivatives **77**, finally deprotected to **78** (Scheme 17).[39]



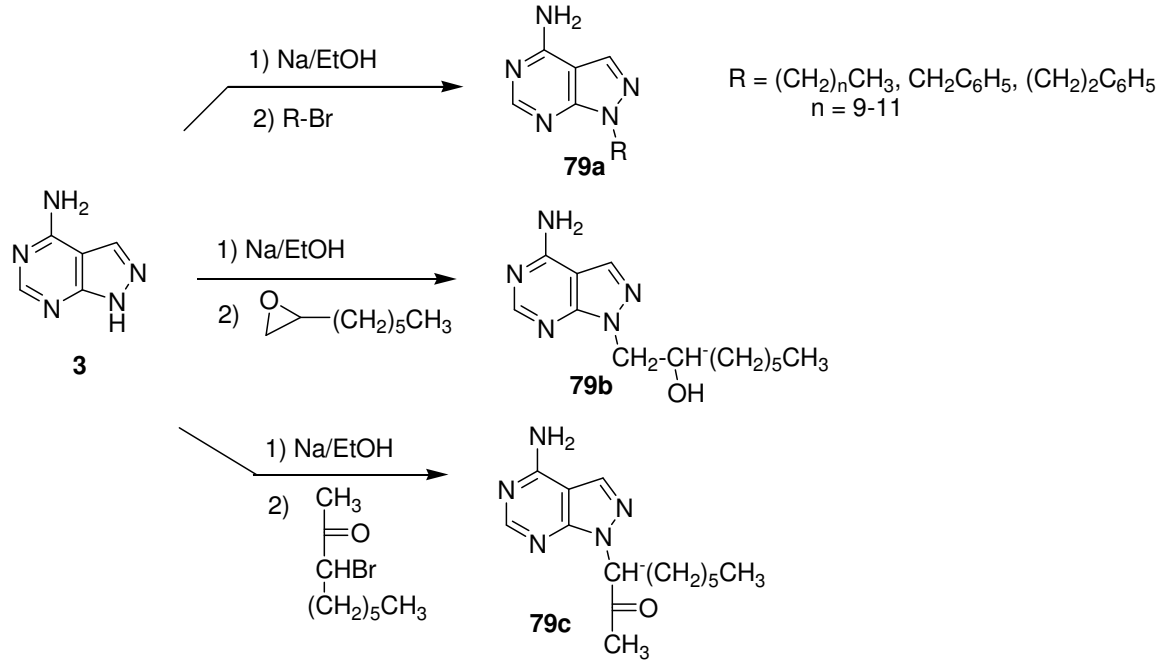
23 **75** **76**

77 **78**

Scheme 17

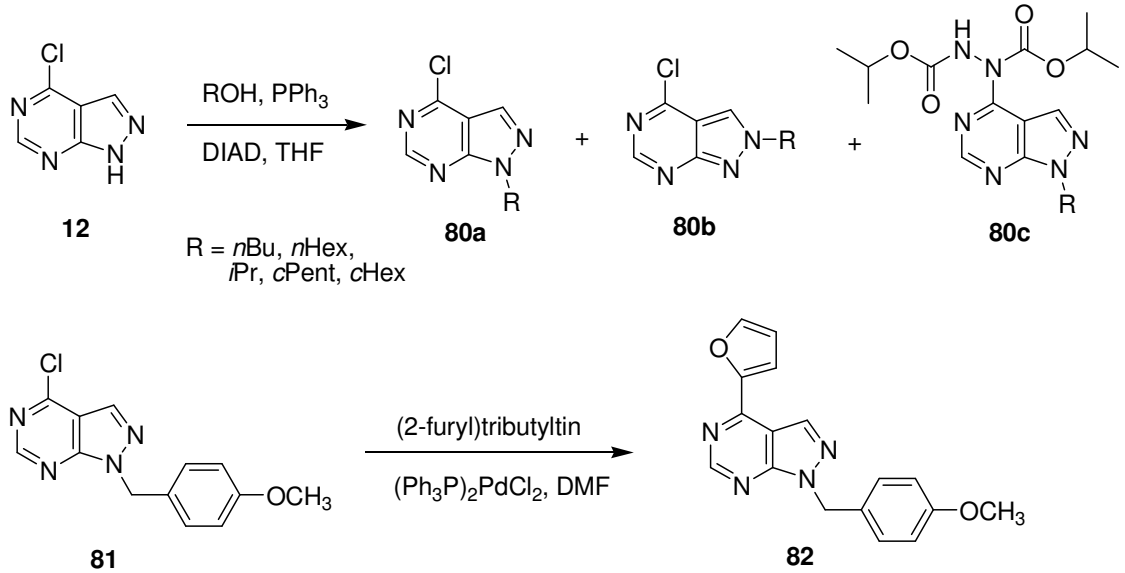
Da Settimo and colleagues have recently synthesized a series of N1 differently substituted 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidines **79a–c** as adenosine deaminase inhibitors, by reaction of 4-APP **3** sodium

salt (prepared with sodium in ethanol) with alkyl halides or oxiranes in DMF. The products were purified by flash chromatography and obtained in yields ranging from 25 to 40% (Scheme 18).[40]



Scheme 18

Efficient and N1-selective alkylation of 4-chloropyrazolo[3,4-*d*]pyrimidine **12** has been recently reported by Gundersen.[41] Reaction of **12** with a number of alcohols under Mitsunobu conditions (triphenylphosphine and diisopropyl azodicarboxylate) led to the predominant formation of the N1 substituted derivatives **80a**, in yield generally ranging from 32 to 77%.



Scheme 19

In some cases, N2 substituted derivatives **80b** together with the C4 substituted product **80c** have been isolated in small percentage. The same Authors also reported the C4 functionalization of the compound **81**

(prepared by Mitsunobu reaction with **12** and *p*-methoxybenzyl alcohol) by reaction with (2-furyl)tributyltin, $(Ph_3P)_2PdCl_2$ in DMF, to obtain the derivative **82** in 82% yield, representing the first example of a palladium-catalyzed coupling reaction on a 4-halopyrazolo[3,4-*d*]pyrimidine (Scheme 19).[41]

4. Biological activity of 4-aminosubstituted pyrazolo[3,4-*d*]pyrimidines

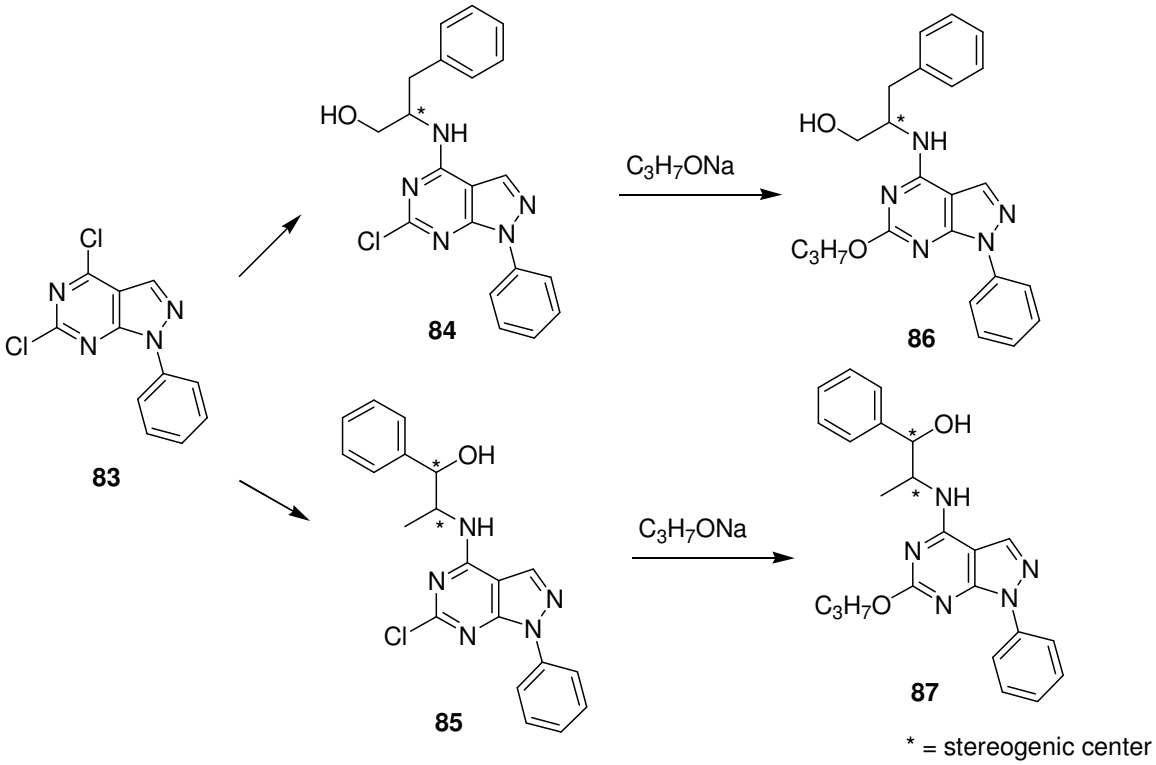
N1-Substituted or N1-unsubstituted 4-aminopyrazolo[3,4-*d*]pyrimidines showed a broad spectrum of biological activities including adenosine receptor antagonism, tyrosine kinases inhibition, cyclin-dependent kinase 2 (CDK2) inhibition,[42] cyclooxygenase-2 inhibition together with anti-angiogenic activity,[43] anti-enterovirus[44] and antimicrobial activity.[45]

Our attention will be focused on pyrazolo[3,4-*d*]pyrimidines acting as A_1 adenosine receptor antagonists and tyrosine kinase inhibitors.

4.1. Adenosine receptor antagonists

Adenosine is an endogenous neuromodulator distributed in a wide variety of tissues, in both the periphery and the central nervous system. The effects exerted by adenosine are mediated by its interactions with four receptor subtypes named A_1, A_{2A}, A_{2B}, A_3.

A_1 adenosine receptor antagonists have therapeutic potential in the treatment of various forms of dementia, such as the Alzheimer's disease, depression and as cognition enhancers in geriatric therapy. Moreover, selective A_1 antagonists are kidney-protective diuretics, useful in the treatment of congestive heart failure (due to their diuretic and positive inotropic effects), of bradyarrhythmias and asystolic arrest.



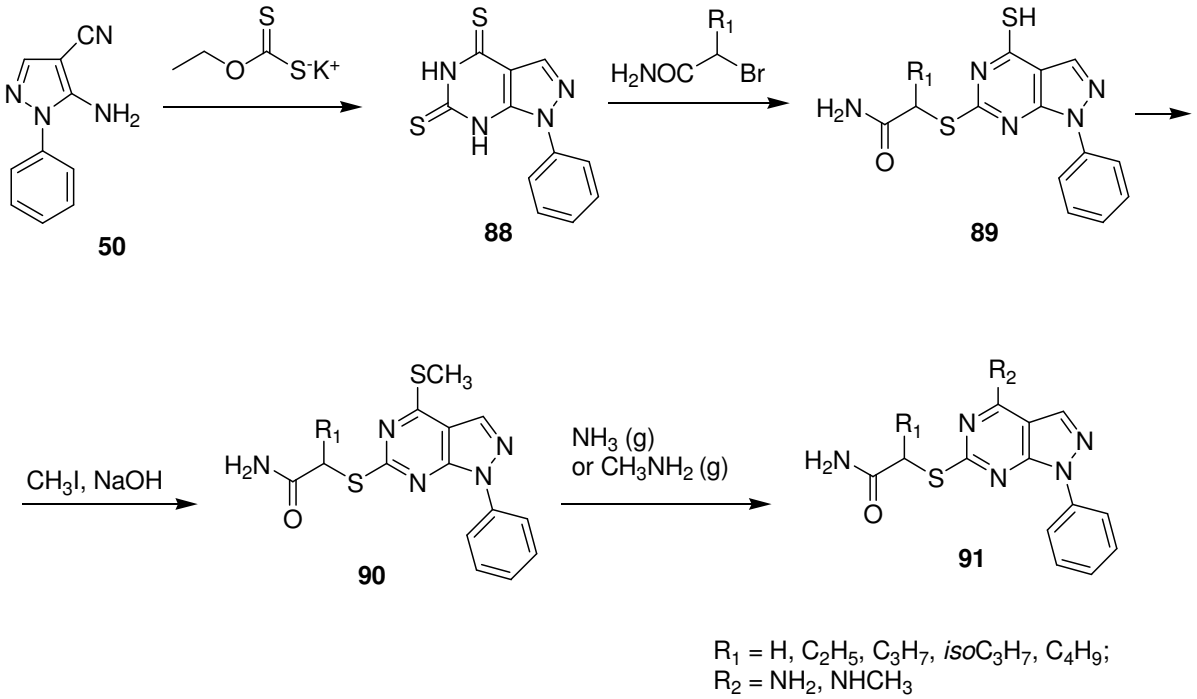
Scheme 20

Peet and colleagues in 1992 synthesized, among other derivatives, a series of chiral (phenylisopropyl)-amino-substituted pyrazolo[3,4-*d*]pyrimidines with selectivity for adenosine A_1 and A_2 receptors, with K_i

values in the range 0.35–1 μM for both the two subtype receptors. The synthesis has been performed starting from the Robins 4,6-dichloro derivative **83**, in which the two chlorine atoms have been selectively substituted: the chlorine in C4 was substituted by treatment with (*S*)-(-)- or (*R*)-(+)-2-amino-3-phenyl-1-propanol or with (1*R*,2*S*)- or (1*S*,2*R*)-1-hydroxy-2-methyl-1-phenylethylamines in ethanol at room temperature for 24 hours to give derivative **84** and **85**, respectively. When these products were treated with sodium propoxide at 90 °C for two hours, also chlorine atom in C6 was substituted producing compounds **86** and **87** in good yields. It is worth to point out that the (*R*) enantiomer of **86** and the (1*R*,2*S*) of **87** were more active in comparison with the opposite enantiomers (Scheme 20).[46]

A wide series of C6 thiosubstituted pyrazolo[3,4-*d*]pyrimidines has been synthesized by Quinn, Poulsen and colleagues as A_1 and A_{2A} adenosine receptor antagonists. 1-Phenyl-5*H*,7*H*-pyrazolo[3,4-*d*]pyrimidines-4,6-dithione **88** was prepared starting from the cyano pyrazole **50** by cyclization with potassium *O*-ethylxanthogenate, following a previously reported procedure.[47]

C6 sulphur alkylation was then achieved by reaction with a 1 mol equivalent of bromoalkylamide in pyridine at room temperature, leading to intermediates **89**, in turn methylated at C4 with iodomethane in aqueous NaOH. Aminolysis of the methylthio compounds **90** with ethanolic ammonia or ethanolic methylamine at 110 °C in a pressure-sealed flask for 72 hours gave the desired products **91**. These products are potent A_1 adenosine antagonists with a K_i ranging from 0.7 to 2.7 nM, while they showed a reduced activity on A_{2A} subtype receptor (K_i in the range 35–247 nM) (Scheme 21).[48–50]



Scheme 21

One of the most interesting compounds being **92**, which showed K_i of 0.74 nM against A_1 and high selectivity over the adenosine A_{2A} receptor. Authors, using the same procedure, also synthesized compounds **93**, bearing alkyl groups on the terminal amide moiety; the most active derivatives showed an increased affinity for A_{2A} receptor (Figure 7).[51]

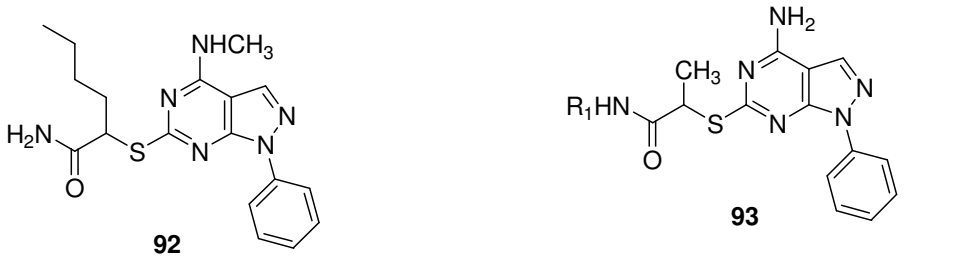
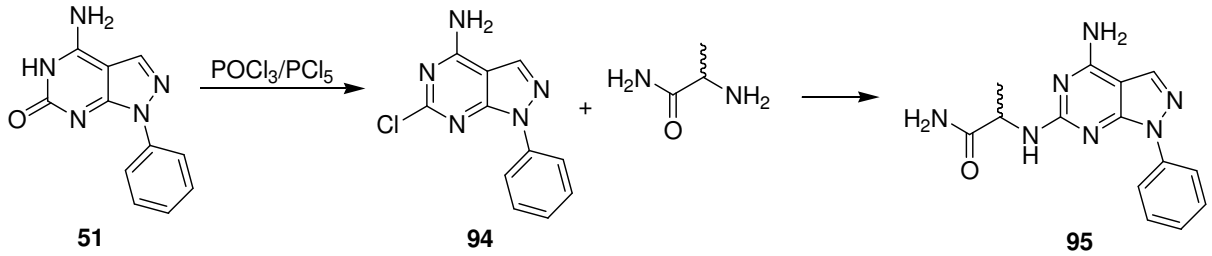


Figure 7

Synthesis and biological data of the 6-aminosubstituted derivative **95** have been also reported. Starting from the intermediate **51**, reaction with phosphorous oxychloride and phosphorous pentachloride, afforded the 6-chloro derivative **94**. Interestingly, the C6 chlorine atom did not give nucleophilic aromatic substitution with 2-aminopropanamide in DMF and *N*,*N*-diisopropylethylamine (DIPEA) even after 4 days at reflux, but it has been substituted in high pressure conditions (15 kbar) at 40 °C for 7 days. Using this procedure, the Authors synthesized both racemic **95** and the two separate enantiomers, starting from the appropriate amines. The (S) enantiomer resulted to be more active than (R) against A_1 adenosine receptor, with a K_i value of 49 nM (Scheme 22).[52]



Scheme 22

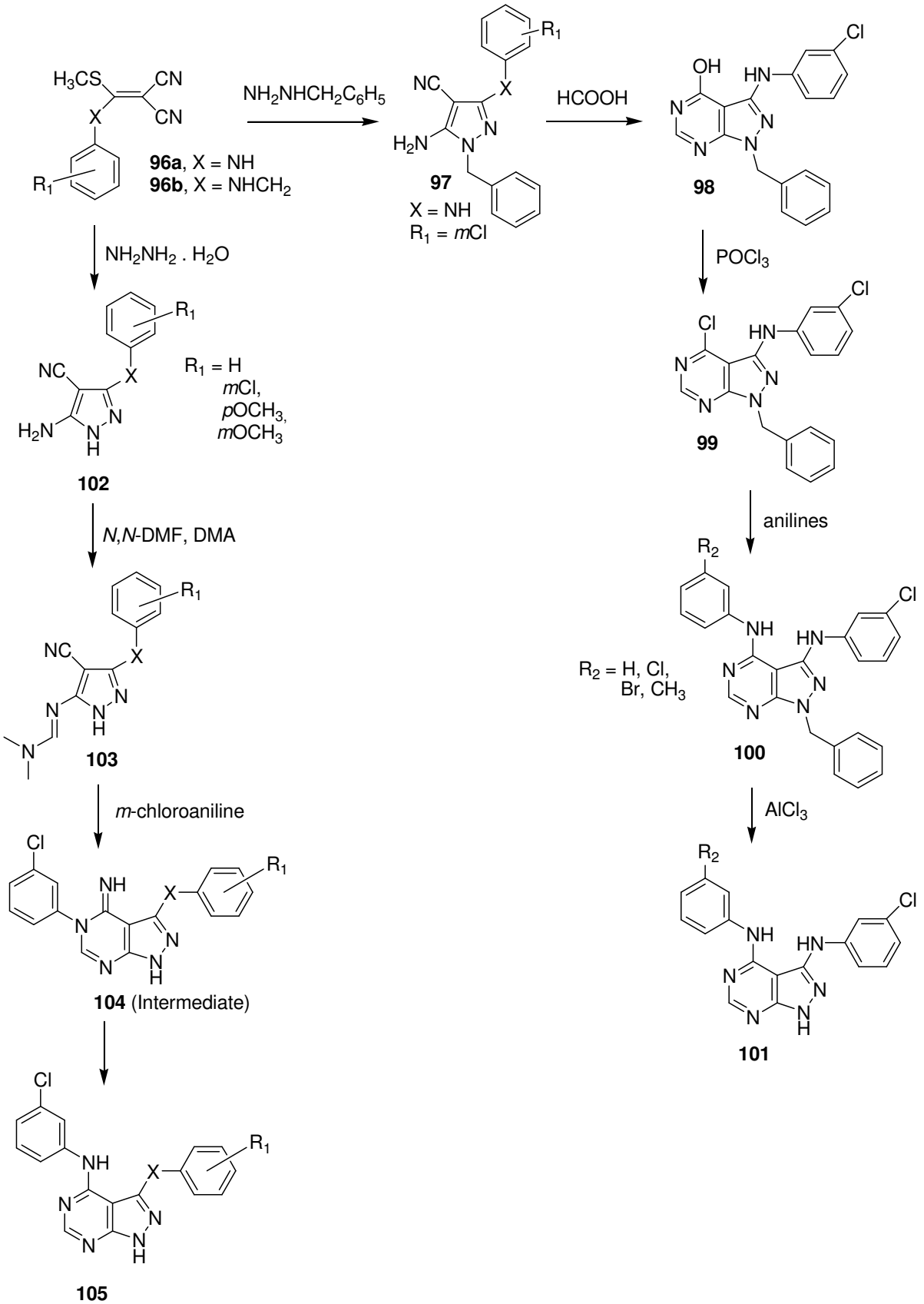
4.2. Tyrosine kinases inhibitors

Protein Tyrosine Kinases (TKs) are enzymes that catalyze the transfer of the terminal phosphate of ATP to specific tyrosine residues present on a target substrate and regulate the growth, differentiation, migration, adhesion and apoptosis in mammalian cells.

TKs are subdivided into two families: the first is represented by the transmembrane receptor family (receptor tyrosine kinases, RTKs), activated by ligand binding with the extracellular domain and include the epidermal growth factor receptor (EGF-R), platelet-derived growth factor receptor (PDGF-R), vascular endothelial growth factor receptor (VEGF-R), fibroblast growth factor receptor (FGF-R), nerve growth factor receptor (NGF-R), insulin receptor (IGF-R), Eph, Axl, Tie and other families. The second family of TKs is represented by the cytoplasmatic or non-receptor TKs, which are activated by different mechanisms and include Src, Csk, Abl, Jak, and Fak families. Deregulated TK activity has been observed in many proliferative diseases, first of all solid or haematological malignancies.

4.2.1. EGFR TK inhibitors

EGFR TK belongs to the class of the transmembrane growth factor receptors and is implicated in different tumors of epithelial origin and in proliferative disorders of epidermis such as psoriasis. Inhibitors of this TK have great therapeutic potential in the treatment of malignant and non malignant epithelial diseases.



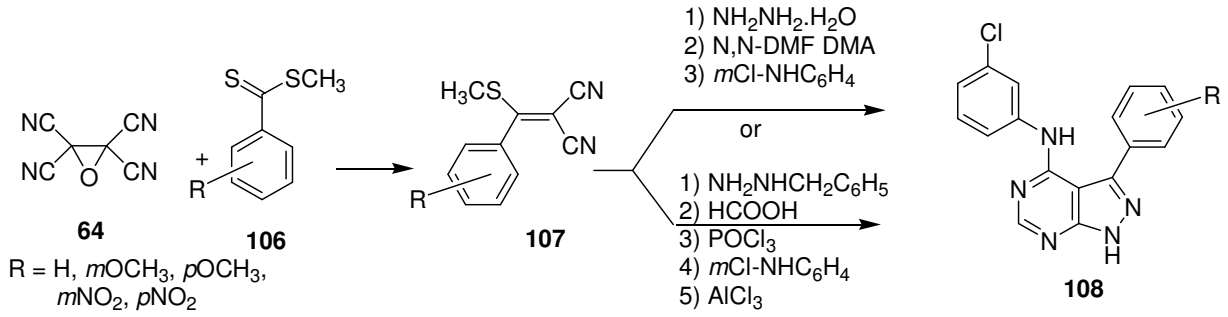
Scheme 23

Traxler and colleagues at Novartis synthesized a wide series of 4-phenylaminopyrazolo[3,4-*d*]pyrimidines as highly potent and selective inhibitors of EGFR TK, the most active compounds showing

IC_{50} values below 10 nM in enzymatic assays and below 50 nM in EGF stimulated cell assays. We are reporting here as examples the synthesis of interesting inhibitors performed by Traxler.

The substituted 3-anilino-3-methylthio-2-cyanoacrylonitriles **96a**, obtained with the already reported Tominaga method,[29] was reacted with benzylhydrazine affording the corresponding 5-amino-4-cyano-pyrazole **97**. Ring closure was achieved refluxing the latter with 85% formic acid, to give intermediate **98**, which was converted into the corresponding chloride **99** by reaction with phosphorous oxychloride. Substitution of the C4 chlorine atom with different anilines gave the 4-phenylaminopyrazolopyrimidines **100**, which, after removal of the benzyl group, led to the final products **101**. Reaction of **96a** and **96b** with hydrazine monohydrate leads to pyrazoles **102** that are starting products for an improved shorter synthesis, avoiding benzyl protection. Reaction of **102** with *N*,*N*-dimethylformamide dimethylacetal in toluene afforded the amidines **103**, directly converted to the final product **105** with *m*-chloroaniline in boiling alcohols; Authors reported that probably the reaction proceeds *via* an imino intermediate **104**, isolated in some cases, which rearranges to the final products (Scheme 23).

The synthesis of compounds **108**, bearing an aromatic moiety directly attached on C3 of the pyrazole ring, was performed using a different Tominaga method[32] starting from the commercially available tetracyanoethylene oxide **64** and methyl dithiocarboxylates **106**. The corresponding 3-phenyl-2-cyano-3-(methylthio)acrylonitriles **107** was reacted in the two different reaction conditions, as reported in Scheme 24, to give the desired products **108**.[53,54]



Scheme 24

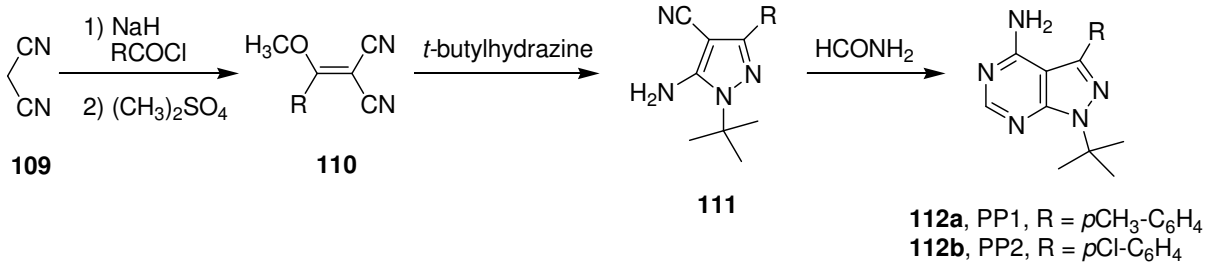
4.2.2. Src TK inhibitors

The Src Family Kinases (SFKs) is constituted by non-receptor or cytoplasmatic enzymes and comprise 11 members in humans: Blk, Brk, Fgr, Frk, Fyn, Hck, Lck, Lyn, c-Src, Srm, c-Yes. On the basis of their amino acid sequences, SFKs can be further divided into two subfamilies: the first one includes Src, Fyn, Yes and Fgr and it is widely presents in different tissues. The second subfamily comprises Lck, Blk, Lyn and Hck, and is restricted to hematopoietic cells. An increased Src activity is found transiently in almost every aspect of a normal cell life in response to different physiological conditions, including mitogenesis, proliferation, survival, adhesion and motility. All these processes are deregulated during cancer progression.

Changes in the levels of Src protein and/or kinase activity are present in different solid or haematological tumors and appear to be correlated with their grade of malignance. For these reasons, different classes of SFKs inhibitors have been developed in the last few years and many of them are substituted pyrazolo[3,4-*d*]pyrimidines.[55]

The first reported Src-selective kinase inhibitors are the two pyrazolo[3,4-*d*]pyrimidines PP1 and PP2 synthesized by Pfizer researches.[56] Reacting the sodium salt of malononitrile **109** (prepared with NaH) with

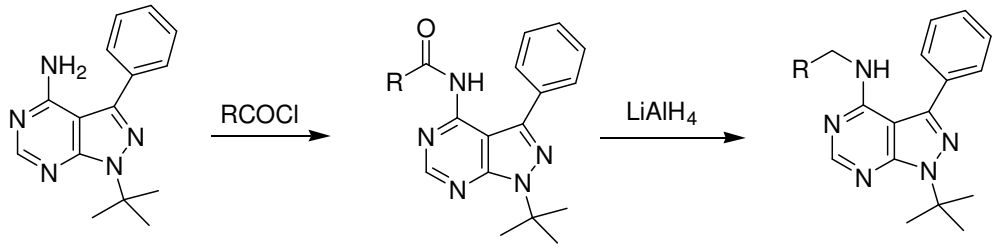
the appropriate acyl chloride in THF, followed by methylation with dimethyl sulphate, leads to the dicyanoethylenes **110**, in turn cyclized to the corresponding pyrazoles by reaction with *t*-butylhydrazine. Reaction of **111** with boiling formamide gave the desired products **112a** (PP1) and **112b** (PP2) (Scheme 25). The two compounds showed IC_{50} values in the low nanomolar range toward different members of SFKs.[57]



Scheme 25

PP1 and PP2 have been the most utilized compounds for biological studies on the SFKs pathway cascades and they are also commonly used as reference compounds to evaluate the potency of newly synthesized inhibitors. Recently, it has been demonstrated that PP1 also inhibits Kit and Bcr-Abl TKs, two other cytoplasmatic TKs.[57]

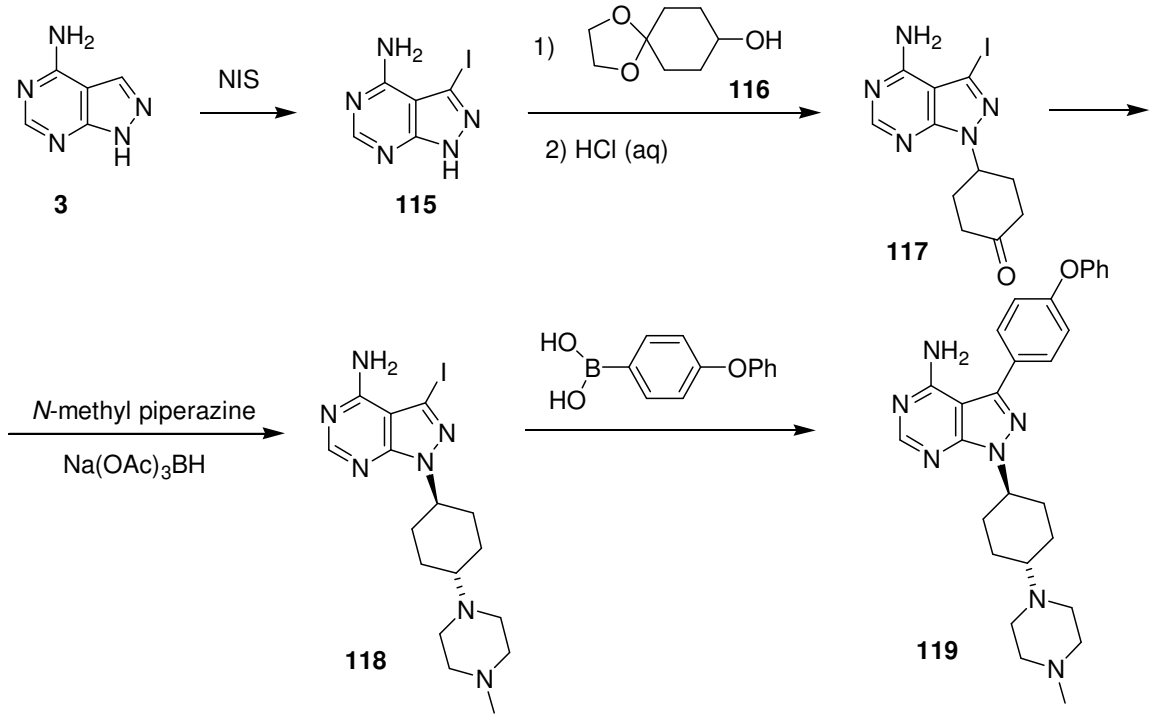
Very interesting studies using pyrazolo[3,4-*d*]pyrimidines were performed by Bishop and Shokat to get further insights into kinases signalling pathway. In this new approach, combining chemistry and genetics, Authors developed high specific cell-permeable inhibitors of the oncogenic tyrosine kinase v-Src (viral-Src, a variant of the human c-Src), modified with a functionally silent active-site mutation to distinguish it from other kinases. As an example, compounds **114** have been synthesized starting from **112c** (a PP1analogue), by acylation of C4 amino group, with different acyl chlorides to give the amide intermediates **113**, which was finally reduced with $LiAlH_4$ to the desired final derivatives (Scheme 26).[58,59]



Scheme 26

Lck is a member of SFKs, expressed primarily in T lymphocytes and plays an essential role in the immune responses. Selective inhibitors of Lck should have therapeutic applications in the treatment of autoimmune diseases and in organ transplant rejection. Abbott researchers synthesized a series of pyrazolo[3,4-*d*]pyrimidines, such as **119**, containing an extended 3-substituent as potent Lck inhibitors, endowed in some cases with good selectivity toward the other SFKs members and good bioavailability in animal models.

For the synthesis of **119**, the Robins derivative **3** was iodinated at C3 with *N*-iodosuccinimide (NIS) to give the pyrazolopyrimidine **115**. Mitsunobu coupling with the ketalalcohol **116**, followed by ketone unmasking, gave the intermediate **117**. Reductive amination with *N*-methyl piperazine gave **118** in a 2.5:1 ratio of *cis*/*trans* diastereoisomer, separated with silica gel flash chromatography, the *trans* possessing the desired configuration. Suzuki coupling with 4-phenoxyphenylboronic acid gave the final product **119** (Scheme 27).[60]



Scheme 27

More recently, the same group synthesized with a similar chemical approach the two pyrazolo[3,4-*d*]pyrimidines A-420983 **120**[61] and A-770041 **121**[62] which act as orally active selective Lck inhibitors and prevent organ allograft rejection in animal models (Figure 8).

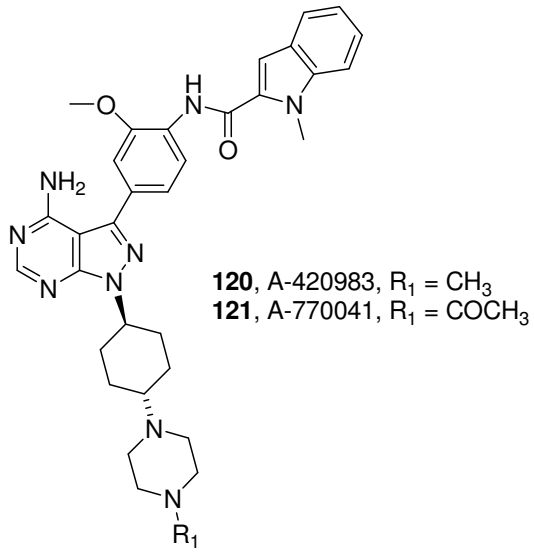


Figure 8

4.2.3. c-Src and Abl inhibitors

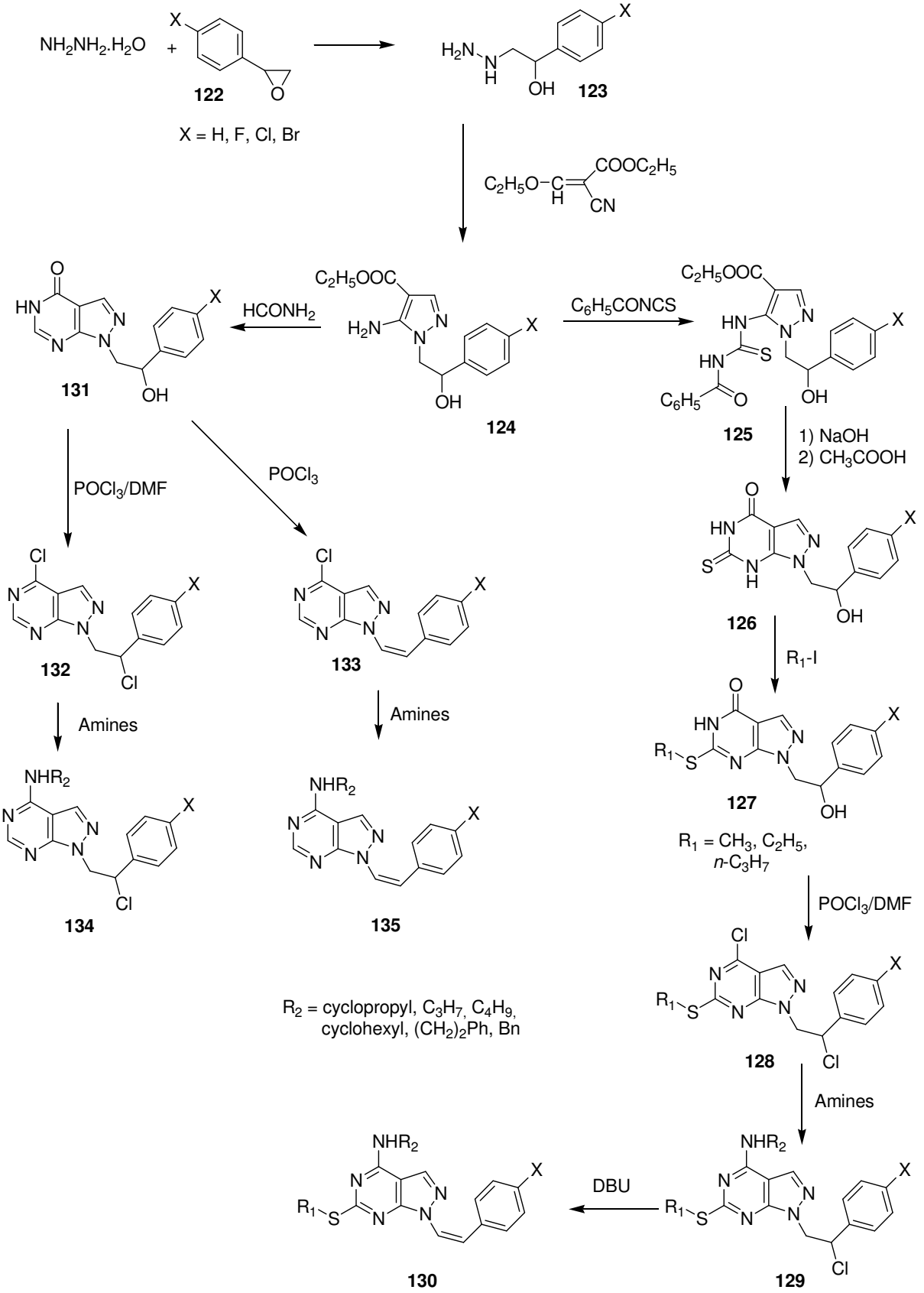
Besides having a role in solid tumors, c-Src is also involved in the progression of haematological malignancies, in particular chronic myeloid leukemia (CML) and acute myeloid leukemia (ALL). These diseases are characterized by the presence of the Philadelphia chromosome, derived from a reciprocal translocation between chromosomes 9 and 22. This translocation fuses the breakpoint cluster region (Bcr) and the Abl genes, forming the Bcr-Abl oncogene which encodes a constitutively active cytoplasmatic tyrosine kinase (TK) Bcr-Abl. This deregulated enzyme causes hyperproliferation of the leukemic cells and the consequent pathology of the disease. The finding that Bcr-Abl is the cause of the leukemic phenotype and that the tyrosine kinase activity of Abl is fundamental for Bcr-Abl-mediated transformation, made this kinase an important target for the development of specific therapies. In the recent past, advances in the selective inhibition of Bcr-Abl kinase activity led to the development of Imatinib mesylate (Gleevec) that now represents the first line treatment for CML. Unfortunately, either overexpression or mutations of Bcr-Abl confer resistance to Gleevec. As a consequence, there is a growing interest in the development of second generation small molecules inhibitors, able to treat Gleevec resistant CML.

It has been recently demonstrated that the activity of Src is elevated in the presence of the Bcr-Abl oncoprotein; Src kinase activity remains high following Imatinib inhibition of Bcr-Abl in leukemic cells, while the simultaneous inhibition of both Bcr-Abl and c-Src kinases results in long-term survival of mice with ALL.

These reasons, together with the striking similarity between the catalytically active states of the c-Src and Abl kinases, prompted medicinal chemists (helped by computational methods) to synthesize dual Src/Abl inhibitors that might be active against Philadelphia positive forms of leukaemia.[63] In the continuing efforts to find new anticancer agents, we have recently synthesized several 4-amino substituted pyrazolo[3,4-*d*]pyrimidines **129**, **130**, **134**, **135**, **137** and **140**. The starting products for the synthesis of these derivatives are the substituted phenyloxiranes **122** that reacting with hydrazine monohydrate, led to the corresponding 2-hydrazinoethanols **123** (Scheme 28).[64] Reaction of **123** with ethyl(ethoxymethylene)cyanoacetate afforded the ethyl esters of 5-amino-1*H*-pyrazole-4-carboxylic acids **124**, which were in turn treated with benzoyl isothiocyanate for 12 h in refluxing THF to give **125**. These intermediates were cyclized to the pyrazolo[3,4-*d*]pyrimidinones **126** by treatment with 2M NaOH, followed by acidification with acetic acid. Alkylation of the thio group at C6 with the appropriate alkyl iodide in refluxing THF afforded the 6-alkylthio derivatives **127**, which were in turn treated with the Vilsmeier complex ($POCl_3$:DMF) to obtain the dihalogenated compounds **128**, bearing a chlorine atom both at C4 and at the N1 side chain. Regioselective substitution of the chlorine at C4 with an excess of various amines, afforded the products **129** in good yields. Treatment of **129** with DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) heating for 4 h at 90 °C led to the corresponding styryl compounds **130**.

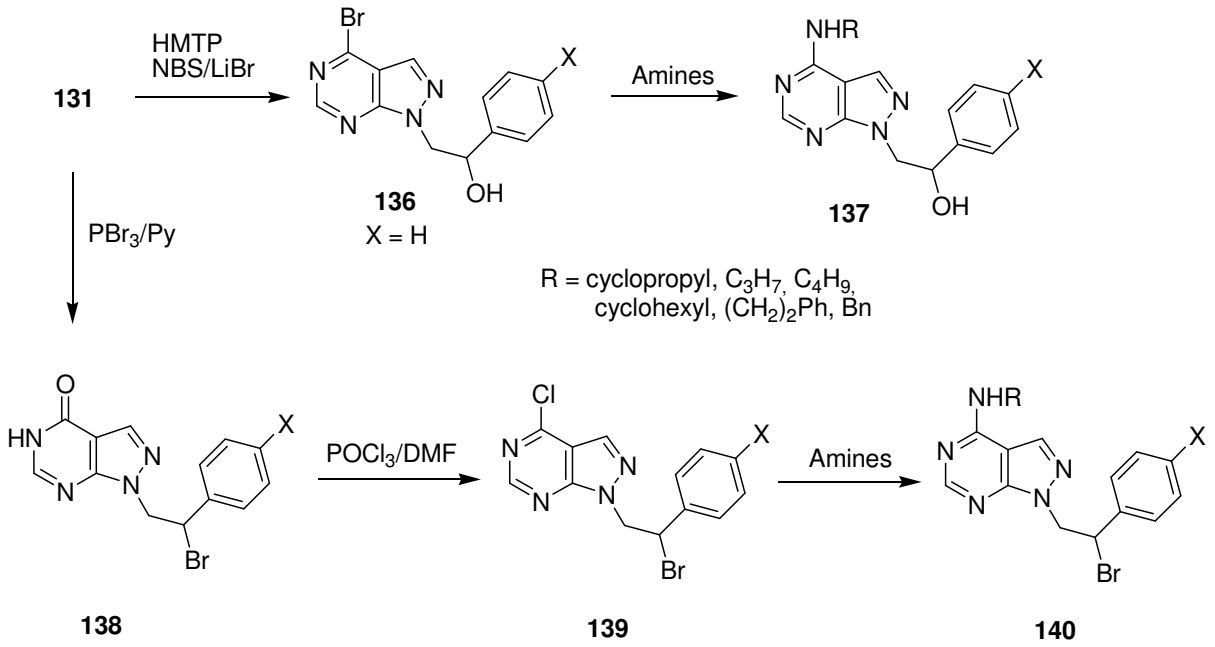
Reaction of **124** with an excess of formamide at 190 °C afforded the pyrazolopyrimidinones **131** which was transformed into the dichloro derivatives **132** after treatment with the Vilsmeier complex. Alternatively, compounds **131** were transformed into the styryl derivatives **133** by reaction with $POCl_3$ at reflux. Treatment of **132** and **133** with different amines afforded the desired 6-unsubstituted derivatives **134** and **135** (Scheme 28).[65,66] Compound **136** was prepared following the Beal and Véliz procedure[67] by treatment of **131** with a mixture of hexamethylphosphorous triamide/*N*-bromosuccinimide (HMPT/NBS) in acetonitrile at −20 °C

followed by addition of LiBr and refluxing for 6 hours. It is interesting to point out that the secondary OH on the side chain remains unaltered with this procedure.



Scheme 28

The C4 bromo derivative **136** was treated with the appropriate amines and gave the final compounds **137**.[68,69] Reaction of the pyrimidinone **131** in DMF with a solution of phosphorous tribromide, pyridine and toluene at room temperature for 3 days led to the intermediate **138**, bearing a bromine atom on the N1 side chain. Compound **138** was in turn chlorinated at C4 by treatment with the Vilsmeier complex, to afford the intermediates **139** which were finally reacted with an excess of various amines to obtain the derivatives **140** in high yields (Scheme 29).[70]



Scheme 29

The library of compounds **129** and **133**, bearing a 2-chloro-2-phenylethyl N1 side chain showed a submicromolar to nanomolar activity toward isolated Src as well as antiproliferative activity toward the epidermoid (A431) and breast cancer (BC-8701) cell-lines (that overexpress Src) blocking Src phosphorylation and inducing apoptosis with potency about two-fold higher than that of the reference compound 4-amino-5-(4-chlorophenyl)-7-(*t*-butyl)pyrazolo[3,4-*d*]pyrimidine (PP2) **112b**.[65,66,68,69] The most potent compounds of the series were also used to investigate the role of c-Src in the control of the invasive prostate carcinoma cell line, PC3. The molecules reduced proliferation, migratory ability and adhesive capacity of PC3 cells.[70] Moreover nanomolar concentrations of these c-Src inhibitors have a highly selective antiangiogenesis effect, by reducing the production of VEGF (Vascular Endothelial Growth Factor) and decrease tumor volume promoted by A431 implanted in nude mice.[71]

Derivatives **129**, bearing an aniline, benzylamino or phenylethylamino substituents on C4 possessed, together with c-Src inhibitory properties, antiproliferative activity on human osteogenic sarcoma (SaOS-2) cells, reduced bone resorption when used to treat mouse osteoclast without interfering with normal osteoblast growth and reduced the volume of human SaOS-2 xenograft tumor model in nude mice.[72]

Based on the fact that compounds acting as c-Src inhibitors often showed also activity toward Brc/Abl, a set of these pyrazolo[3,4-*d*]pyrimidine derivatives have been tested on Abl isolated enzyme and on a panel of leukemia cell lines. The studied compounds were able to inhibit Bcr/Abl and c-Src phosphorylation, induced apoptosis and, as the activation of Src and Abl is an important step in the progression of leukemia

cells (in particular, CML), reduced cell proliferation.[73] More interestingly, some of these compounds have very recently shown to be active on imatinib resistant CML cells.[74]

5. Conclusions

The most common methods for the synthesis of pyrazolo[3,4-*d*]pyrimidine scaffold have been reported starting from the earlier work of Robins, when the biological behaviour of these compounds was still in an embryonic state, up to recent days. We have described how the evolution of chemical methodologies, which led to many new derivatives, tightly accompanied the evolution of modern biology, pharmacology and modern medicine. It is fascinating how the functionalization of the pyrazolo[3,4-*d*]pyrimidine scaffold can gives rise to selective inhibitors for many different biological targets, which number is in rapid evolution. Further work in this field is expected to give even more interesting results in modern molecular medicine; it is a proof of concept that the recent work by Smithgall[75] on the use of such derivatives on stem cells has opened a new avenue on the war against tumors.

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RECENT DEVELOPMENTS IN PYRIDINE-BASED LIGANDS: SYNTHESES AND APPLICATIONS

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Abstract. *This chapter is devoted to the most recent progresses in the chemistry of bidentate and tridentate heterocyclic ligands containing at least one pyridine group. In this family of organic ligands derived from the pyridine unit, we indeed present the recent advances in the well-known and tremendously developed chemistry of 2,2'-bipyridine, 1,10-phenanthroline and 2,2':6',2''-terpyridine and their respective derivatives but we also report the synthesis of new chelating ligands incorporating original five-membered heterocyclic rings such as imidazole, pyrazole or triazole. We describe the different strategies recently developed for the synthesis and the functionalization of these organic compounds. The pyridine-based ligands presented in this chapter have also been specifically selected amongst the vast literature dealing with these compounds to illustrate the numerous applications in which they are now involved, such as nonlinear optical (NLO) materials, organic light emitting diodes (OLEDs) or in nanotechnologies.*

Contents

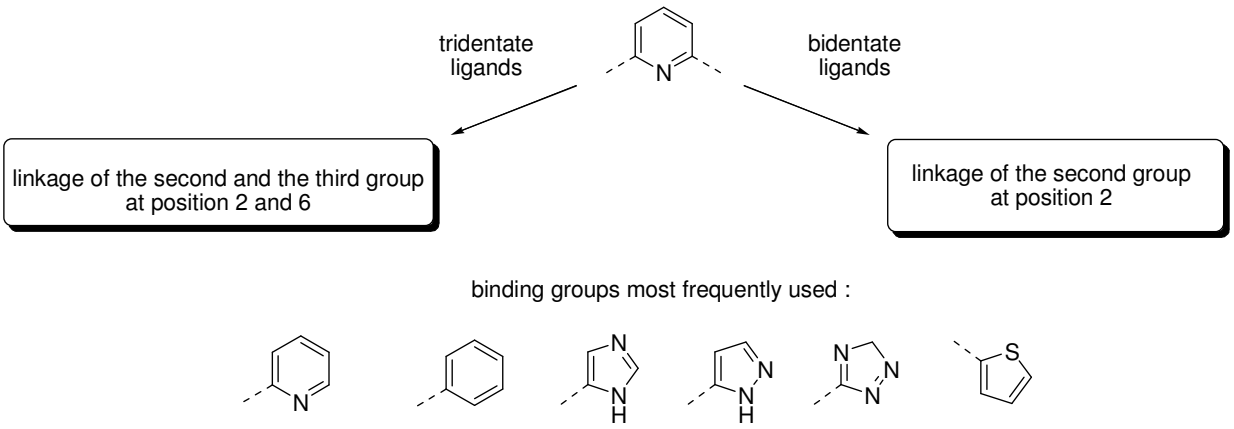
1. Introduction

Pyridine is one of the most important nitrogen-containing heterocycle present in numerous natural and synthetic molecules. Its synthesis has been intensively investigated.[1a–b] Pyridine is also a key building-block to prepare polydentate ligands able to coordinate metals.[1c–d] These chelating ligands, based on the pyridine unit, are named polypyridyl ligands when they are exclusively composed of pyridines. But polydentate ligands can also bear only one pyridine unit. Among polydentate ligands, polypyridyl ligands are one of the most important classes of chelating agents as they coordinate various transition metal ions. In the past decade, the structure of these ligands has been widely tuned to obtain structure-properties relationships for targeted applications ranging from optical applications to nanoelectronic devices. In this chapter, our aim is to present bidentate and tridentate ligands bearing at least one pyridine unit as binding site. This chapter will first focus on the recent development in the syntheses of these ligands and will highlight works recently published with the different strategies used for these syntheses. The second part will be devoted to the most relevant applications for these ligands and their substituted derivatives. Even if the chelating ligands presented here are indeed mainly synthesized and designed to bind metal ions and to generate metal complexes with specific properties, only few of these metal complexes will be presented as it is not the main object of this chapter. For the applications, three main topics will be considered: optical applications, opto-electronic materials and nanoelectronic components. Several ligands mentioned in this chapter have also been used for applications other than materials. When coordinated to a metal, some of these ligands have been used in asymmetric catalysis,[2] for mimicking the electron-donor side of a photosystem II in artificial photosynthesis,[3] in DNA binding and photocleavage[4] or in metal-labeled single stranded oligonucleotides.[5] These different topics are well-reported in the literature and will not be discussed herein.

2. Synthetic approaches to polypyridyl ligands

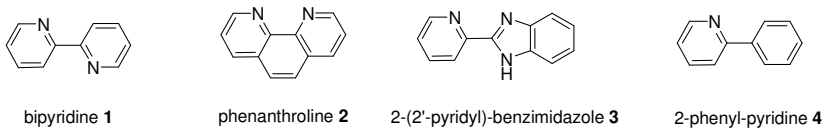
2.1. Nature of the chelating ligands

Bidentate and tridentate chelating ligands constitute an important class of compounds for the construction of transition metal complexes. For all these ligands, the binding ability depends on the geometry and the angle at which donor atoms of the chelating ligand ‘bite’ into the transition metal. Various groups have been covalently linked to the central pyridine in order to modify the distance between two consecutive donor atoms. The main structures employed as second or third binding substituent are pyridine, phenyl, imidazole, pyrazole, triazole and thiophene groups (Scheme 1).



Scheme 1

Among bidentate ligands, the most widely used is undoubtedly the 2,2'-dipyridyl (bipyridine **1**) combining easy functionalization, redox stability and luminescence properties when complexed with a metal. Bipyridine **1** is both a σ-donor and a π-acceptor ligand.[6] The nitrogen lone electron pair can form σ-bond(s) with a central atom, while the aromatic system can be involved in π back-bonding. **1** stabilizes soft metal ions, especially transition metal ions in low oxidation states. Another specificity lies in the fact that it is a neutral ligand, compared to dianionic ligands derived from catechol or monoanionic acetylacetonate. The oxidation state of the metal and the resulting overall charge of the complex can have a strong impact on its solubility, crystallization, stability or optical properties. Moreover, **1**, having two nitrogen donor atoms separated by two carbons, form five-membered rings, which are the most stable structures. Numerous multifunctional compounds derived from **1** have been synthesized (Scheme 2). For example, introduction of an additional aromatic ring linking two pyridine groups generates a rigid framework and led to the development of the chemistry of phenanthroline and phenanthroline derivatives.[7] Recent years have also witnessed an increasing interest for ligands containing five-membered heterocyclic rings such as pyrazole, imidazole or triazole. Notably, introduction of such five-membered rings in the ligands led to a series of blue-emitting iridium[8] and osmium[9] complexes.

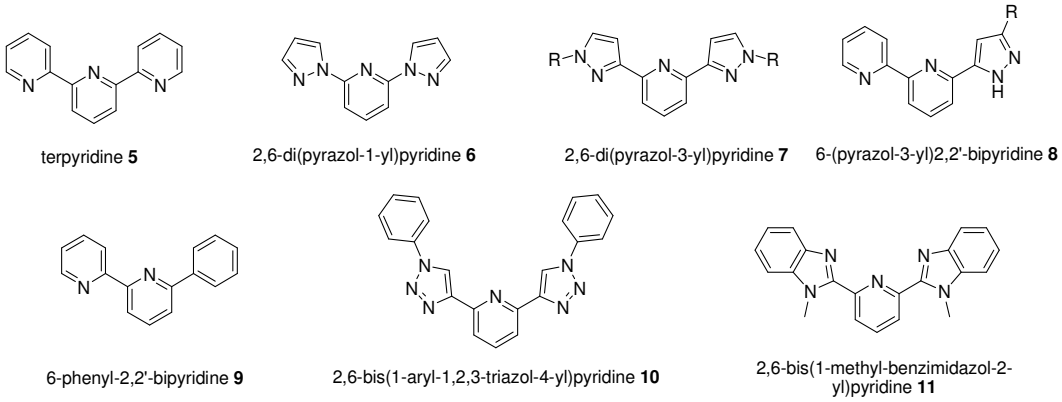


Scheme 2

Ligands can also be modified by changing the nature of the binding site. The replacement of the nitrogen donor atom by the less electronegative carbon atom led to the 2-phenyl-pyridine ligand **4** capable of reacting with various transition-metal ions through direct C-H bond activation.[10] In particular, the use of this cyclometalated ligand enabled the formation of neutral complexes, for instance with iridium, exhibiting room temperature phosphorescence suitable for organic light-emitting diodes (OLEDs) devices.[11]

Tridentate ligands such as terpyridine **5** and its derivatives have also been the subject of intensive investigations due to the multitude of potential applications for these systems.[12,13] Special redox and

photophysical properties have been obtained when metals in various low and high oxidation states are coordinated to these ligands. The family of tridentate chelating ligands has been extended to compounds based on 2,6-di(pyrazol-1-yl)pyridine **6**, 2,6-di(pyrazol-3-yl)pyridine **7**, 6-(pyrazol-3-yl)-2,2'-bipyridine **8** and 6-phenyl-2,2'-bipyridine **9** (Scheme 3).[14] Compared to the conventional terpyridine, in which the central pyridine is substituted by two equivalent rings, these last families contain binding groups of different basicities. By deprotonation of the phenyl ring of **9**, luminescent platinum-acetylide complexes have been prepared.[15] Ligand 2,6-*bis*-(1-aryl-1,2,3-triazol-4-yl)pyridine **10**, which is widely used in supramolecular chemistry, has been prepared by a "click chemistry" based approach.[16] The last type of tridentate ligand presented in this chapter is the 2,6-*bis*-(1-methyl-benzimidazol-2-yl)pyridine **11** which reacts with lanthanide ions to generate luminescent complexes.[17]



Scheme 3

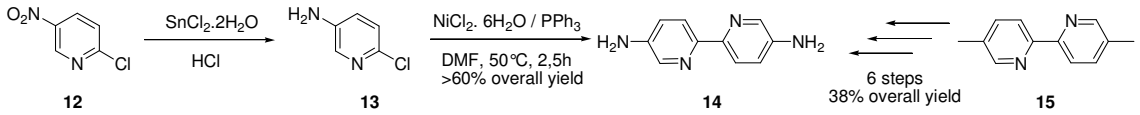
Each of the previous ligands **1–11** represent the "basic" structures of a variety of families of substituted ligands. Sections 2.2. and 2.3. will be devoted to the syntheses of these substituted ligands.

2.2. Synthesis of bidentate ligands

Preparation of the ligands is subjected to the stability and the compatibility of the functional groups on the pyridine ring. As a consequence, there are two possible synthetic routes towards all bidentate ligands described above. The first method involves the preliminary functionalization of the different rings followed by a final coupling linking the functionalized rings and generating the final bidentate ligand. This approach is now an efficient and flexible large-scale preparative method with the development of cross-coupling methods using mild conditions. When the pyridine, or its counterpart, is conveniently substituted, this pathway is certainly the most efficient approach to prepare dissymmetric ligands. The second method consists on the synthesis of the entire ligand backbone and the subsequent selective functionalization of the core of the ligand.

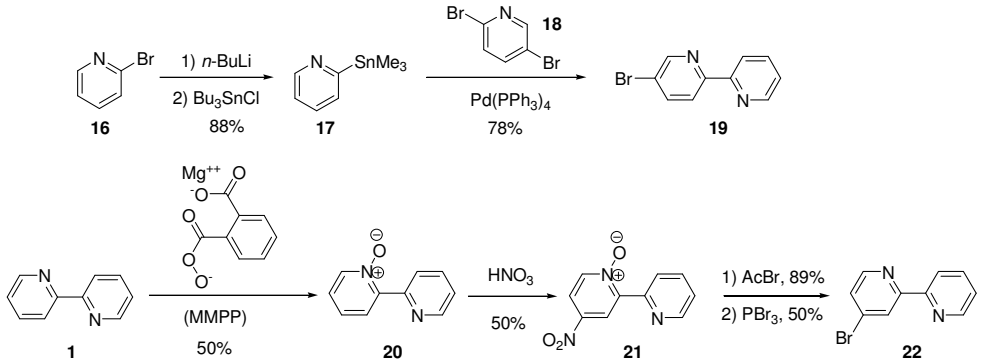
2.2.1. Pre-functionalization

A short synthesis to prepare 5,5'-diamino-2,2'-bipyridine **14** has been recently reported.[18] In the former synthesis described by Whittle,[19] **14** was prepared in six steps starting from 5,5'-dimethyl-2,2'-bipyridine **15** with an overall yield of 38%. In the new synthesis, involving reduction of the commercially available 2-chloro-5-nitropyridine **12** with $SnCl_2.2H_2O$ and reductive coupling reaction with $NiCl_2.6H_2O/PPh_3/Zn$, **14** has been isolated with an overall yield above 60% (Scheme 4).



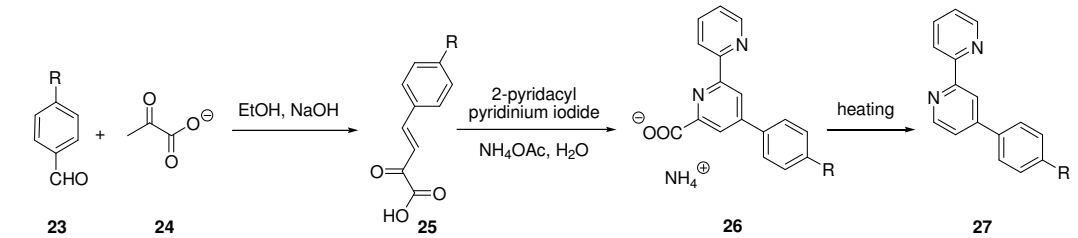
Scheme 4

Syntheses of 4- and 5-bromo-2,2'-bipyridine have been recently revisited.[20b] Initial synthesis of 5-bromo-2,2'-bipyridine **19** was hardly reproducible[20a,21] and **19** was obtained in low yield (12%).[22] **19** has been isolated in 78% yield using a Stille coupling reaction of 2-trimethylstannylpyridine **17** with 2,5-dibromo-pyridine **18** (Scheme 5). 4-Bromo-2,2'-bipyridine **22** has been synthesized in three steps,[20b] starting from **1**, by modification of published procedures.[23] Bipyridine **1** has been first converted to bipyridine *N*-oxide **20** with magnesium monoperoxyphthalate (MMPP) and then nitrated by use of nitric acid at 100 °C. Replacement of the nitro group has been realized by addition of acetyl bromide and removal of the *N*-oxide with PBr_3 in **21** finally afforded **22**.



Scheme 5

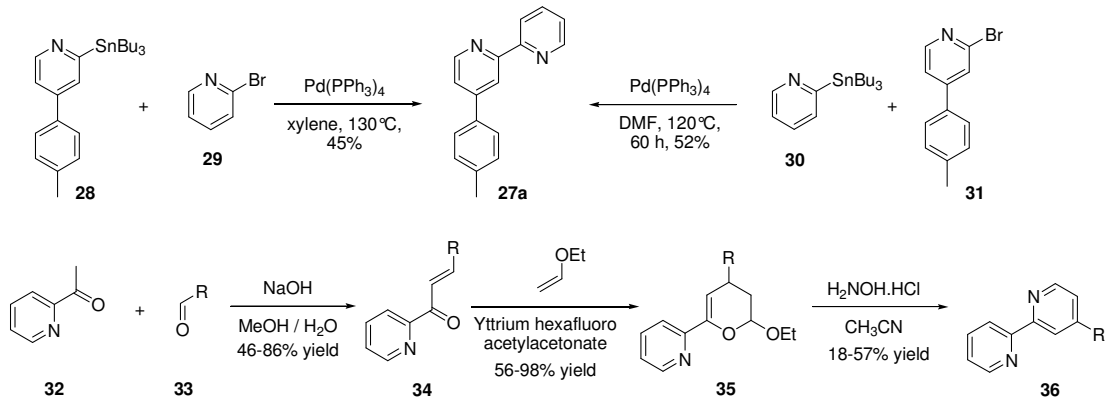
Introduction of a phenyl substituent in the 4- position of a bipyridine can be realized following two different strategies: the first one is based on a ring closure procedure whereas the second one is based on a cross coupling reaction. Using both methods, several substituents have been introduced in the *para*-position of the phenyl ring. 4-Phenyl-2,2'-bipyridine **27** has been obtained following the ring closure route. 4-Substituted benzaldehyde **23** and pyruvate **24** have been condensed to give acid **25**. The chalcone has been then condensed with 2-pyridacyl pyridinium iodide and treatment with ammonium acetate afforded carboxylate **26**. **26** has been finally decarboxylated by strong heating to give **27** (Scheme 6).[24,25]



Scheme 6

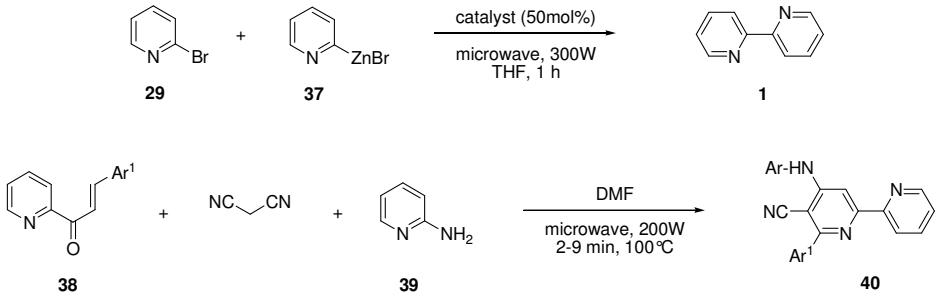
The second strategy to prepare **27a** relies on a Stille cross-coupling reaction between appropriated stannanes and pyridyl halides (Scheme 7).[26] The new family of bipyridine derivatives **36**[27a] has been

obtained using a strategy initially developed by Akermark *et al.*[27b] to prepare terpyridine derivatives *via* an aldol condensation and a Michael addition reaction. The first step consists in an aldol condensation of a substituted benzaldehyde with 2-acetylpyridine. Dihydropyrans **35** are then obtained by reaction of ethyl vinyl ether with **34** catalyzed by yttrium hexafluoroacetylacetonate. Reaction of **35** with hydroxylamine finally afforded **36** with yields ranging from 18 to 51% with the substituent (Scheme 7).



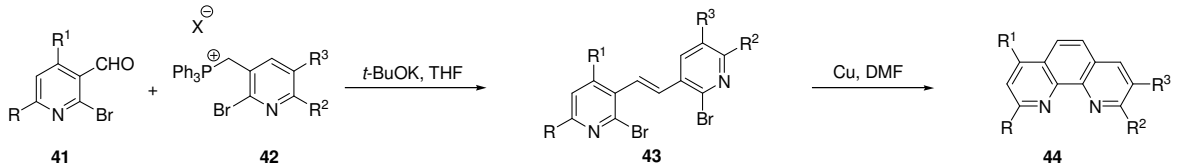
Scheme 7

Microwave-assisted syntheses is a new approach recently developed to isolate 2,2'-dipyridyl **1** (Scheme 8).[28a] Various derivatives of **1** have also been obtained with yields ranging from 81 to 88% using microwave irradiation (Scheme 8).[28b]



Scheme 8

An approach to prepare functionalized 1,10-phenanthroline core has been recently published.[29] The synthesis of 1,10-phenanthroline derivatives **44** has been achieved by construction of the polycyclic aromatic scaffold under Skraup conditions.



41
41a: R = R^1 = H
41b: R = Me, R^1 = H
41c: R = R^1 = Me

42
42a: R^2 = R^3 = H
42b: R^2 = Me, R^3 = H
42c: R^2-R^3 = -CH=CH-CH=CH-

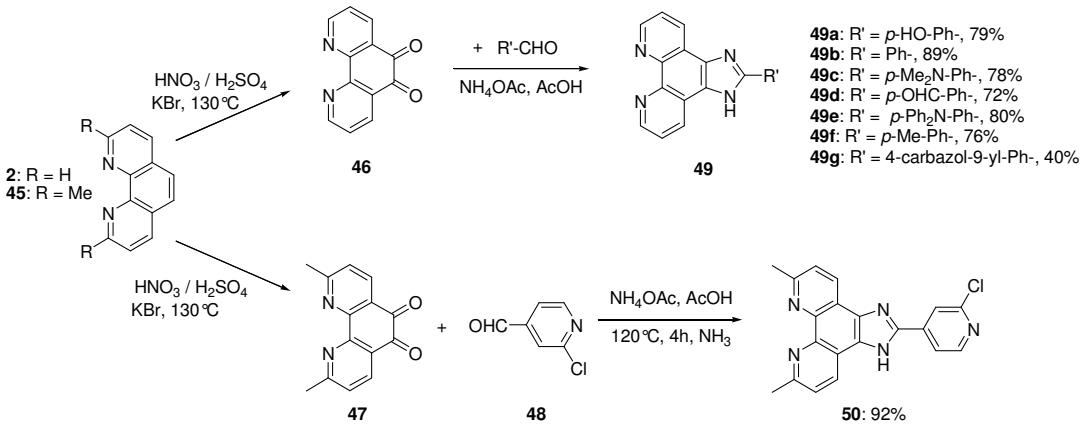
43
43a: R = R^1 = R^2 = R^3 = H, 94%
43b: R = Me, R^1 = H, R^2 = R^3 = H, 94%
43c: R = R = R^2 = Me, R^1 = R^3 = H, 97%
43d: R = R^1 = Me, R^2 = R^3 = H, 88%
43e: R = Me, R^1 = H, R^2-R^3 = -CH=CH-CH=CH-, 95%
43f: R = R^1 = Me, R^2-R^3 = -CH=CH-CH=CH-, 32%

44
44a: R = R^1 = R^2 = R^3 = H, 67%
44b: R = Me, R^1 = H, R^2 = R^3 = H, 75%
44c: R = R = R^2 = Me, R^1 = R^3 = H, 32%
44d: R = R^1 = Me, R^2 = R^3 = H, 24%
44e: R = Me, R^1 = H, R^2-R^3 = -CH=CH-CH=CH-, 24%
44f: R = R^1 = Me, R^2-R^3 = -CH=CH-CH=CH-, 35%

Scheme 9

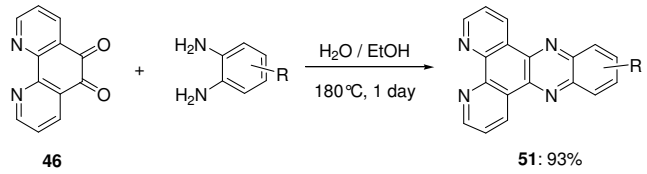
An advantage of this new methodology lies in the fact that both pyridines are conveniently functionalized before the coupling. Both pyridines have been covalently linked by a Hörner-Wadworth-Emmons reaction and an Ullmann intramolecular coupling generated the phenanthroline core (Scheme 9).

Another strategy used for the functionalization of the phenanthroline is based on the generation of its corresponding 1,10-phenanthroline-5,6-dione. Dione **46** has been previously obtained in quite harsh conditions by oxidation using fuming nitric acid in sulfuric acid at 90 °C.[30] Recently, several groups optimised the synthesis, and diones **46** and **47** can be obtained now with high yields (Scheme 10).[31] Coupling of **46** with different substituted aromatic aldehydes generated the target molecules **49** with yields ranging from 40 to 90%.[32] Concerning the neocuproine **47**, only one example of reaction with an aldehyde, namely 2-chloropyridine-4-carbaldehyde, is reported to date, providing the modified phenanthroline **50** in 92% yield (Scheme 10).[33]



Scheme 10

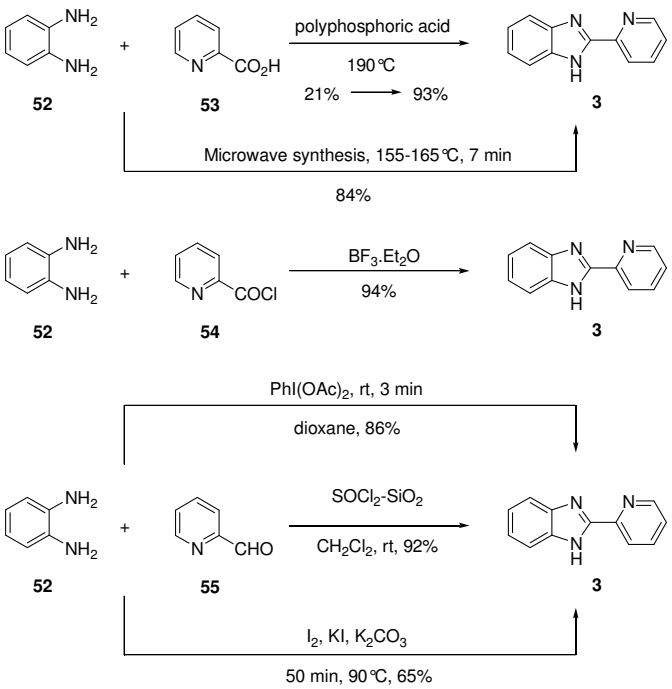
1,10-Phenanthroline-5,6-dione **46** is also a key intermediate for the synthesis of several bidentate ligands such as dipyrido[3,2-*a*:2',3'-*c*]phenazine **51** (Scheme 11).[34]



Scheme 11

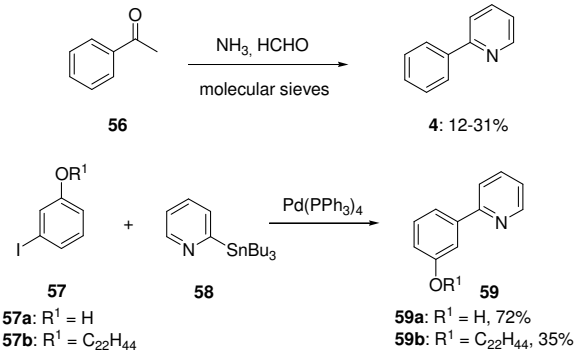
The novel chemosensory material 2-(2'-pyridyl)-benzimidazole **3** has been obtained by condensation of *o*-phenylene diamine **52** and picolinic acid **53** in polyphosphoric acid at 190 °C in moderate yield (21%) (Scheme 12).[35] By modification of the reaction conditions (quantity of polyphosphoric acid, temperature, reaction time), **3** has been obtained with yields up to 93%.[36] Several efficient and rapid syntheses were also developed to prepare **3** without the use of polyphosphoric acid as solvent. Using $BF_3.Et_2O$ as cyclodehydrating and deacylating agent, **3** has been obtained in 94% yield from **54**.[37] Microwave-assisted synthesis shortened the reaction time to seven minutes and provided **3** in 84% yield.[38] Starting from pyridine-4-carbaldehyde and by use of the hypervalent iodine reagent $PhI(OAc)_2$ in dioxane, **3** was obtained

from **52** in three minutes at room temperature in 86% yield (Scheme 12).[39] **3** was also prepared by chemoselective reaction of a stoichiometric amount of **52** and **55** with silica-supported thionyl chloride in dichloromethane at room temperature in 92% yield.[40] Finally, a green synthesis of **3** was recently developed, based on an oxidation process of the carbon-nitrogen bond with iodine, potassium iodide and potassium carbonate in water (Scheme 12).[41]



Scheme 12

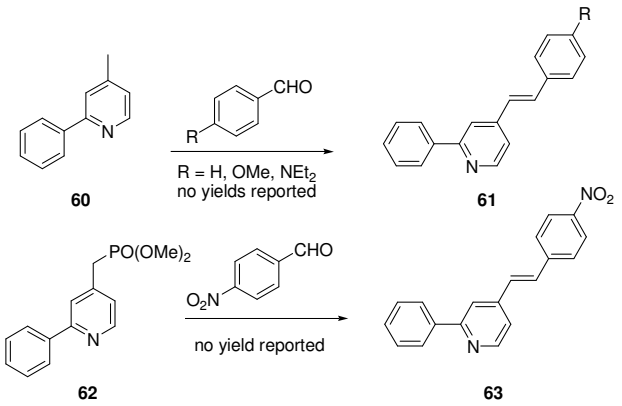
Traditionally, 2-phenylpyridine **4** was synthesized by the arylation of pyridine with phenyllithium (78% yield)[42] or by a Grignard reaction with phenylmagnesium chloride (62% yield).[43] A green synthetic approach, using acetophenone **56**, ethanol and ammonia over molecular sieves has been reported (Scheme 13).[44] With a yield of 12–31%, this procedure is not adapted for large scale syntheses. The most common method to prepare substituted phenyl-pyridine is the Stille cross coupling reaction (Scheme 13).[45]



Scheme 13

Extended phenyl-pyridine systems (4-styryl-2-phenylpyridine) can be easily prepared starting from substituted derivatives **60** and **62**. The syntheses of the styryl ligands **61** and **63** have been achieved either by

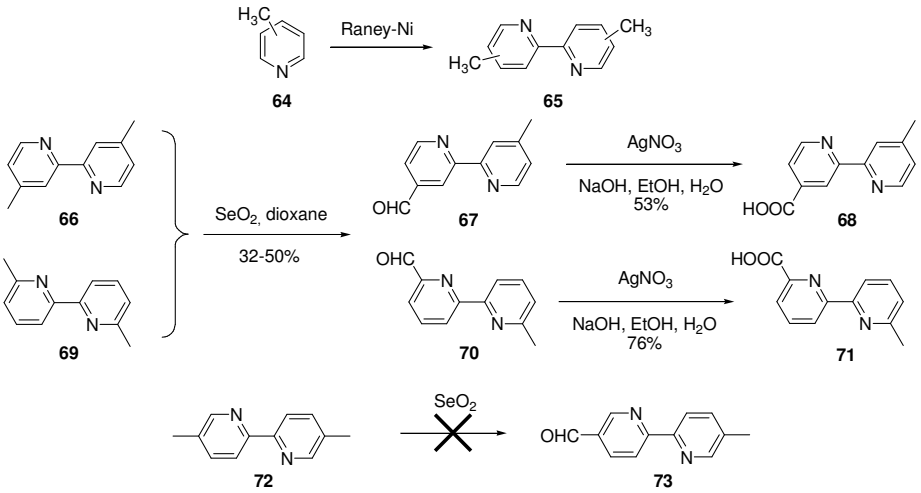
a Knoevenagel-type condensation between the appropriate aldehyde and 4-methyl-2-phenylpyridine **60** or by means of a Hörner-Wadworth-Emmons reaction between *p*-nitrobenzaldehyde and 4-diethylphosphonato-methyl-2-phenylpyridine **62** (Scheme 14).[46]



Scheme 14

2.2.2. Post-functionalization

The post-functionalization approach is a strategy that has been mainly developed for robust structures such as bipyridine and phenanthroline. This method often requires harsh conditions resulting in unsatisfactory yields and low tolerance towards functional groups. However, for bipyridine and phenanthroline, it constitutes an alternative strategy to introduce substituents such as an aldehyde, an acid or a bromomethyl group without the necessity of a multi-step synthesis. Nevertheless, as already stated previously, this is not the most convenient method to prepare dissymmetric ligands. Bipyridine **1** itself and its dimethyl-substituted derivatives **65** are undoubtedly the main starting reagents to generate functionalized bipyridine by post-functionalization. Dimethyl-2,2'-bipyridines are mainly obtained by reductive coupling of the corresponding pinacoline using Raney-Nickel alloy.

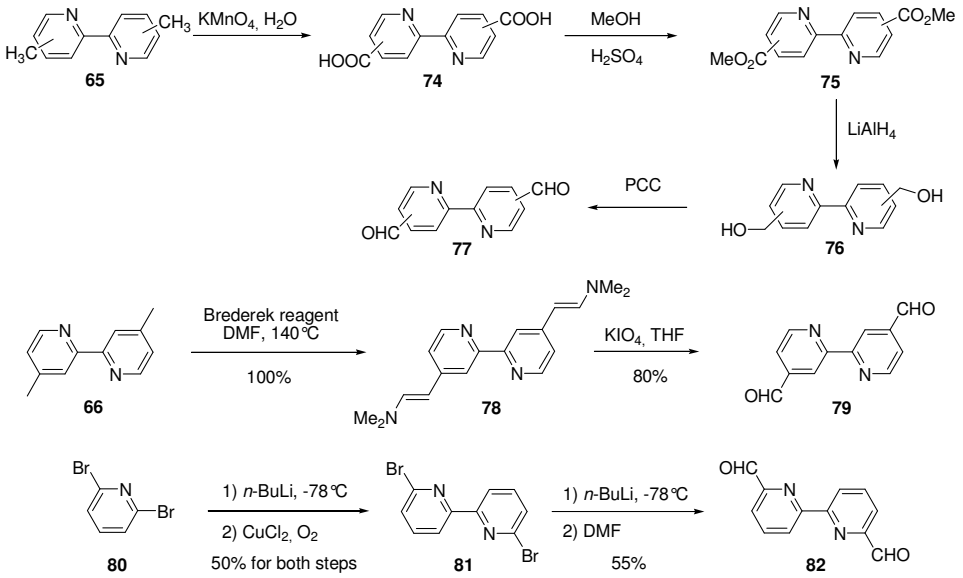


Scheme 15

The conditions to introduce a single aldehyde function on dimethyl-substituted 2,2'-bipyridine vary depending on the position of the methyl groups. One aldehyde function can be directly synthesized by the

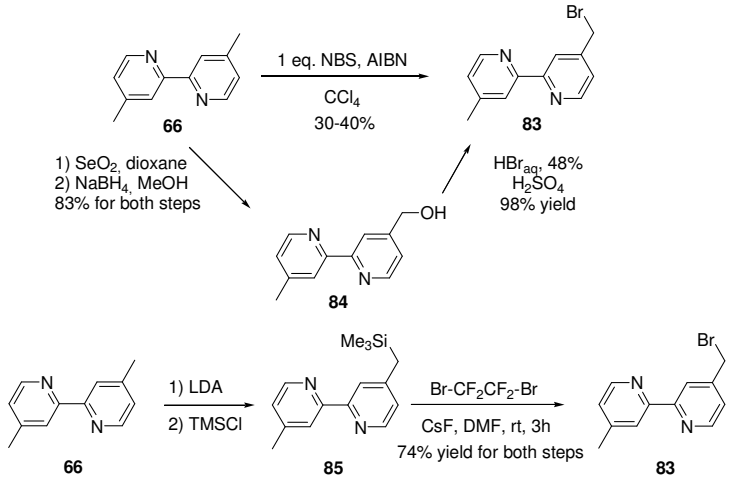
selective oxidation of one methyl group using selenium oxide, starting with 4,4'-dimethyl-2,2'-bipyridine **66** or 6,6'-dimethyl-2,2'-bipyridine **69**. Monoaldehydes **67**[25,47] and **70**[48] have been obtained in moderate yield (29–50%) and have been then converted to the corresponding monoacids **68**[46] and **71**,[49] respectively, using silver nitrate (Scheme 15). It has not been possible to isolate monoaldehyde **73** when the same reaction conditions are applied to 5,5'-dimethyl-2,2'-bipyridine **72**.

Several strategies have been developed to introduce two aldehyde functions in **65**. The typical one consists in oxidizing both methyl groups using $KMnO_4$, $K_2Cr_2O_7$ or CrO_3, followed by the esterification of the resulting acids **74**, the reduction of the resulting esters **75** in their corresponding alcohols **76** and finally the oxidation of the alcohols with various oxidants such as SeO_2, $KMnO_4$, PCC (pyridinium chlorochromate) or MnO_2 to afford dialdehydes **77** (Scheme 16). This four-step procedure gives the dialdehydes in low yields. A high yield two-steps synthesis has been developed to generate 4,4'-diformyl-2,2'-bipyridine **79**. Enamination of bipyridine **66** with Bredereck reagent *tert*-butoxy-*bis*-(dimethylamino)methane gave **78** in quantitative yield. Further oxidation of the enamine with potassium periodate provided **79** in 80% yield (Scheme 16).[46a,50] Introduction of two aldehyde functions in 3,3'- positions has been realized by monolithiation of 2,6-dibromopyridine **80** and oxidative coupling.[51] Double lithium-halogen exchange reaction followed by quenching with DMF afforded dialdehyde **82** (Scheme 16).[52] Substitution of bipyridine core by a formyl group has been widely studied in order to generate extended conjugated framework, notably valuable for NLO applications.



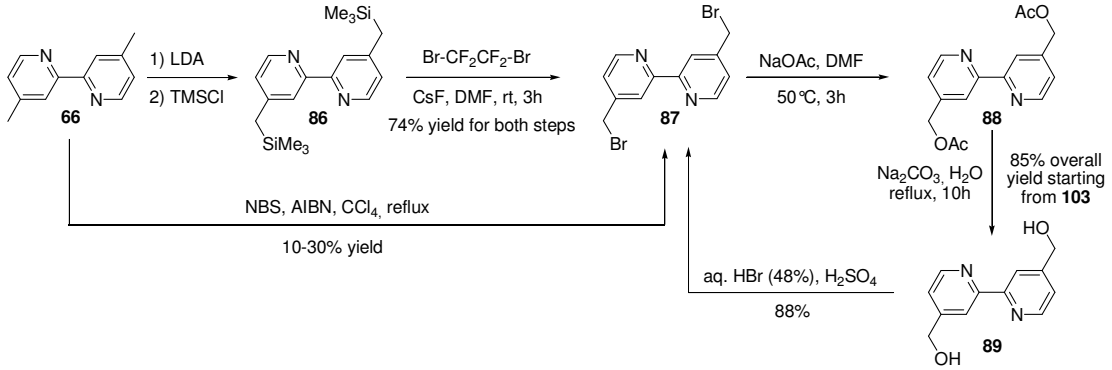
Scheme 16

Mono- and *bis*-bromination of 4,4'-dimethyl-2,2'-bipyridine **66** and 5,5'-dimethyl-2,2'-bipyridine **72** have been extensively studied and several variations of published procedures leading to improved yields have been recently reported. Monobrominated bipyridine **83** has been obtained in various yields by bromination of **66** with *N*-bromosuccinimide (NBS) and a radical initiator (AIBN, benzoyl peroxide) in CCl_4.[53,54] **83** has also been synthesized in high yield by halogenation of the alcohol **84** (Scheme 17).[46c] Improved synthesis by lithiation of **66**, silylation with trimethylsilyl chloride and bromination with 1,2-dibromotetrafluoroethane has been reported with an overall yield of 74% (Scheme 17).[55]



Scheme 17

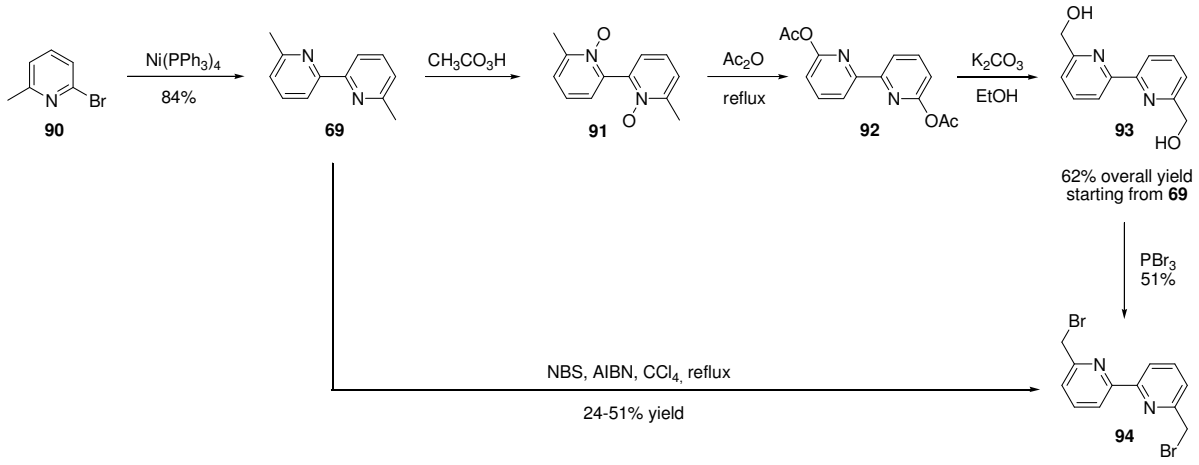
A similar procedure (lithiation, silylation and bromination) has been developed to synthesize 4,4'-dibromomethyl-2,2'-bipyridine **87**, starting from **66** and with an overall yield of 74%.[56] This overall yield is quite low, considering that a yield as high as 97% has been previously reported to convert **86** in **87**.[57] However, yields ranging from 10 to 30% had been previously obtained using former procedures to synthesize **87** starting from **66**.[58] **87** has also been used in an alternative procedure to prepare 4,4'-dihydroxymethyl-2,2'-bipyridine **89**, *via* the *bis*-ester **88**.[56] **87** has also been obtained from **89** by halogen substitution of the dialcohol **89** in 88% yield (Scheme 18).[59]



Scheme 18

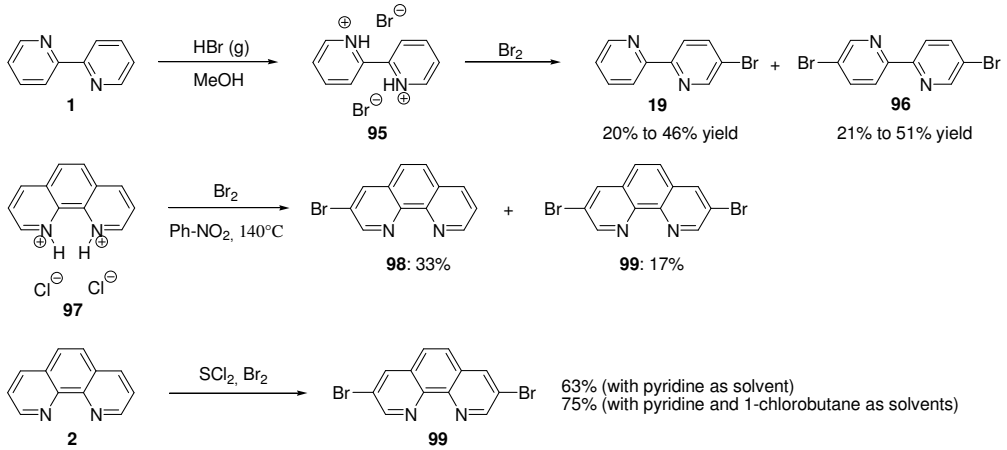
6,6'-*Bis*-bromomethyl-2,2'-bipyridine **94** has been prepared in five steps, starting from 6-bromo-2-methylpyridine **90** (Scheme 19).[60] 6,6'-Dimethyl-2,2'-bipyridine **69** has been obtained in 84% yield by reductive coupling using $Ni(PPh_3)_4$. The two methyl groups have been then converted into *bis*-methanol groups (62% overall yield) following the procedure described by Newkome.[61] *Bis N*-oxide **91** has been readily prepared by treatment of **69** with an excess of peracetic acid. **91** has been then refluxed with acetic anhydride to afford the *bis*-ester **92**. Treatment of **92** with potassium carbonate in ethanol induced a complete transesterification. 6,6'-*Bis*-(hydroxymethyl)-2,2'-bipyridine **93** has been further transformed into 6,6'-*bis*-bromomethyl-2,2'-bipyridine **94** with PBr_3, using the standard method (51% yield). Bromination of **69** allows for the direct synthesis of **94** in similar yields (24–51% yield) compared to the five steps

procedure. However, this method results in the formation of side products that are often difficult to separate.[62]



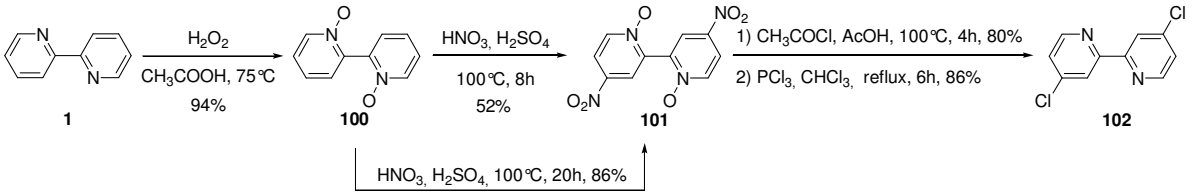
Scheme 19

Halogenation of 2,2'-bipyridine (5,5'- positions) and 1,10-phenanthroline (3,8- positions) constitutes a key-step for the functionalization of these ligands. Similar strategies have been used to prepare both halogenated ligands. These strategies lead to tedious work-up, for example to remove the side products by column chromatography, low yields and problems of reproducibility. Consequently, this crucial step is still under intensive investigations. Monobrominated bipyridine **19** has been obtained with yields ranging from 20%[56] to 46%[22] and *bis*-brominated bipyridine **96** with yields ranging from 21%[63] to 51%[22] (Scheme 20). *Mono*- and *bis*-bromination of 1,10-phenanthroline **2** have been performed with bromine in nitrobenzene, using the hydrochloride derivative of **2**, but proceeded in low yield (Scheme 20).[64] Improvement of this reaction has been proposed with sulfur dichloride and pyridine (63% yield).[65] It has to be noticed that the direct chemical modification of the 1,10-phenanthroline backbone has not been widely investigated and only few examples of regioselective introduction of substituents are known.[66] Sauvage *et al.* have published a modified procedure to prepare 3,8-dibromo-1,10-phenanthroline **99**, improving the yield from 63% to 75% by using pyridine and 1-chlorobutane as solvents (Scheme 20).[67]



Scheme 20

Halogenation of **1** (4,4'- positions) has been easily realized using its *N*-oxide derivative **100**. Bipyridine **102** has been obtained in moderate yield by nitration of **100** and subsequent conversion of the nitro groups into halogens.[68] The nitration of **100** had been previously reported with a higher yield by elongation of the reaction time (Scheme 21).[69]

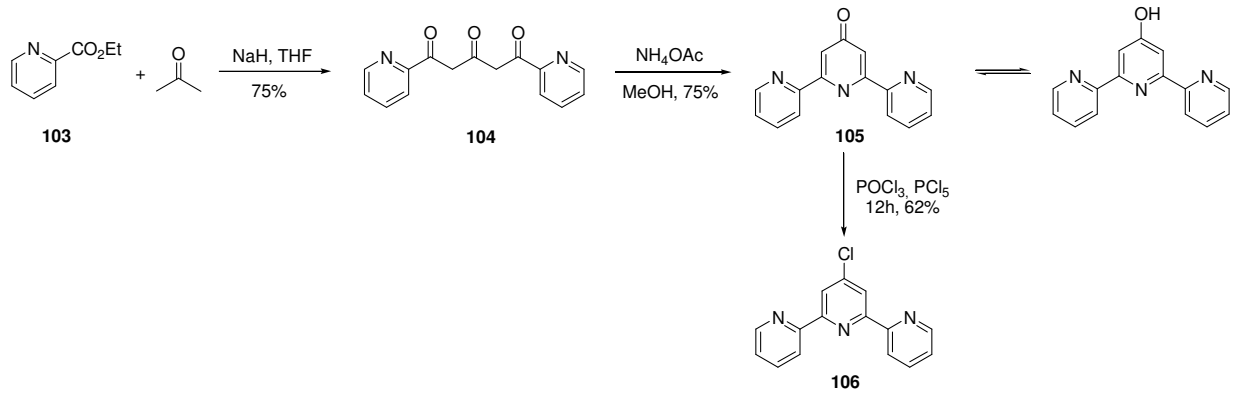


Scheme 21

2.3. Synthesis of tridentate ligands

2.3.1. Cyclisation

Strategies to prepare symmetrically or unsymmetrically substituted terpyridines are indeed different but they also depend on the nature of the substituent in the 4- position. For symmetric terpyridines, introduction of an hydroxyl or a chlorine group in the 4- position has been realized according to the following procedure: reaction of ethyl 2-pyridinecarboxylate **103** with acetone in the presence of a base afforded 1,5-dipyridin-2-yl-pentane-1,3,5-trione **104** in 75% yield.[70a] 2,6-*Bis*-(2'-pyridyl)-4-pyridone **105** has then been obtained by ring closure using ammonium acetate in methanol. Finally, prolonged reflux of **105** with PCl_5 in boiling $POCl_3$ generated chloroterpyridine **106** in 62% yield (Scheme 22).[70]

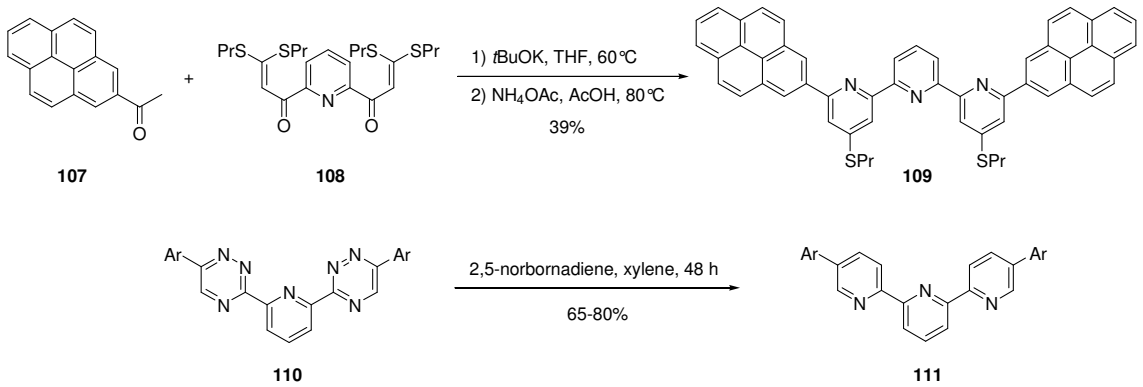


Scheme 22

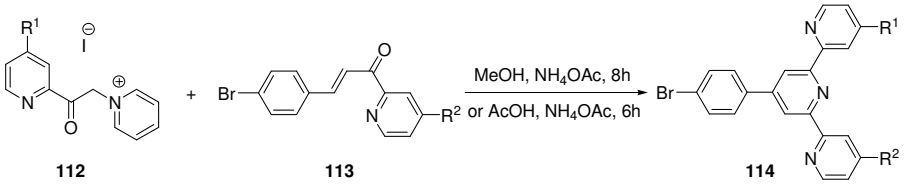
Reaction between a central pyridine bearing a *bis*-Michael acceptor unit and two equivalents of acetyl derivatives have been used to synthesize the symmetrically substituted terpyridine **109** (Scheme 23). This procedure, initially developed by Potts,[71] is at the root of several opto-mechanical supramolecular devices recently prepared by Lehn *et al.*[72a] Another method has been developed to obtain terpyridines, without substituent on the central pyridine, *via* an aza-Diels-Alder reaction, starting from 1,2,4-triazines (Scheme 23).[72b]

For symmetric terpyridines substituted by an aromatic ring in the 4- position, the main strategies are ring assembly and coupling methodology. The most common ring assembly based method is the Kröhnke

procedure or its various improved procedures.[73] Several modifications of the initial approach, based on the condensation of a *N*-heteropyridinium salt with enones in ammonia, have been introduced and unsymmetrical terpyridines can now be prepared.[74] The procedure developed by Newkome *et al.* is convenient for the synthesis of mono and symmetrically or asymmetrically disubstituted 4'-(4-bromophenyl)terpyridine.[75] Reaction of the pyridinium salt of the modified 2-acetylpyridines **112** with functionalized 4-bromo-aza-chalcones **113** *via* a Michael-type addition, followed by ring closure with ammonium acetate, afforded unsymmetric terpyridines **114** with yields ranging from 33 to 73% (Scheme 24).

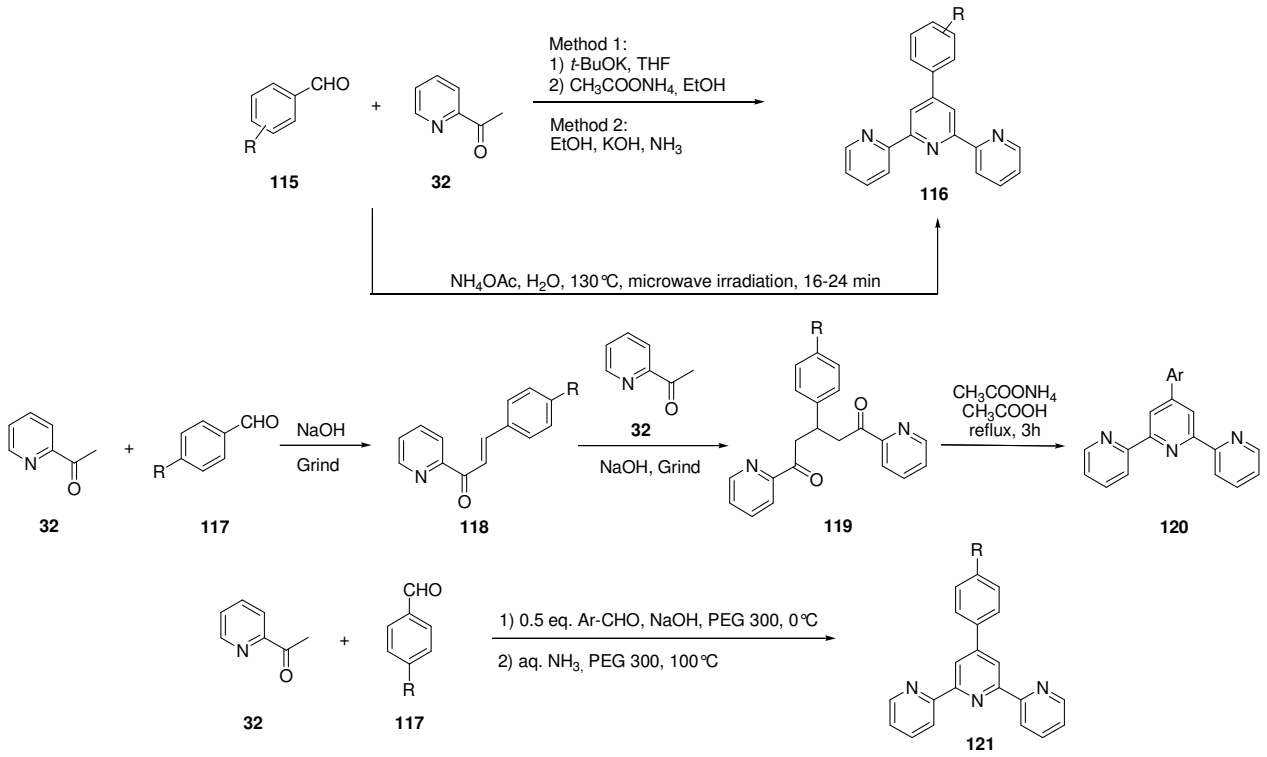


Scheme 23



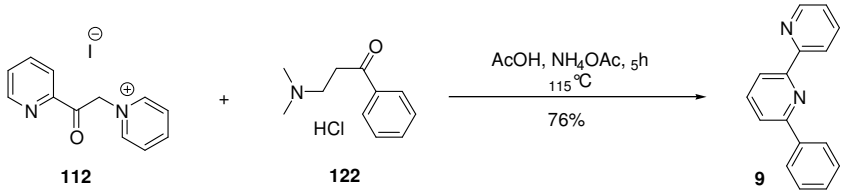
Scheme 24

Other approaches have been developed to prepare terpyridines bearing an aromatic ring in the 4- position. The method developed by Constable *et al.* is based on the condensation of an aromatic aldehyde **115** with 2-acetylpyridine **32** in THF and in the presence of a base, followed by ring closure with ammonium acetate in refluxing alcohol under aerobic conditions (method 1).[75] A sequential solvent-free version of this procedure, based on the grinding of the reactants, has also been published.[76] A one-pot synthesis has also been described in which aldehyde **115** and 2-acetylpyridine **32** are mixed together with a base in a mixture of solvents (ammonia and alcohol, method 2).[77] Microwave-assisted high-speed chemistry can also be used to prepare terpyridines. A one-pot reaction of 2-acetylpyridine **32**, aromatic aldehydes and ammonium acetate in glycol under microwave irradiation and without catalyst was investigated.[78] Terpyridines were obtained in high yields ranging from 81 to 91%. Recently, an environmental friendly version of this reaction was developed in water and terpyridines were obtained in similar yields (Scheme 25).[79] A green and straightforward synthesis of 4-substituted terpyridines **121** involves the reaction of the enolate anion of 2-acetylpyridine **32** with aromatic aldehydes **117**, followed by oxidative cyclization in the presence of concentrated aqueous ammonia.[80] The reaction is performed in polyethylene glycol (PEG 300) and ammonia (Scheme 25).

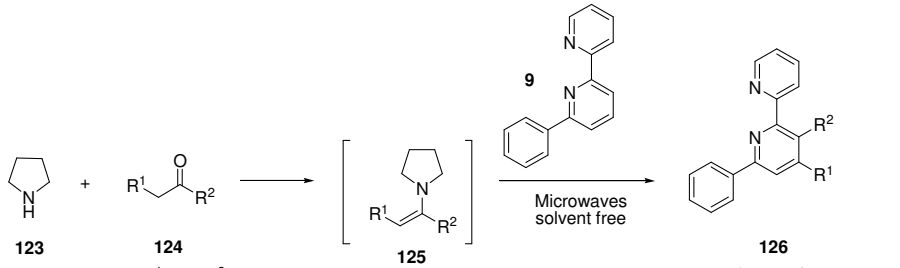


Scheme 25

6-Phenyl-2,2'-bipyridine **9** has been synthesized in a similar way as described above for terpyridines. **9** has been isolated in 76% yield by reaction of [2-(2-pyridyl)-2-oxoethyl]pyridinium iodide **112**, dimethyl(3-oxo-3-phenylpropyl)ammonium chloride **122** and ammonium acetate in acetic acid (Scheme 26).[81]



Scheme 26



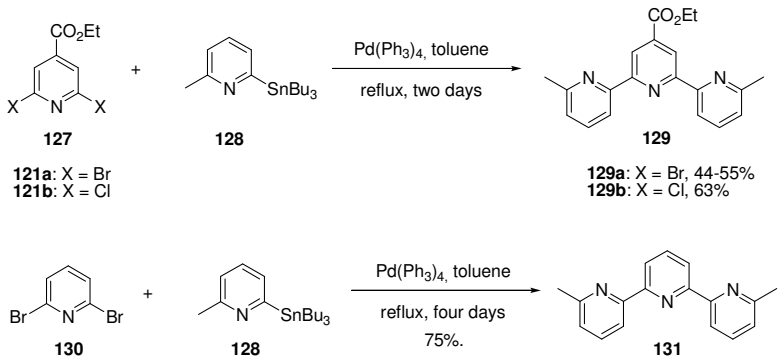
Scheme 27

Improved methodology for the preparation of disubstituted 6-phenyl-2,2'-bipyridine **126** has recently been developed from 1,2,4-triazine derivatives *via* the inverse-electron-demand Diels-Alder reaction. The

interest of this reaction lies in the fact that this microwave-promoted, solvent-free route affords **126** in good yields with relatively short reaction times and avoids the need of a separate aromatization step (Scheme 27).[82]

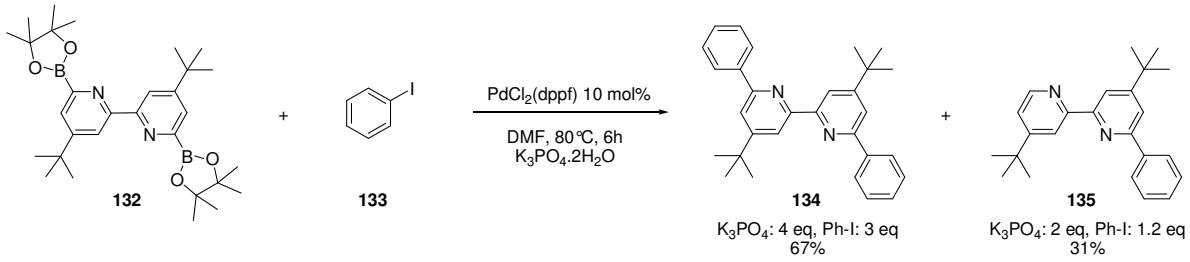
2.3.2. Coupling reactions

In the family of tridentate ligands, terpyridine derivatives have been extensively studied and remain the focus of considerable attention. The recent synthetic approaches to prepare terpyridines consist in cross-coupling reactions, and Stille coupling is the most widely used.[83] Yields obtained with such reactions are highly dependent on the nature of the substituent on the central pyridine (Scheme 28).



Scheme 28

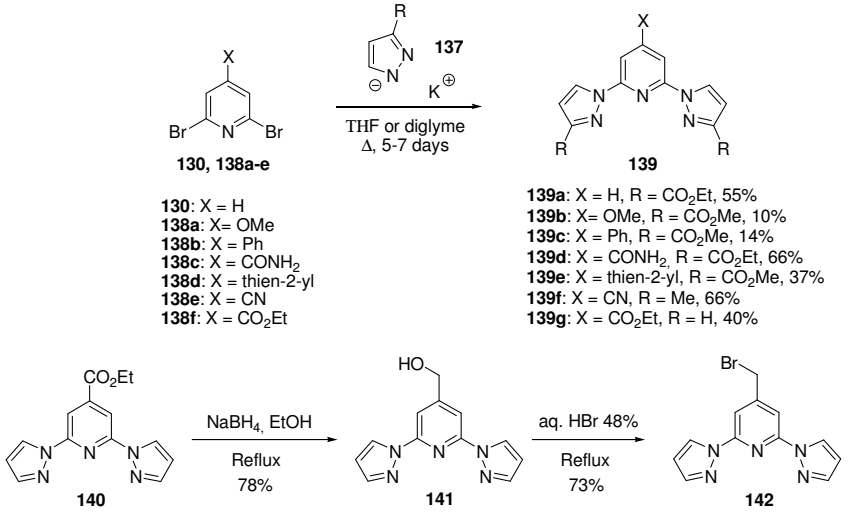
Suzuki cross-coupling reaction has also been used for the synthesis of substituted 6-phenyl-2,2'-bipyridine **135**.[84] Starting from **132**, monosubstituted **135** and disubstituted **134** have been obtained by controlling the number of equivalents of phenyl iodide and base (Scheme 29). **132** had been elegantly obtained by the regioselective borylation of 4,4'-*tert*-butyl-2,2'-bipyridine in *ortho* to the nitrogen atoms.



Scheme 29

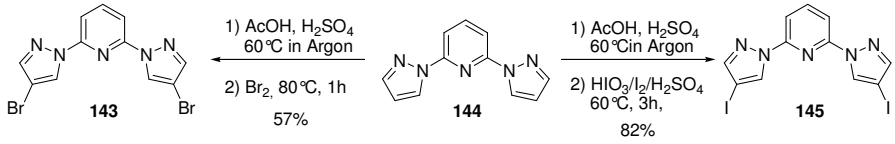
Parallel to the terpyridine derivatives chemistry, recent years have witnessed the rapid development of pyridine-centred ligands containing heteroatomic five-membered rings. The most common method to prepare 2,6-di(pyrazol-1-yl)pyridines **7** is the nucleophilic coupling of deprotonated pyrazole with 2,6-bromopyridine **130**, even if the use of 2,6-dichloropyridine **136** leads to similar yields of 85% and 80%, respectively (Scheme 30).[85] When a 3-(5-substituted)pyrazole ring has been used, a mixture of regioisomeric products has been obtained and, in all cases, the mono-substituted pyridine is obtained as a by-product. This coupling has proved to be highly dependent on the nature of the substituent on the pyridine ring. Up to now, the only substituents that have been introduced in the 4- position of the pyridine ring are OMe, Ph, $CONH_2$,

thien-2-yl, CN and CO_2Et (Scheme 30).[85] **141** and **142**, bearing a hydroxymethyl and a bromomethyl group, respectively, in the 4- position of the central pyridine ring have been recently obtained by reduction of **140** in ethanol with $NaBH_4$ for **141**, followed by bromination in refluxing conditions for **142** (Scheme 30).[86]



Scheme 30

Functionalization of the 4'- and 4''- positions of the pyrazole groups has been successfully realized by halogen exchange on 2,6-di(pyrazol-1-yl)pyridine **143**, in a one-pot synthesis, and led to symmetrically substituted 2,6-di(pyrazol-1-yl)pyridines (Scheme 31).[87] **144** and **145** are indeed interesting synthons for further functionalization.

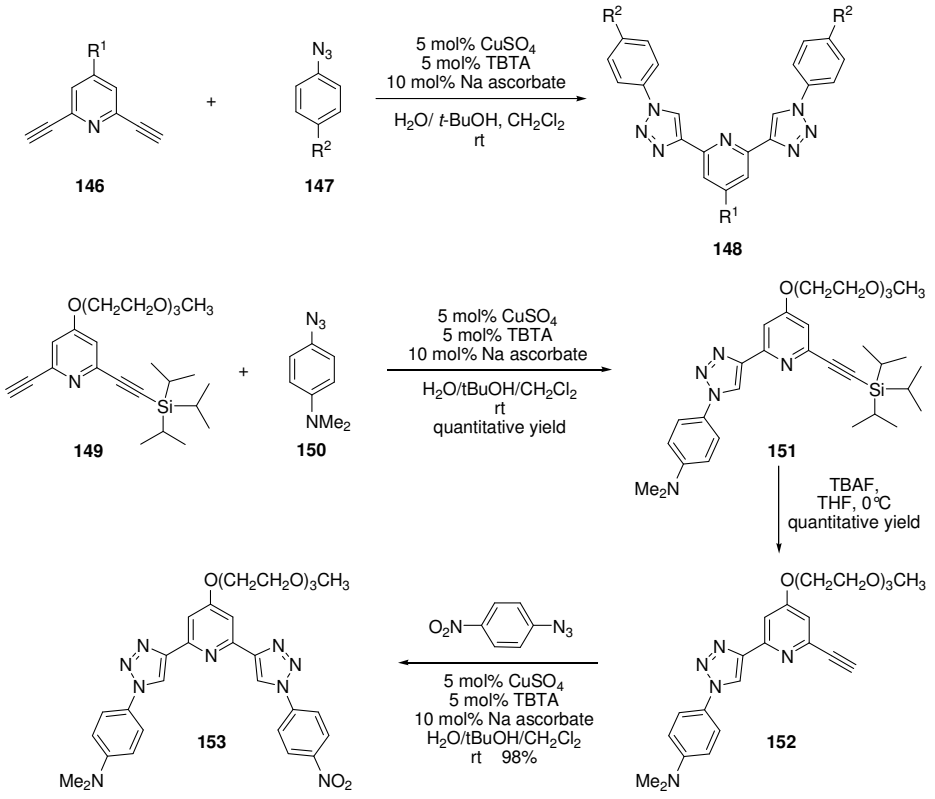


Scheme 31

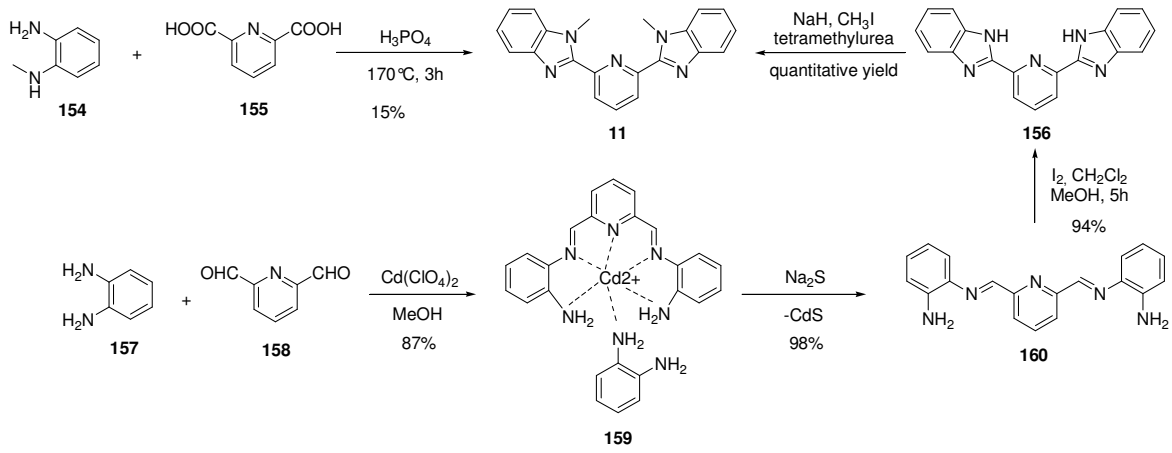
Recently, a new family of chelating ligand named "clickates" has been reported.[16] Their synthesis has been realized in high yield by click chemistry between 2,6-diethynyl-4-substituted pyridines **146** and aryl azides **147** (Scheme 32). Authors also proved this method to be suitable to prepare symmetrical and unsymmetrical ligands. The dissymmetry has been generated by sequential coupling using in the first step the monodeprotected 2,6-diethynylpyridine **149** (Scheme 32).[16] A similar procedure has been described to substitute the triazole moiety by alkyl chains.[88]

2,6-*Bis*-(1-methyl-benzimidazol-2-yl)pyridine **11** has been used to isolate metal complexes exhibiting photoluminescence properties.[89] The synthesis of **11** was first reported in 1987 by condensation of *N*-methylbenzene-1,2-diamine dihydrochloride **154** with pyridine-2,6-dicarboxylic acid **155** in H_3PO_4 at 170 °C (15% yield). Recently, a three-step synthesis of 1H,1H'-2,2'-pyridine-2,6-diyl-*bis*-benzoimidazole **156** has been reported.[90] Using this procedure, **156** has been obtained with an overall yield of 80% starting from **157** and **158** (Scheme 33). Condensation of 1,2-diaminobenzene **157** with 2,6-diformylpyridine **158** in the presence of $Cd(ClO_4)_2$ afforded the polydentate Schiff's base **159**. Reaction of **159** with sodium sulfide afforded the free ligand **160**, which has been then oxidized with iodine in methanol to give **156**. **156** can then

be alkylated using iodomethane, sodium hydride and tetramethylurea and therefore constitutes a key-intermediate for the synthesis of **11**.[91]



Scheme 32



Scheme 33

3. Applications

3.1. Optical properties

3.1.1. Nonlinear Optical (NLO) materials

Coordination compounds are of particular interest for the design of new dyes with large second-order nonlinear optical (NLO) susceptibilities. Metallic complexes based on lanthanide[92] or d-transition metal, proved to exhibit high dipolar[93] or octupolar[94] nonlinearities response. However, the understanding of the

electronic origin of increased second-order NLO properties is still limited and far from being rationalized in terms of preferred molecular architectures, so that intensive researches are still conducted to prepare metal complexes with high NLO activity.[95] Polypyridinic ligands have largely contributed to the development of a variety of NLO-phores based on metal complexes.[95] The first demonstration of their potential use for NLO applications was reported by Zyss *et al.* and concerned the $Ru(bpy)_3^{2+}$ complex.[96] By modifications of the bipyridinic core, Le Bozec *et al.* have significantly contributed to the molecular engineering around 4,4'-substituted-2,2'-bipyridine and they have also characterized the ruthenium complex with the highest quadratic optical nonlinearity ever obtained.[97] These modifications have been now extended to the terpyridinic ligands in order to coordinate, for example, lanthanide ions.[92,98] In this section, we will focus on the most commonly used 4,4'-disubstituted-2,2'-bipyridine and terpyridine derivatives as well as their syntheses to obtain highly active NLO complexes.

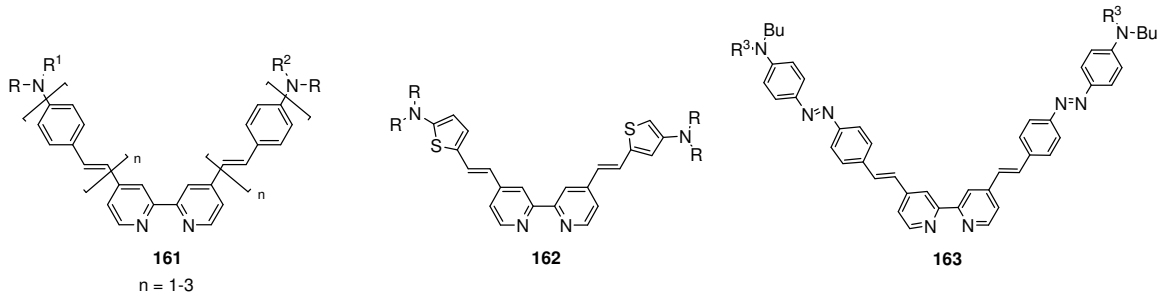
3.1.1.1. Molecular engineering based on 4,4'-substituted-2,2'-bipyridine

All molecules having a large second order NLO response are characterized by their hyperpolarizability coefficient β, and contain a π-conjugated chain which serves as a bridge for the mobile electrons between an electron donor (D) and an electron acceptor (A) functionality.[99] Electron releasing moieties are generally composed of dialkylaminoaromatic groups, such as phenyl or thienyl systems and the π-bridge system is characterized by the presence of oligophenylenevinylene or oligovinylene π-conjugated backbones. Contrary to the purely organic push-pull molecules exhibiting a well-defined acceptor moiety, the electron withdrawing group of the chelating ligand in coordination complexes is only generated by coordination of the pyridine moiety with the metal. Substitution of the 2,2'-bipyridine on its 4,4'- positions has been performed in order to establish an optimal communication between the donor and the acceptor moieties. A similar approach has been previously used with purely organic push-pull molecules[100,101] and this strategy has been now extended to prepare three-dimensional NLO-phores.[102]

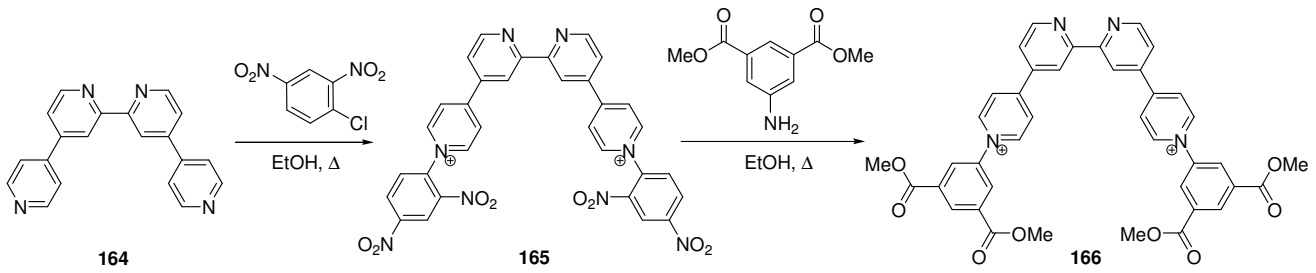
The most convenient method to synthesize a large variety of 4,4'-substituted-2,2'-bipyridines with an electron donating moiety in conjugation with the pyridine group is to use the 4,4'-dicarboxaldehyde-2,2'-bipyridine. The final ligand is then obtained by a Hörner-Wadsworth-Emmons condensation or a Wittig reaction of the appropriate phosphonates ($RCH_2P{=}O(OMe)_2$) or phosphonium ($RCH_2P(Ph)_3^+$) with the dialdehyde. Le Bozec *et al.* prepared a series of ligands using this strategy (Scheme 34). The aim was to finely tune the NLO response of the final complexes as a function of the nature of the donating substituents, the metal and the conjugated spacer. Ligands **161** have been used to generate supramolecular assemblies and polymers.[95,103,104] This study showed an enhancement of the NLO response of the ruthenium complexes when the number of ruthenium centres was increased from one (monomer) to seven (heptamer) and a decrease of the NLO response between the heptamer and the polymer (14 ruthenium centres). **163** differs from **161** and **162** by the presence of an azobenzene group. This function, which is introduced before the final coupling with the substituted bipyridine, allows the incorporation of photoactive molecules in polymer matrices with an acentric arrangement of the metallo-octupolar units obtained by the so-called "all-optical poling".[103,105]

Several 4,4'-(π-conjugated)substituted-2,2'-bipyridines have also been prepared to act as "push-pull" systems for third order NLO applications.[102] The starting bipyridine **1** was substituted in 4,4'- positions by two pyridine units affording **164**. **164** has been then reacted with 2,4-dinitrochlorobenzene in ethanol to form

the activated substituted quaterpyridinium **165**. Ligand **166** has been finally obtained after addition of an excess of dimethoxy-5-aminoisophthalate to **165** in ethanol at reflux (Scheme 35).



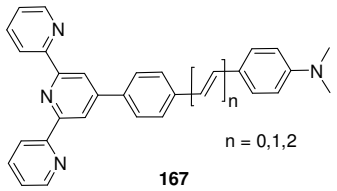
Scheme 34



Scheme 35

3.1.1.2. Molecular engineering based on 2,2':6',2''-terpyridine

A variety of terpyridine derivatives have been used for NLO applications. In ligand **167**, the electron donor group, namely a dialkylaminophenylene group, is covalently linked to the terpyridine fragment by a bridging polyenic spacer (Scheme 36). **167** was obtained by a Hörner-Wadworth-Emmons condensation of 4-(2,2':6',2''-terpyridyl-4')-benzyltriphenyl phosphonium with the appropriate carboxaldehyde.[106,107]

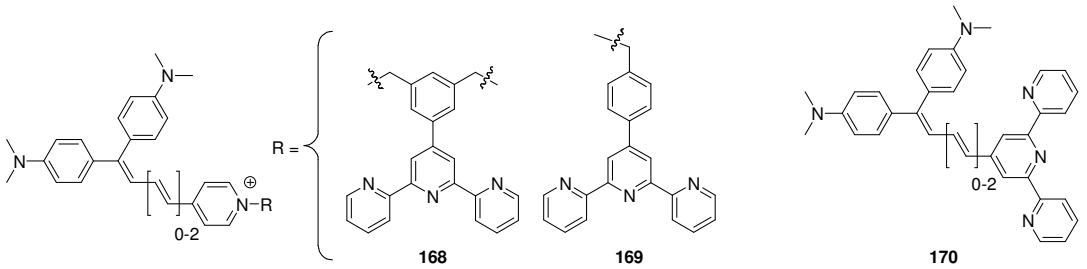


Scheme 36

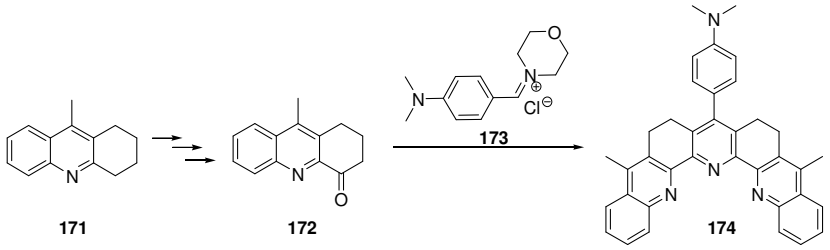
Based on Michler's ketone, two different approaches have been developed to prepare new stilbazolium -like dyes potentially valuable for quadratic NLO applications (Scheme 37). The first one consists in the covalent linkage of purely organic chromophores to a terpyridine group. The second one is based on the substitution of the terpyridine core by a donating group using a spacer of variable length.[108]

NLO properties of lanthanide complexes of terpyridyl-like ligand **174** have been recently studied. **174** has been synthesized from acridine **171**. One ketone function has been introduced by a multistep reaction to

give **172**. Reaction between **172** and iminium chloride **173**, followed by cyclisation in the presence of an excess of ammonia, afforded **174** after purification by column chromatography (Scheme 38).[92]



Scheme 37



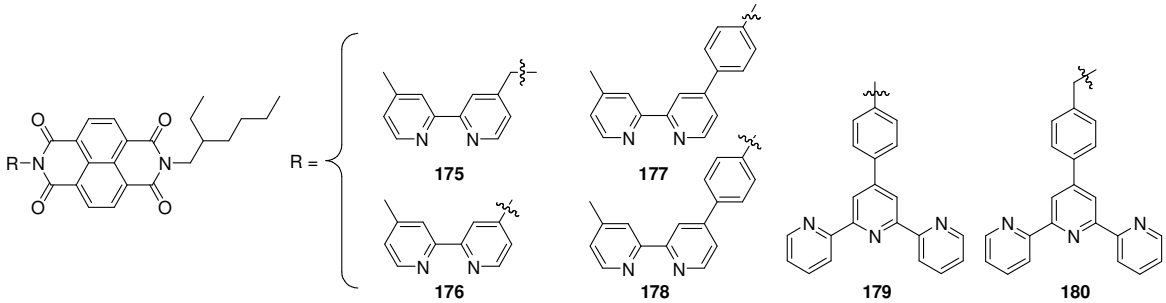
Scheme 38

3.1.2. Luminescence properties

Many publications are available on polypyridinic ligands used for luminescence applications or used as photosensitizers for dye-sensitized solar cells. In this section, we will only focus on the latest developments in the design of polypyridyl ligands for this type of applications.

3.1.2.1. Bipyridines and terpyridines with naphthalene subunits

Many efforts have been devoted to the functionalization of polypyridinic ligands with a naphtalene group. This type of systems indeed allows for the formation of electron donor-acceptor dyads (Scheme 39).[24] The grafting of the naphthalene unit, using flexible linkers, has been realized by condensation of an aminopolypyridine with the naphthalic anhydride group.

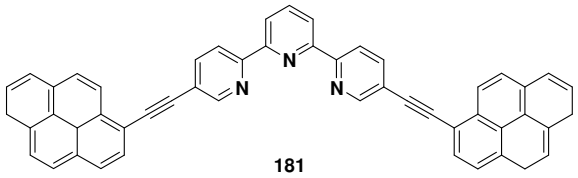


Scheme 39

3.1.2.2. Terpyridines with pyrene subunits

The photophysical properties of ruthenium(II) *bis*-terpyridine complexes are often less attractive than their analogous ruthenium(II) *tris*-bipyridine complexes, especially their luminescence properties at room

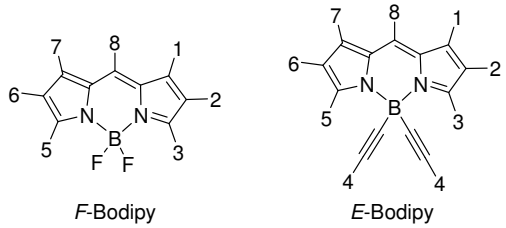
temperature. However, addition of adapted chemical groups can drastically improve these photophysical properties, as in the case of the pyrene group.[109] Synthesis of **181** (Scheme 40) has been realized by a Sonogashira reaction between ruthenium complexes of the 5,5"-dibromo-2,2':6',2"-terpyridine and the 1-ethynyl-pyrene. Incorporation of an ethynyl junction between the central terpyridine and the pyrene groups considerably improved the luminescence properties of the ruthenium complexes.[110]



Scheme 40

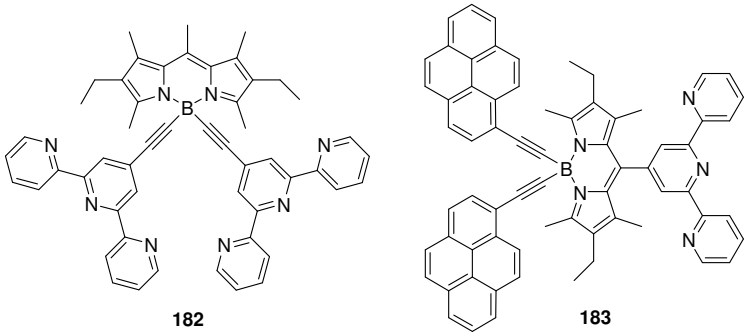
3.1.2.3. Polypyridines with boron dipyrromethene dyes

Among organic fluorescent molecules, the bodipy family is well-known as luminescent tag and as laser dye.[111] Incorporation of bodipy in chelating ligands has been achieved by Ziessel *et al*. Two main families of Bodipy are listed and represented in Scheme 41, the *F*-Bodipy and *E*-Bodipy.



Scheme 41

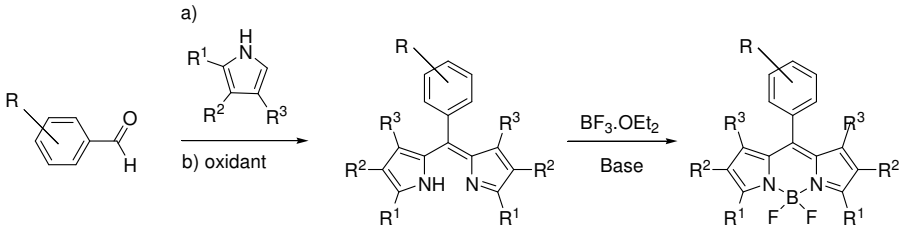
In the *E*-Bodipy family, the functionalization of the 4- position has been only described with 4'-ethynyl-terpyridine.[112] **182** has been obtained by reaction of *F*-Bodipy with lithium acetylides of terpyridine in THF. In **183**, one terpyridine group has been inserted at the 8- position while pyrene groups occupy the two 4- positions (Scheme 42).[113]



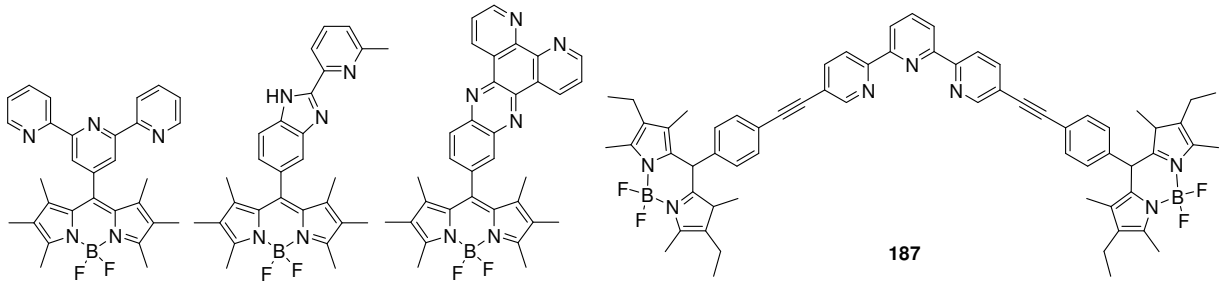
Scheme 42

For the *F*-Bodipy family, their functionalization by chelating ligands was easier since the synthesis of dipyromethane requires a carboxaldehyde function, as outlined in Scheme 43. Consequently, *F*-Bodipy

functionalized at the 8- position by a variety of bidentate and tridentate polypyridine ligands have been characterized (Scheme 44).[111]



Scheme 43



Scheme 44

3.1.3. Photochromism

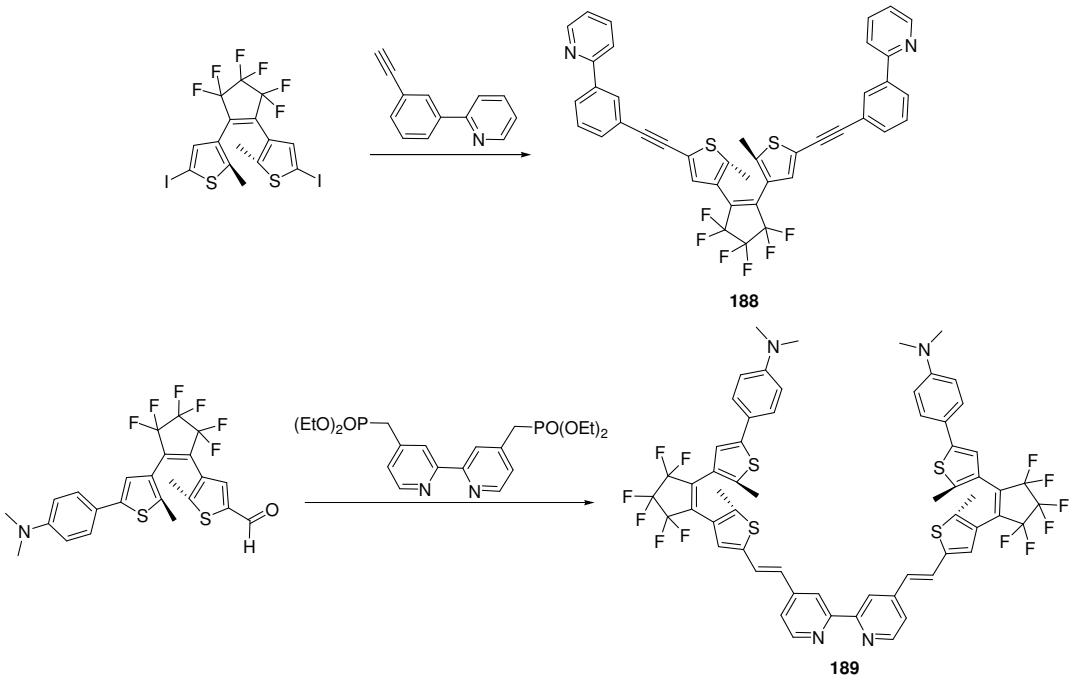
Photochromic compounds are extensively studied due to their potential application in optical memory, data storage or photoswitchable nonlinear optical devices.[114] Comparatively, photochromic species containing polypyridine ligands have only been scarcely described. Three illustrative examples are presented below.

3.1.3.1. Dithienylethene

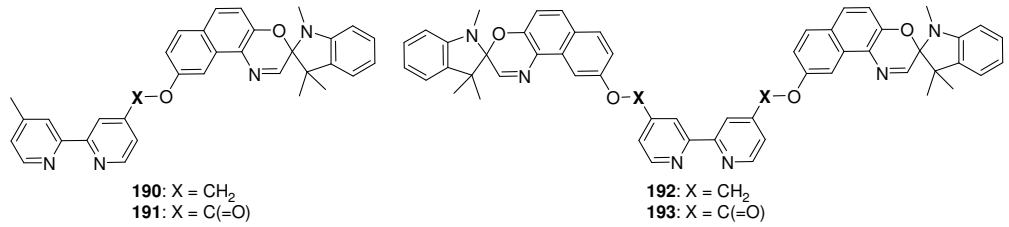
Dithienylethene (DTE) derivatives have been first described in 1988 by Irie and Mohri.[115] They display a variety of valuable properties ranging from photochromism to electrochemical and nonlinear optical properties.[116] In **188**, the DTE links two 2-phenylpyridine groups through an ethylenic function. **188** has been obtained by a Sonogashira coupling reaction (Scheme 45).[117] In **189**, two DTEs have been fixed at the 4,4'- positions of a central bipyridine. **189** has been synthesized using a Hörner-Wadworth-Emmons reaction of DTE-carboxaldehyde with 4,4'-*bis*-(phosphonate)bipyridine (Scheme 45).[118]

3.1.3.2. Spirooxazine

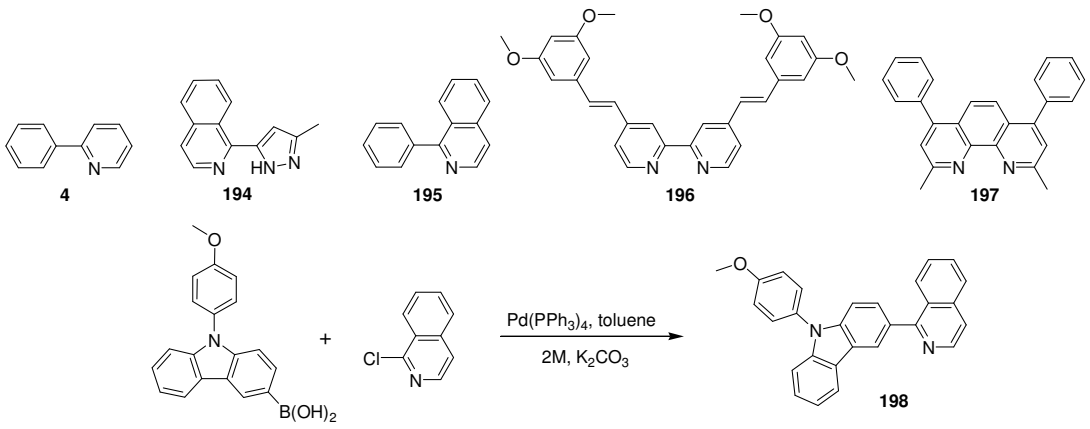
Spirooxazines are a second class of photochromic molecules with high fatigue resistance and photostability.[119] 2,2'-Bipyridine has been functionalized by spirooxazine through an ester function or an ether function at the 4,4'- positions. Symmetric and unsymmetric 2,2'-bipyridine precursors such as mono- and di-carboxybipyridine or mono- and di-bromomethylbipyridine allowed for the synthesis of mono- and di-functionalized bipyridine **190–193** (Scheme 46).[120]



Scheme 45



Scheme 46



Scheme 47

3.1.4. Organic light emitting diodes (OLEDs)

Since the report of Tang and VanSkyle on the first thin film hetero-junction organic light emitting diode (OLED),[121] considerable efforts have been devoted to this application. OLEDs using phosphorescent materials are mostly designed with iridium(III) or ruthenium(II) complexes. Ligands used in these

complexes are based on 2-phenylpyridine **4**,[122] isoquinolylpyrazolate **194**[123] or isoquinolylphenyl **195**[124] derivatives. These ligands are obtained by cross-coupling reactions, as illustrated for the synthesis of **198** (Scheme 47).[125] A blue organic light-emitting diode was prepared using the highly fluorescent 4,4'-di-(2-(2,5-dimethoxyphenyl)ethenyl)-2,2'-bipyridine **196**.[126] **196** has been synthesized in a one-pot procedure by condensation of 4,4'-dimethyl-2,2'-bipyridine **66** with 2,5-dimethoxybenzaldehyde in the presence of potassium *t*-BuOK. Blue-red,[127] white phosphorescent[128] and orange-red light-emitting diodes[129] were obtained with bathocuproine **197** (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline).

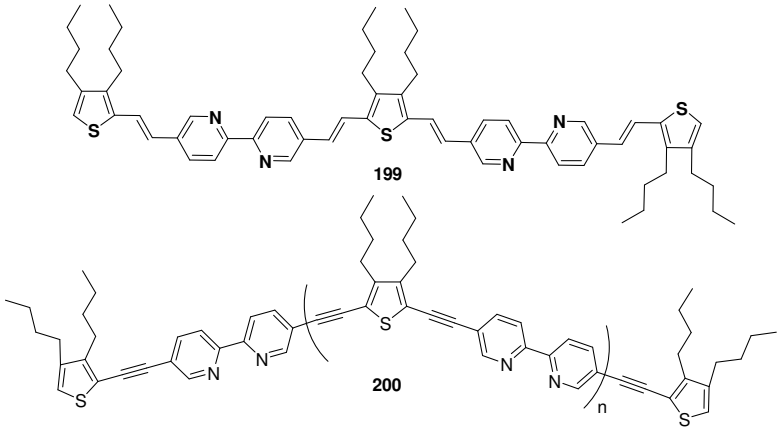
3.2. Towards inorganic polymers

A great attention is currently devoted to the synthesis of polynuclear transition-metal complexes for their photochemical, photophysical and electrochemical properties.[130]

3.2.1. Oligomers

3.2.1.1. Linear oligomers

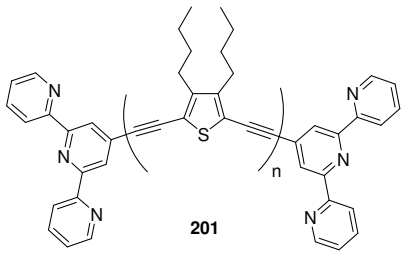
Many oligomers have been designed for long-distance electron transfers. An example has been provided by Ziessel *et al.* with the synthesis of various ethenylthiophene-bipyridine ligands. In these oligomers, prepared by Sonogashira coupling, bipyridine units are covalently linked to each others by a *bis*-ethenylthiophene spacer (Scheme 48).[131,132] The connection between the chelating groups can also be ensured by vinylic functions.[133] In these systems, alkyl chains have been introduced on the thiophene rings in order to improve the solubility of the overall assembly. It has to be noted that only symmetric oligomers are generated by cross-coupling reactions. Indeed, polynuclear assemblies have been then obtained by reaction of these oligomers with metal ions.



Scheme 48

In the case of main-chain metal-containing oligomers, the metallic cation ensures the formation of the oligomers by connecting the ligands, containing two chelating groups, to each others. In that case, the properties of the oligomers are determined by the physico-chemical properties of the metal complexes, and the structure and the orientation of the coordinating sites determine the architecture of the oligomer. The electronic communication between metallic complexes is ensured by the spacer used in each ligand. Several terpyridine ligands such as **201** have been prepared and further used for the synthesis of main-chain metal-

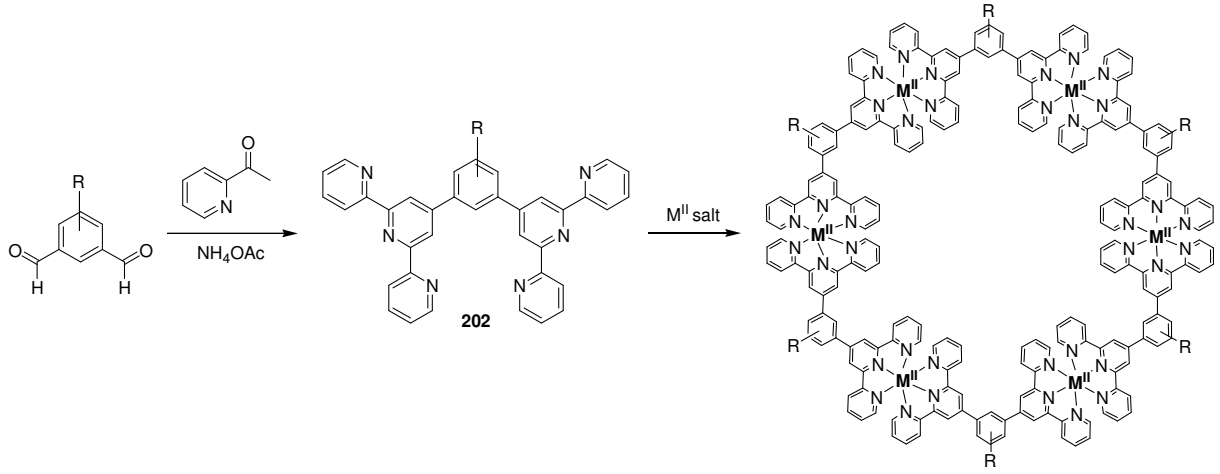
containing oligomers (Scheme 49).[134] Once again, alkyl chains have been introduced on the thiophene rings to improve the solubility of the final systems.



Scheme 49

3.2.1.2. Cyclic oligomers

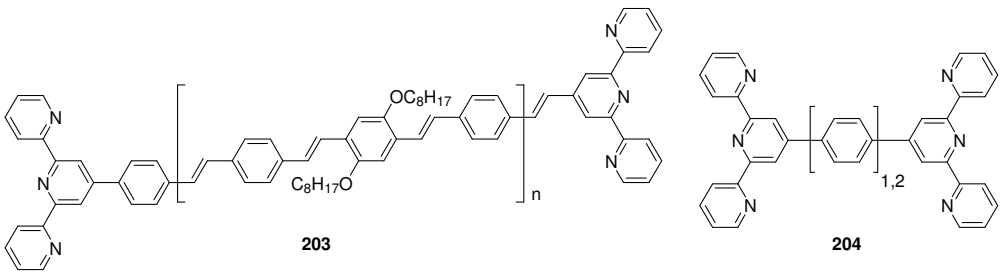
Cyclic metallic hexamers prepared with *bis*-terpyridine ligands have been recently reported by Newkome *et al.*[135] The strategy developed to synthesize the *bis*-terpyridines involved a double Kröhnke reaction of 3,5-phenylene-*bis*-carboxaldehyde with four equivalents of 2-acetylpyridine, followed by a cyclisation with ammonium acetate in excess.[136] Ligands **202** thus generated have been then reacted with metal ions to generate hexametallic complexes (Scheme 50).



Scheme 50

3.2.2. Molecular wires

In polymer electronic devices, metallic complexes are used for their specific optical and electrochemical properties. In this field of research, *bis*-terpyridines are extensively studied due to their topology perfectly adapted for the generation of linear polymetallic complexes.



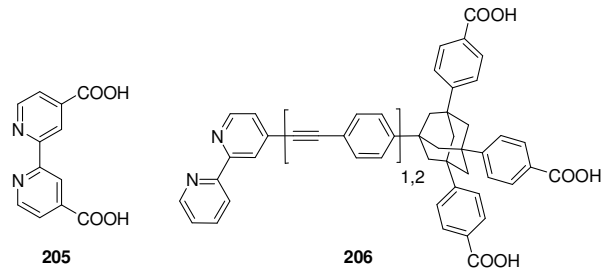
Scheme 51

The two terminal chelating terpyridine groups can be connected *via* a variety of fully conjugated spacers in order to facilitate, for example, electron transfers in the final molecular wires. Two illustrative examples are shown in Scheme 51. In **203**, the two pendant terpyridines are connected by an oligophenylenevinylene spacer bearing long alkoxide chains to enhance the solubility of the system.[137] In **204**, a polyphenylene bridge ensures the connection between the terpyridine units.[138]

3.3. Surface functionalization

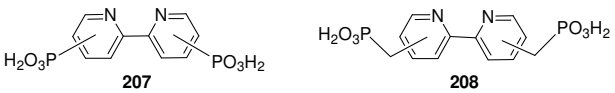
3.3.1. Functionalization of oxometallic surfaces

Dye-sensitized solar cells (DSSCs) are of particular interest due to their possible low-cost alternative to conventional solid-state photovoltaic devices.[139] Efforts to increase device cell efficiencies of DSSCs include varying anchoring groups,[140] structural modification of ancillary ligands of well-known photosensitizers,[141] increasing the excited-state lifetime, decreasing the band gap and increasing the range of absorbed wavelengths.[142] Most of the DSSCs are based on modified *bis* or *tris*(bipyridine)Ru(II) complexes and functional groups such as carboxylic acid or phosphonate are introduced on the bipyridine unit for the anchorage of the metallic complexes onto titanium oxide surface. Among bidentate ligands employed for DSSCs, the most widely used is the 4,4'-dicarboxy-2,2'-bipyridine **205**, initially investigated by Grätzel.[139] More sophisticated anchoring groups have been recently developed such as the tripodal sensitizers **206** (Scheme 52).



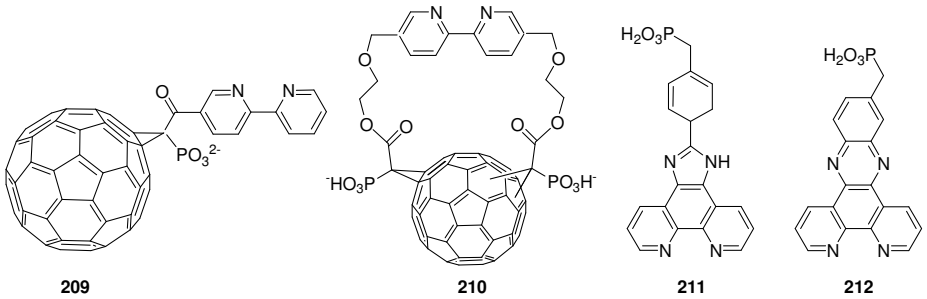
Scheme 52

Phosphonates are suitable alternative groups able to ensure a strong adhesion with TiO_2 surfaces. Numerous bipyridines have been designed with phosphonate pendant moieties (Scheme 53).[143] **207** have been synthesized by palladium cross-coupling reaction of diethyl phosphite with the appropriate dibromo-bipyridine.[144] **208**, containing an additional methylenic spacer compared with **207**, have been obtained by an Arbuzov reaction between the appropriate *bis*-(bromomethyl)bipyridine and triethyl phosphite.[145]



Scheme 53

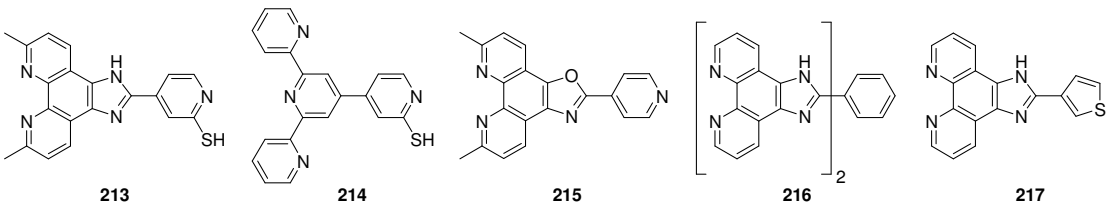
Original dyads **209** and **210** have also been designed in which mono- and di-phosphonate-bearing bipyridines have been functionalized by fullerene by way of Bingel-type reactions (Scheme 54).[146] Phosphonate groups have also been covalently attached to phenanthroline through various spacers such as imidazole **211** or bipyrazine **212** as shown in Scheme 54.[147,148]



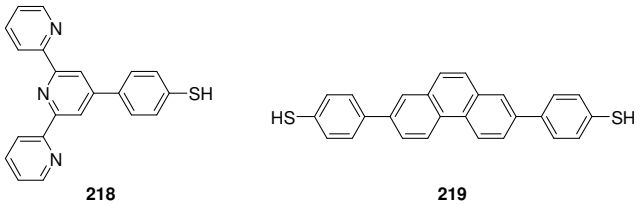
Scheme 54

3.3.2. Functionalization of metallic surfaces

Metallic surface and metallic nanoparticles (NPs) such as gold, silver, palladium or platinum NPs are currently attracting a great attention due to the numerous recognized and potential applications for these systems. In this ever-growing research area, the functionalization of metallic surfaces or metallic NPs by metal complexes has recently emerged.[149,150] The idea behind this combination is to induce a synergy between the intrinsic properties (optical, electrochemical...) of each component, namely the metallic surface and the metal complex. An important specificity of metallic surfaces, especially with gold, is their facile functionalization using electron donor anchorage points such as thiols, phosphines, carboxylates, pyridines, polypyridines,...[151] The connection between the metal complex grafted on the metallic surface and the metallic surface itself is often realized through a long alkyl chain. Indeed, this long alkyl chain is not adapted to favour electronic communication between the metal complex and the metallic surface. We recently developed a family of ligands bearing on one side a function ensuring the grafting on the metallic surface (2-mercaptopyridine, pyridine, phenanthroline, thiophene) and on the other side a pendant polypyridine chelating function (phenanthroline, terpyridine) that will be used to generate the metal complex (Scheme 55).[33,152] An originality of this family of ligands lies in the fully conjugated connection that has been realized between the anchoring function and the chelating pendant group. These ligands have been designed to enhance an electronic communication between the metallic surface and the metal complex and therefore to efficiently tune the physico-chemical properties of the final systems.



Scheme 55



Scheme 56

Polypyridine ligands bearing pendant thiol groups have also been characterized. In **218**, one thiol function has been connected to a terpyridine group through a phenyl moiety[153] while, in 3,8-*bis*-(4-mercaptophenyl)-1,10-phenanthroline **219**, the two thiol pendant groups have been used to prepare self-assembled films with gold NPs (Scheme 56).[154]

4. Conclusion

The optimisation of the physico-chemical properties of metal complexes based on bidentate and tridentate pyridine derivative ligands is currently a growing field of research. In this chapter, different approaches recently used for the synthesis of these ligands have been summarized. A variety of original ligands have been obtained by functionalization of the well-known bipyridine, phenanthroline and terpyridine cores. Parallel to this very active field of research, new families of chelating ligands have been synthesized by incorporation of nitrogen-containing five-membered rings. Such new ligands allow the electronic and steric control of the resulting metal complexes by modification of the bite angle.

We also focused on three main applications of the pyridine-based ligands presented in this chapter: applications based on their optical properties, their use for the formation of inorganic polymers or for the functionalization of metallic surfaces. Obviously, the full potentials offered by these new ligands has not been yet fully exploited. It is expected that they will bring outstanding contributions in a variety of research fields such as supramolecular chemistry or for the design of elaborated systems with specific physico-chemical properties.

Acknowledgments

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SYNTHETIC SOLUTIONS FOR THE TETRAHYDROPYRAN-MOIETY OF ANNONACEAOUS ACETOGENINS

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Abstract. *The tetrahydropyran (THP) substructure of the annonaceaous acetogenins is an attractive synthetic challenge due to the promising antitumor properties of this natural product class. Representative members of THP-containing acetogenins are mucocin, jimenezin, pyranicin, pyragonicin and muconin. This review compares synthetic routes to the THP part of these target molecules, with an emphasis on the different key steps to obtain the tetrahydropyran moiety stereoselectively.*

Contents

1. Introduction

The annonaceaous acetogenins are a class of natural products with various biological properties (antitumor, immunosuppressant, pesticide).[1] A blockage of mitochondrial complex I (NADH-ubiquinone oxidoreductase) of mammalian and insects is considered as the mode of action.[2] Most annonaceaous acetogenins consist of a central cyclic ether part with one side aliphatic chain connected to the lower end and one to the upper end. The upper side chain is terminated by a butenolide unit. Most of the over 400 annonaceaous acetogenins have one, two or three 2,5-disubstituted tetrahydrofurans (THFs) in the cyclic ether part. A small subgroup bears a 2,6-disubstituted tetrahydropyran (THP) moiety in the cyclic ether part. Mucocin[3] has one THP and one not-adjacent THF moiety, while in jimenezin[4] the THF ring is adjacent to the THP ring (Figure 1). All three stereocenters in the THP ring of mucocin and jimenezin have the same absolute configuration.

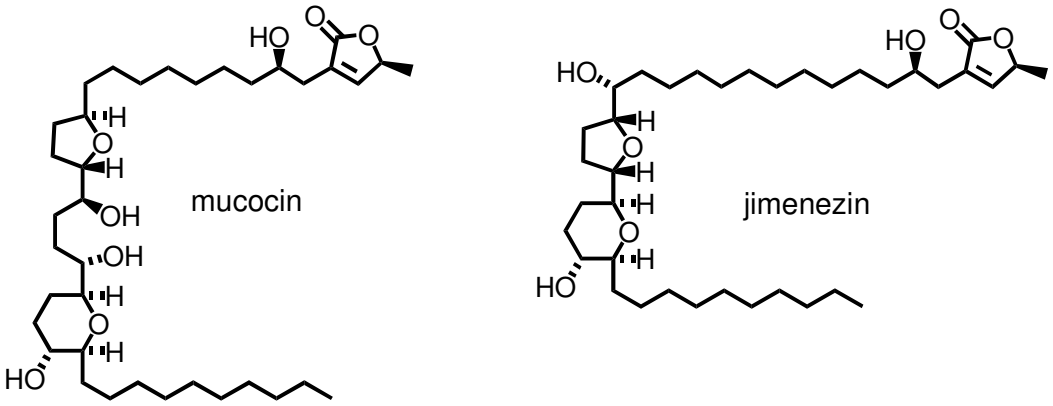


Figure 1

Pyranicin and pyragonicin are two rare annonaceaous acetogenins with no THF ring but possess an identical THP ring (Figure 2).[5] The central cyclic ether part of muconin[6] consists of a THF ring adjacent to a THP ring.

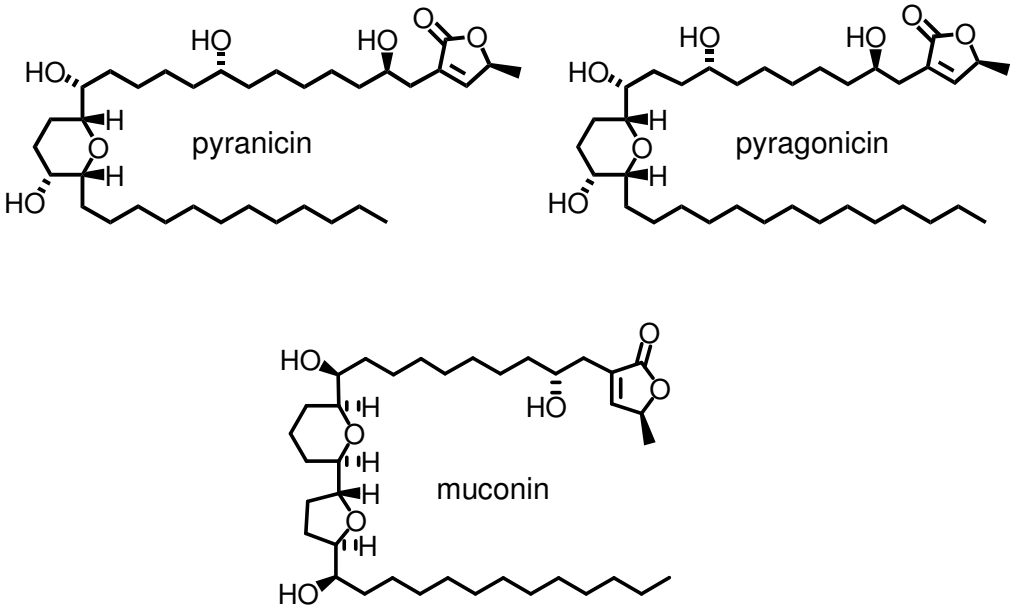


Figure 2

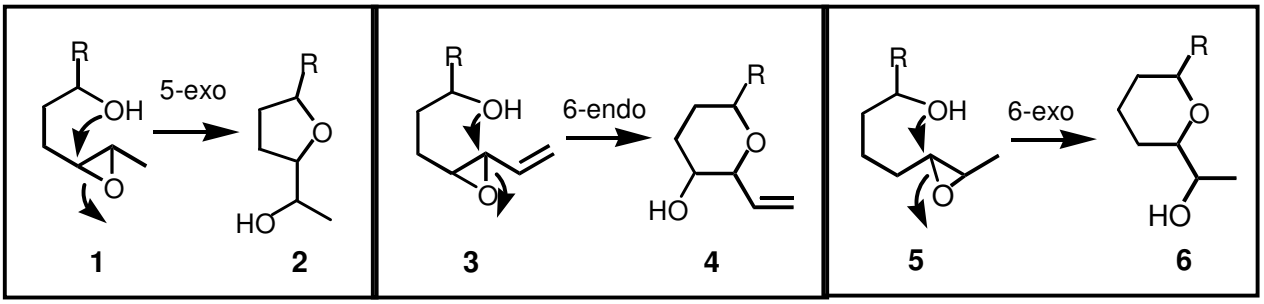
This review covers all synthetic routes to the THP-moiety of THP-containing annonaceaous acetogenins that have been published as part of a total synthesis of the corresponding natural products till August 2007. It is organized according to the key step of the THP-ring synthesis: epoxide opening, acetal/hemiacetal formation/reduction, Nicholas reaction, oxa-Michael addition, SmI_2-induced reductive cyclization, allylboration, ring-closing olefin metathesis, hetero Diels-Alder and chiral pool approach.

2. Ring-closure of the THP ring *via* CO bond formation

2.1. Epoxide opening

The acid-mediated intramolecular opening of a γ-hydroxy-epoxide **1** leads in accordance with Baldwin's rules[7] *via* a 5-exo attack to the THF product **2** with an exocyclic α-hydroxyalkyl substituent (Scheme 1). The regioselectivity of the epoxide opening can be reversed to the 6-endo attack by allylic

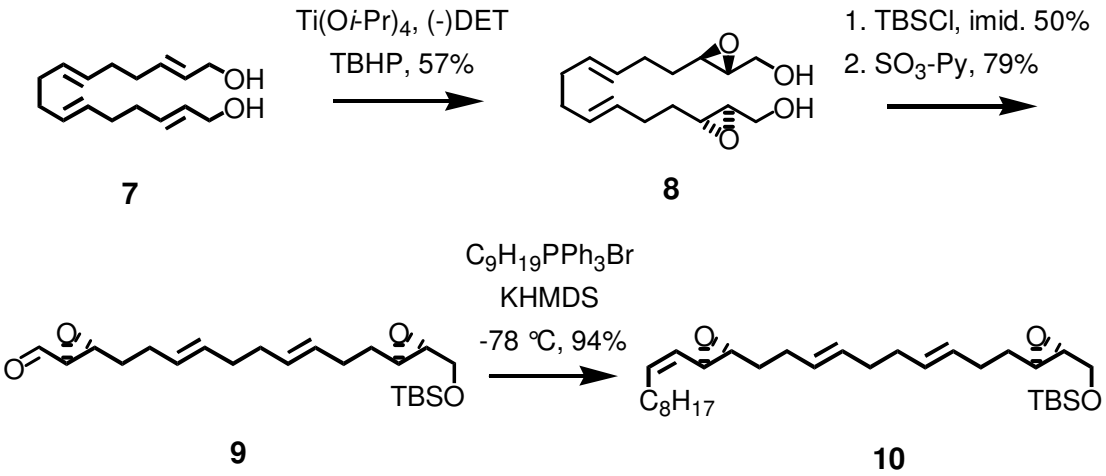
activation.[8] This makes a vinylic epoxide such as **3** an ideal precursor for the THP-substructure **4** found in mucocin, jimenezin, pyranicin and pyragonicin. The THP substructure found in muconin is accessible from the δ-hydroxy-epoxide **5**, which leads *via* a 6-exo attack to the α-hydroxyalkyl-substituted THP **6**.



Scheme 1

The THP-moiety of mucocin was synthesized *via* an allylic assisted intramolecular 6-endo epoxide opening in the course of the total syntheses by Keinan-Sinha[9] and Koert.[10]

An entry point for the synthesis of the THP-part by Keinan was the bis-allylic alcohol **7** (Scheme 2). A twofold Sharpless epoxidation gave the bis epoxyalcohol **8**. The symmetry of **8** was broken in the subsequent monosilylation. The following Parikh-Doering oxidation provided the aldehyde **9**, which was converted *via* a Wittig reaction into the alkenyl epoxide **10**.

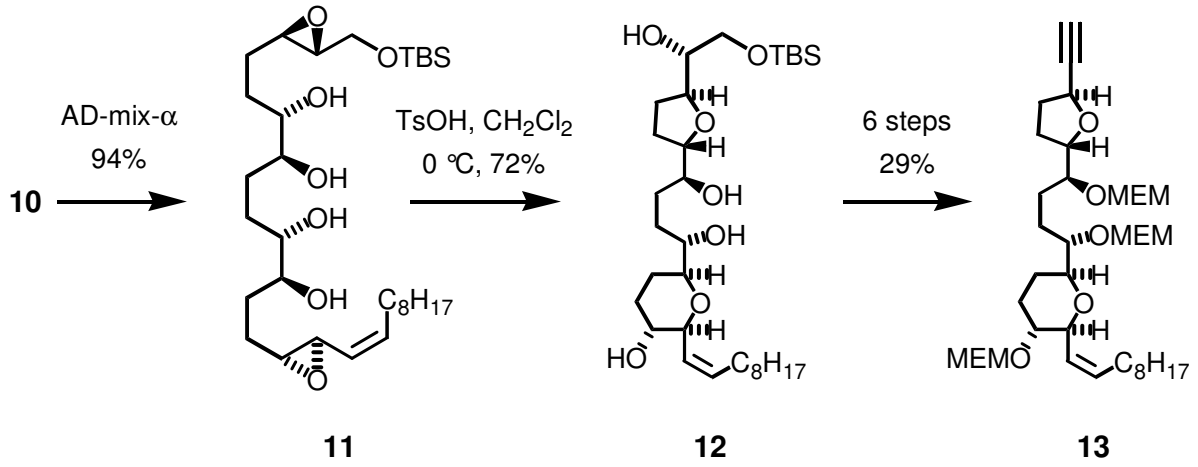


Scheme 2

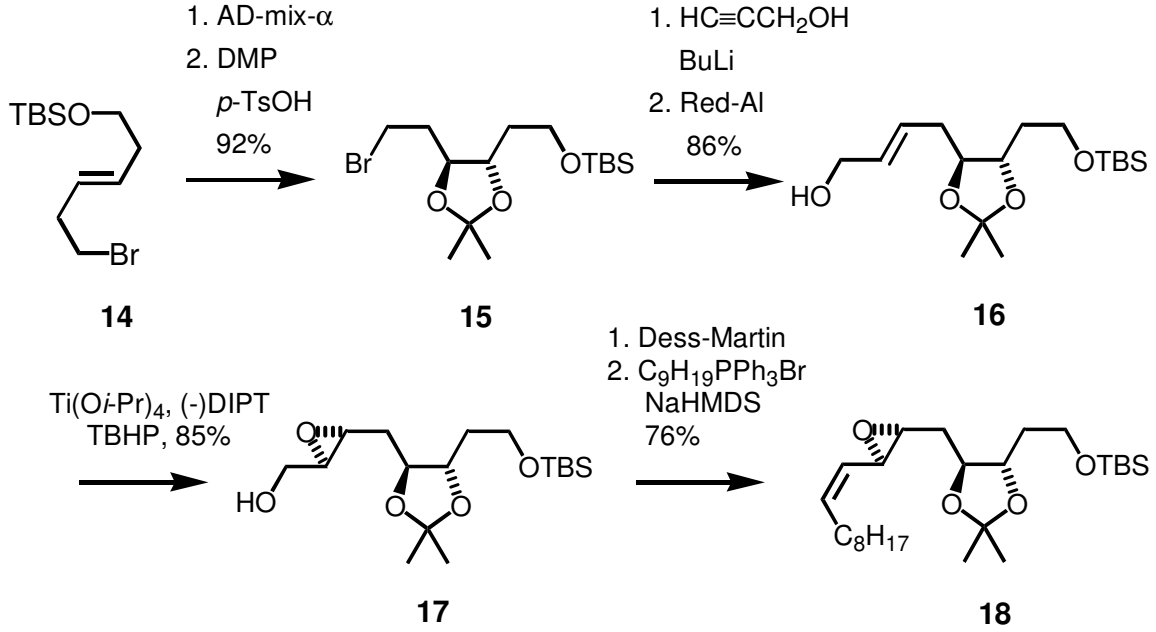
A double Sharpless asymmetric dihydroxylation of **10** installed four stereocenters very efficiently in one step only and gave the tetraol **11** (Scheme 3). Treatment of **11** with *p*-TsOH resulted in a 5-exo epoxide opening of the upper epoxide to a THF ring and in a 6-endo opening of the lower alkenyl-epoxide to a THP ring which gave compound **12**. This key step provided the central ether part of mucocin in just one step only. While the adjacent THP-THP substructure was established very elegantly, the conversion of **12** into the alkine **13** required a number of steps. The terminal alkyne was used in a Sonogashira coupling to add the butenolide side chain and to reach the target molecule mucocin.

Koert's synthetic strategy for mucocin is based on a very late connection of the THP-moiety to the THP-substructure already linked to the butenolide. This highly convergent approach required the synthesis

of an iodide **21** (Schemes 4 and 5). A Sharpless dihydroxylation of **14** and a subsequent acetonide formation gave the bromide **15**, which was converted into the allylic alcohol **16**.



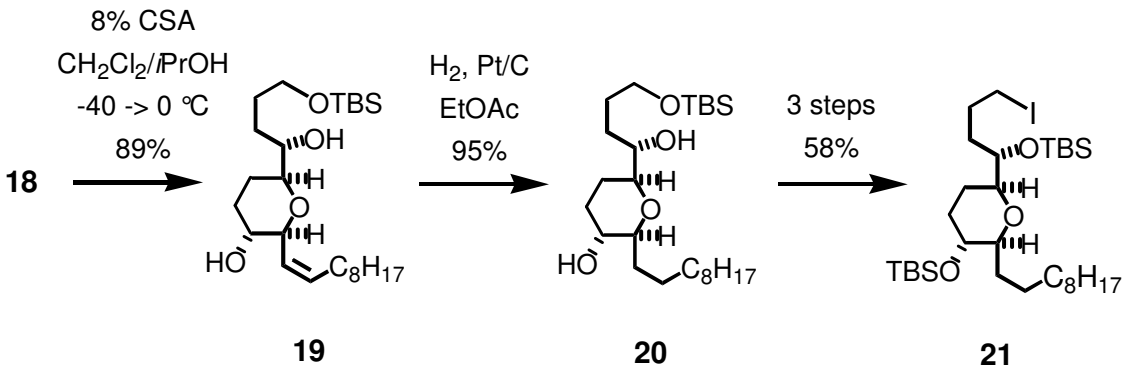
Scheme 3



Scheme 4

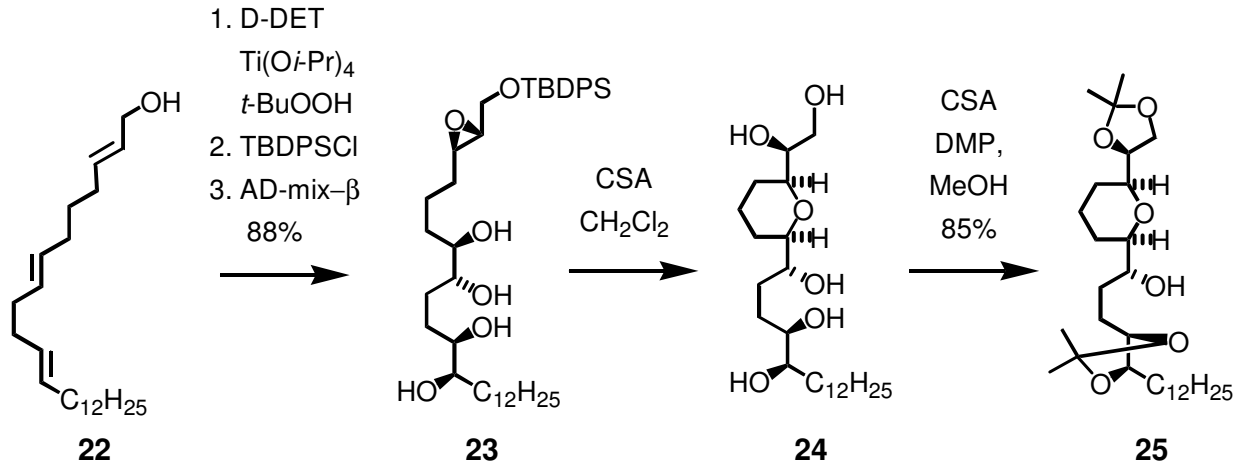
Sharpless epoxidation of the allylic alcohol **16** gave the epoxide **17**, which could be converted *via* a Wittig reaction into the alkenyl epoxide **18**. Treatment of **18** with camphor sulfonic acid resulted in the desired allyl-assisted 6-endo attack on the epoxide and the formation of the THP **19**. An attack of the acetonide and not the free diol on the protonated epoxide is supported by further studies.[10b] A few standard steps led from **19** *via* **20** to the iodide **21**. From **21**, the target mucocin was available in 2 steps only, which shows the efficiency of this convergent approach.

The THP moiety of muconin has been synthesized *via* an intramolecular epoxide opening by Takahashi,[11] Kitahara[12] and Yoshimitsu/Nagaoka.[13] In all three cases the 6-exo attack (**5** → **6**) was very efficient, however the degree of stereoselectivity achieved in introducing the epoxide/hydroxy stereocenters was different. A very convincing solution to this problem was presented in Takahashi's muconin synthesis (Scheme 6).[11]



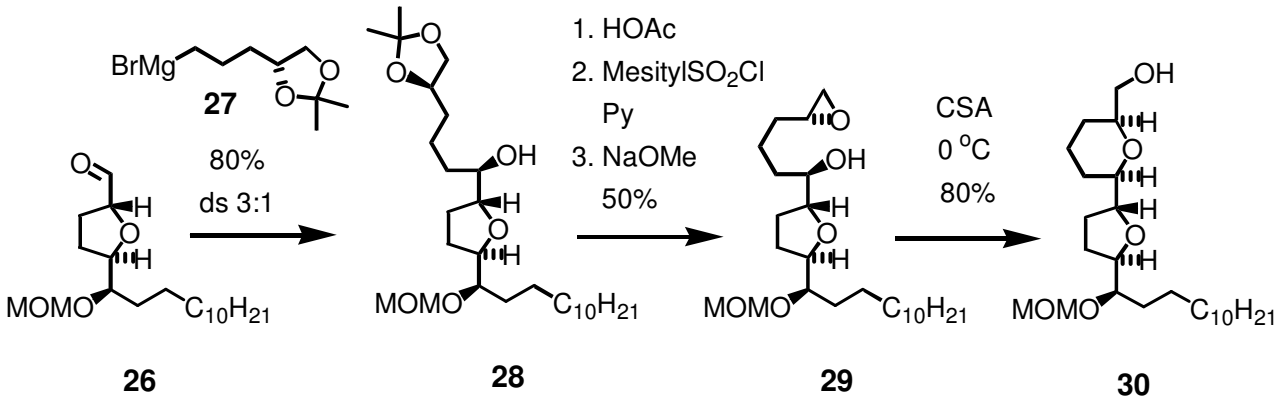
Scheme 5

A remarkable short sequence of Sharpless epoxidation and asymmetric dihydroxylation was used to convert the triene **22** into compound **23** with complete stereocontrol. The epoxide opening (**23** → **24**) succeeded well and the product was isolated as bis-acetonide **25**.



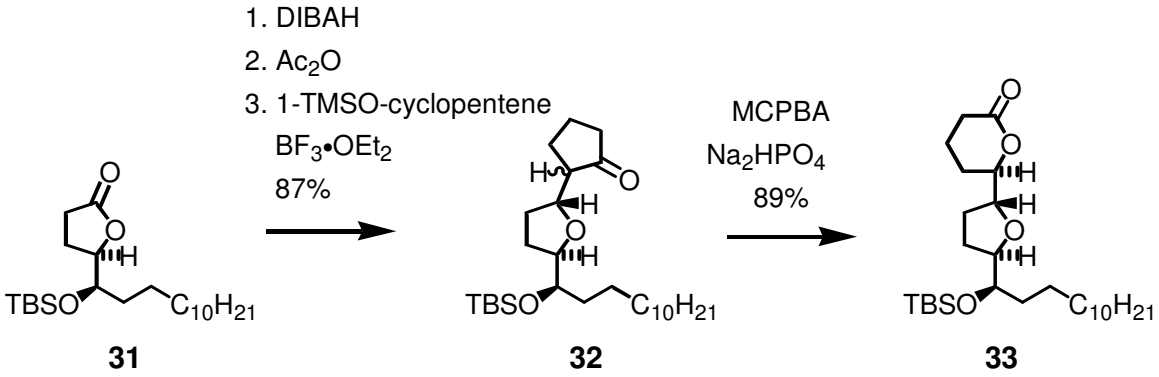
Scheme 6

Kitahara chose a different approach to install the stereocenters of his precursor **29** for the epoxide opening (Scheme 7).[12] A chelation-controlled reaction of the aldehyde **26** with the Grignard compound **27** provided the alcohol **28**. The acetonide group in **28** is a latent epoxide with the stereocenter already in place. In a standard sequence **28** was converted into the epoxy-alcohol **29**, which smoothly performed the intended 6-exo cyclisation to produce **30**.

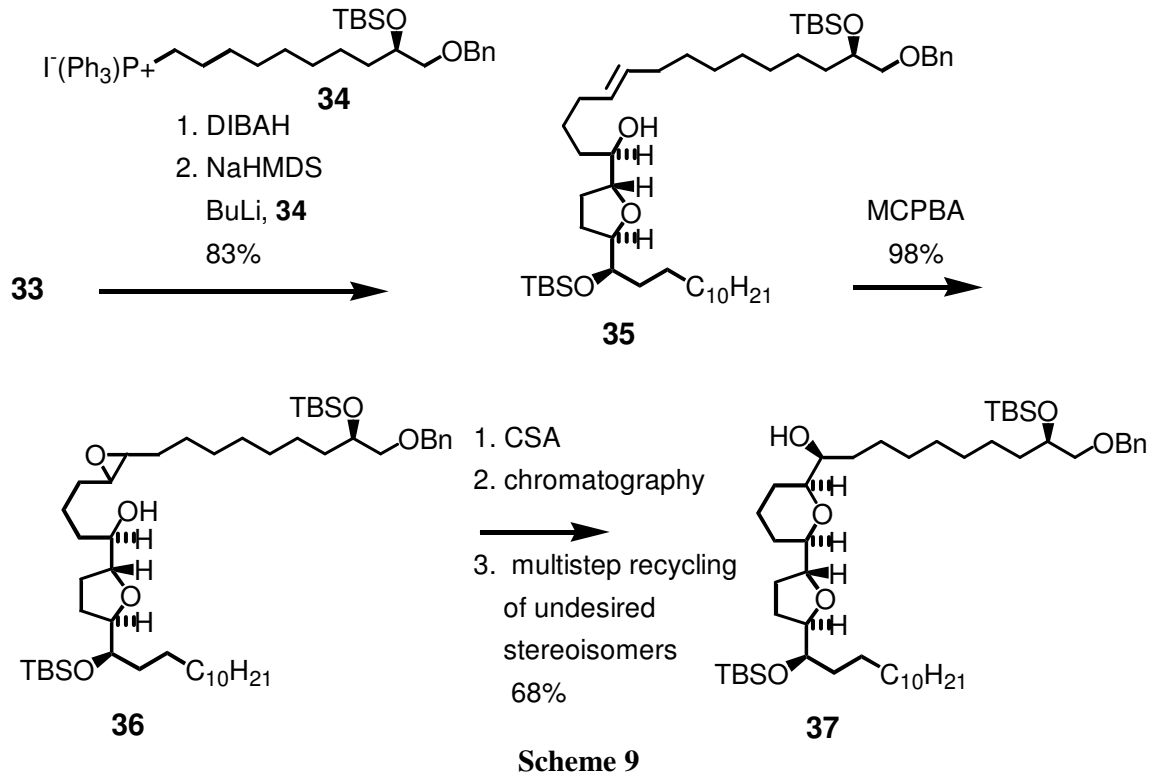


Scheme 7

In comparison with the previous two syntheses of the muconin-THP moiety, the synthesis by Yoshimitsu/Nagaoka[13] exhibits a low degree of stereocontrol and requires extra steps for recycling of the undesired stereoisomers (Schemes 8 and 9). Entry point of the synthesis was the conversion of the compound **31** into the lactone **32**. The stereoselectivity for the *trans* substitution of the THF ring in **32** was satisfying but the stereocenter in the cyclopentanone required correction steps to achieve the overall respectable yield. A Bayer-Villiger oxidation of **32** led to the six-membered lactone **33**. The latter was reduced to the corresponding lactol which underwent a Wittig-reaction to deliver the *E*-alkene **35**. A non-stereoselective epoxidation gave **36**. The epoxide opening of the stereoisomeric mixture and a multistep recycling of the wrong stereoisomer resulted in compound **37** with the THP-THF core of muconin.



Scheme 8

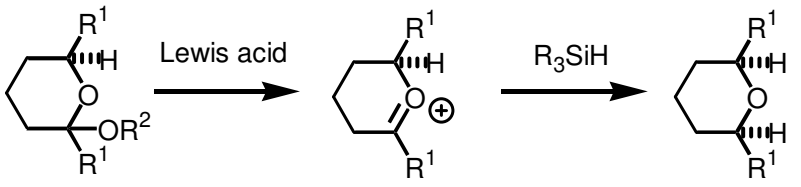


Scheme 9

2.2. Acetal/hemiacetal formation/reduction

The *cis* configuration of all THP moieties in the annonaceous acetogenins makes the *cis*-selective cationic reduction (silane + Lewis acid)[14] a well suited key step for the synthesis of this substructure

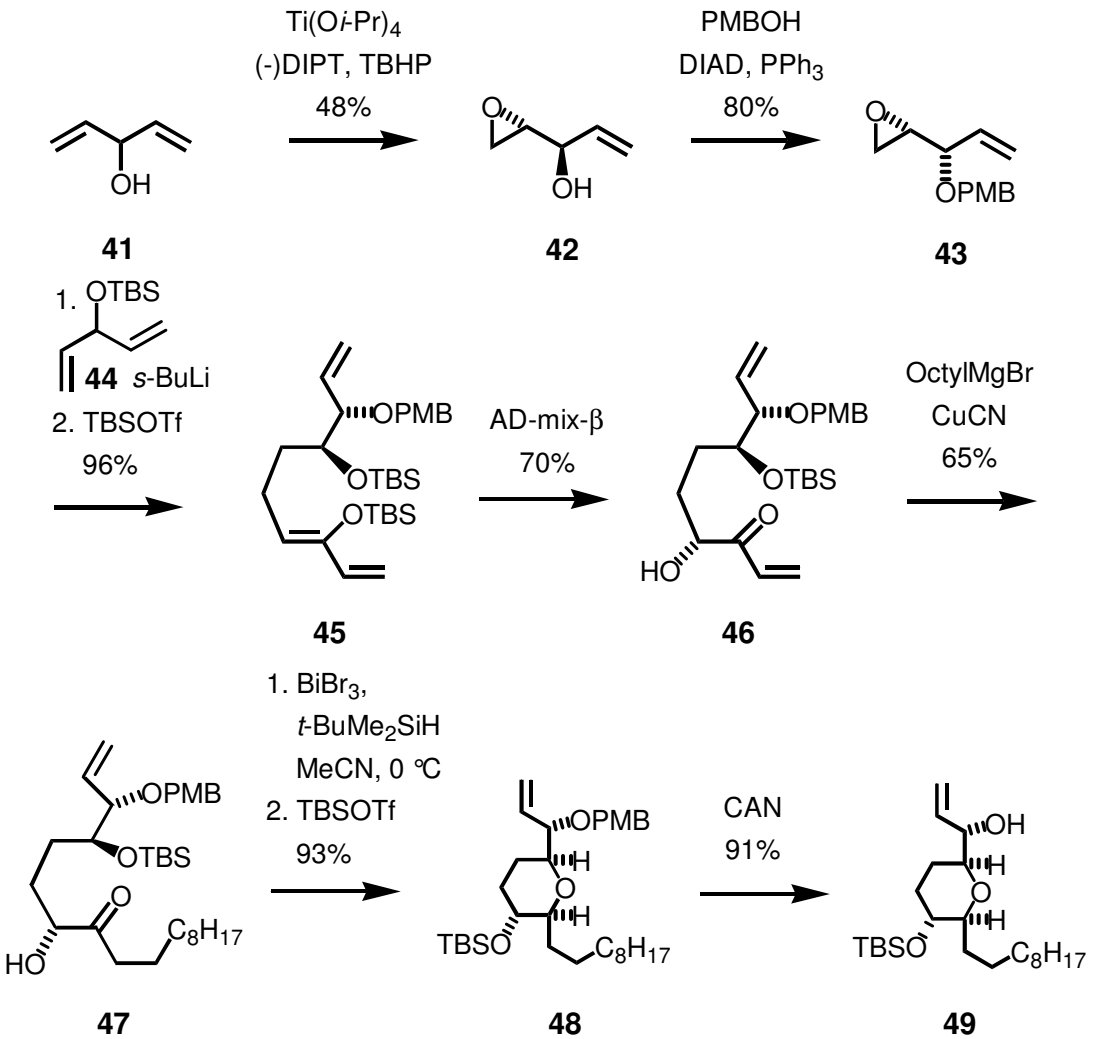
(Scheme 10). Acetals of type **38** can be converted *via* the oxonium ion **39** with very high stereoselectivity into *cis* 2,6-disubstituted THPs **40**.[15]



38 **39** **40**

Scheme 10

The acetal/hemiacetal formation/reduction approach to construct the *cis* THP moiety of annonaceous acetogenins was used by Evans[16] and Mootoo[17] in their syntheses of mucocin.

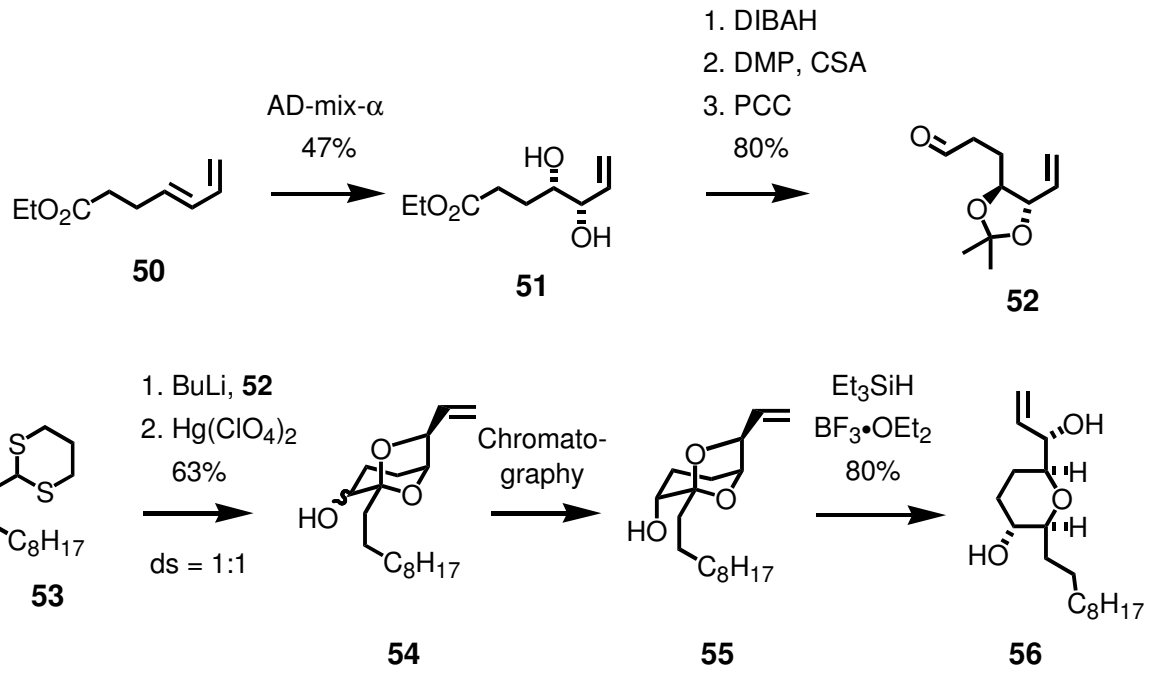


Scheme 11

Evans started his synthesis with a Sharpless epoxidation of the allylic alcohol **41** to obtain compound **42** (Scheme 11).[16] The latter was transformed by a Mitsunobu inversion into the PMB-ether **43**. In the next step, lithiated **44** attacked the epoxide **43** at the terminal position to produce after TBS-protection compound

45. A Sharpless asymmetric dihydroxylation of the enolether in **45** led to the α-hydroxy ketone **46**. In the following step, a Cu-mediated 1,4-addition of an octyl-Grignard reagent introduced the lower alkyl side chain (**46** → **47**) and prepared the stage for the intramolecular hemiacetal formation/reduction. Evans used $BiBr_3$ as the Lewis acid in combination with *t*-$BuMe_2SiH$ to convert **47** into the *cis* THP structure which was subsequently TBS-protected to deliver **48**. Deprotection of the PMB-ether gave the THP building block **49**.

In Mootoo's synthesis of mucocin the first stereocenters were introduced in the asymmetric dihydroxylation of the diene **50** (Scheme 12).[17] The chemoselectivity of this step was less satisfying which resulted in a moderate yield of the diol **51**. A standard sequence converted **51** into the aldehyde **52**. The lithiated thioacetal **53** added to the aldehyde non-stereoselectively to produce after treatment with $Hg(ClO_4)_2$ the hydroxy acetal **54** as a 1:1 epimeric mixture. The desired epimer **55** was obtained in pure form after chromatography and smoothly reduced to the *cis* THP derivative **56**.



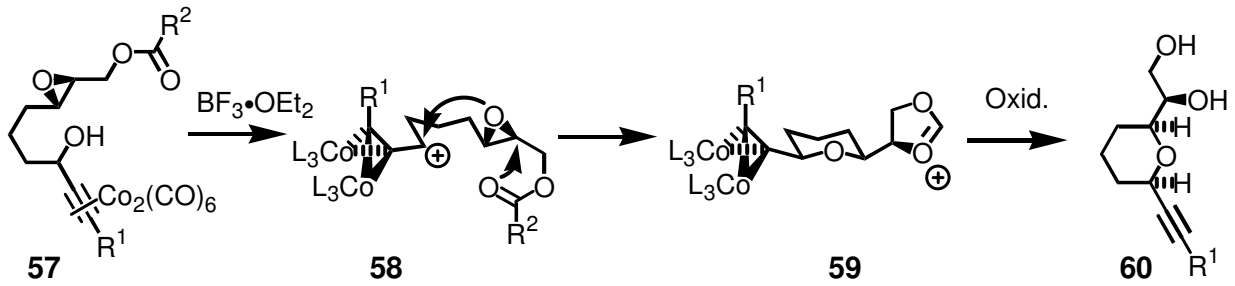
Scheme 12

Compared with Evans's synthesis, Mootoo achieved the same efficiency for the cationic reduction key step but a lower degree of stereocontrol for the synthesis of the precursor.

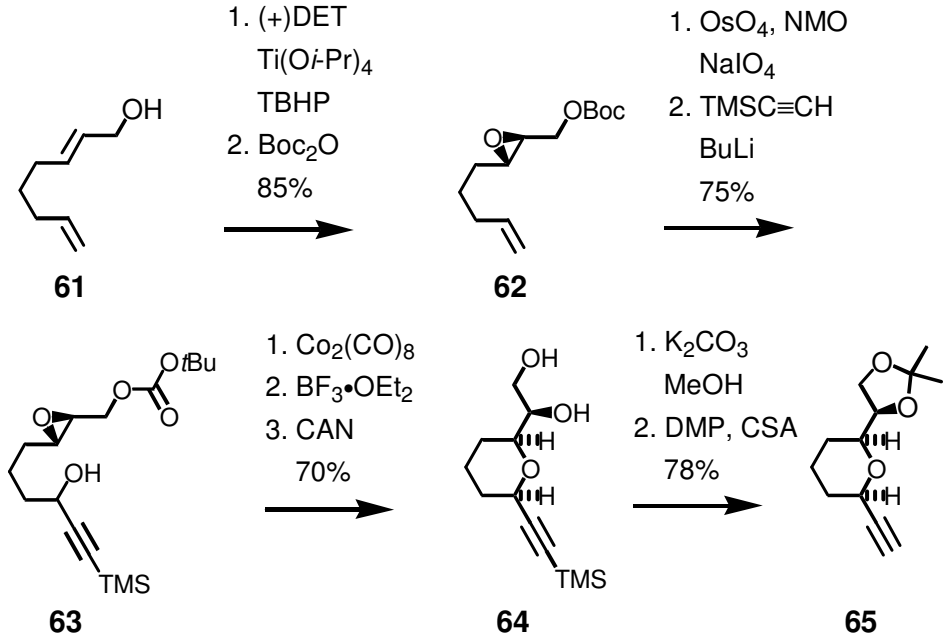
2.3. Nicholas reaction

Martin has developed a protocol for an intramolecular Nicholas reaction[18] leading to *cis* THP compounds of type **60** (Scheme 13).[19] Treatment of the $Co_2(CO)_6$-activated propargylic alcohol **57** with a Lewis-acid leads to the carbocation **58**, which is attacked by the epoxide resulting in the oxonium ion **59** and after oxidative hydrolysis the alkyne-THP-diol **60**.

This intramolecular Nicholas reaction was used by Martin as a key step in a formal synthesis of muconin (Scheme 14).[20] A Sharpless epoxidation of **61** provided after Boc-protection the epoxide **62** which was converted into the propargylic alcohol **63**. The following Nicholas sequence proceeded smoothly to deliver the *cis* THP **64**. One drawback is the wrong stereochemistry of the acetonide, which will require further correction steps in the completion of the total synthesis.



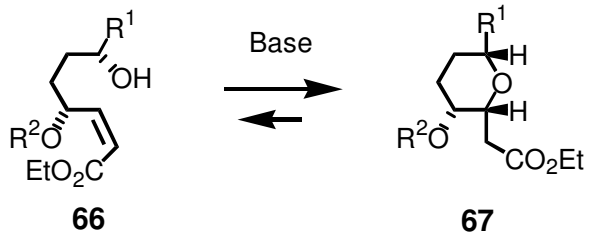
Scheme 13



Scheme 14

2.4. Oxa-Michael-addition

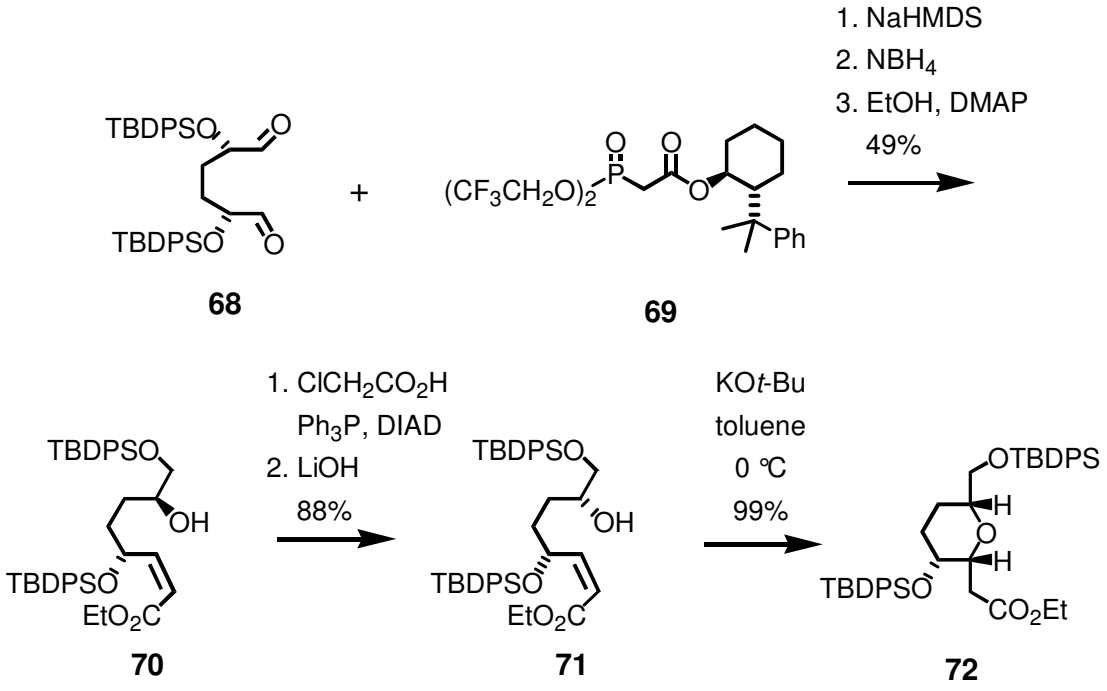
The intramolecular 1,4-addition of an alkoxide to an α,β-unsaturated ester (intramolecular oxa-Michael addition) is another possibility to close the THP ring (Scheme 15). The alcohol **66** can be converted under thermodynamic control into the THP compound **67**, which stereochemically corresponds to the THP-moiety of pyranicin.[21]



Scheme 15

This intramolecular oxa-Michael addition was used by Rein in his total synthesis of pyranicin to establish the THP-moiety (Scheme 16).[21a,b] An asymmetric Horner-Wadsworth-Emmons reaction of the meso-dialdehyde **68** with the Horner-Wadsworth-Emmons reagent **69** gave after aldehyde-reduction/ester-hydrolysis and ethyl ester formation the *Z*-α,β-unsaturated ester **70**. This step was accompanied by migration

of the TBDPS-group from the secondary to the less strained primary position. The next step corrected the OH-stereochemistry by a Mitsunobu reaction (**70** → **71**). The oxa-Michael reaction of the precursor **71** to the THP derivative **72** was achieved in excellent yield and stereocontrol.



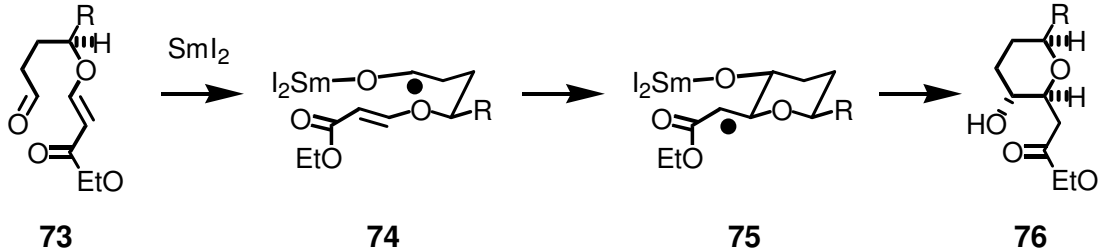
Scheme 16

Pyranicin and pyragonicin exhibit a constitutional and stereochemical identity of their THP-moieties. Rein used therefore the THP-building block **72** in a successful total synthesis of pyragonicin too.[21b,c] Using an oxa-Michael reaction as a key step, Rein also prepared the THP-moiety of mucocin with a different stereochemistry[21d] but so far the total synthesis has not been published.

3. Ring-closure of the THP ring *via* CC bond formation

3.1. SmI_2-induced reductive cyclization

Samarium iodide is a soluble one-electron reductant that can be used for reductive cyclizations.[22] It is a valuable reagent for the ring closure of the THP moiety of the annonaceaous acetogenins *via* CC-bond formation (Scheme 17).



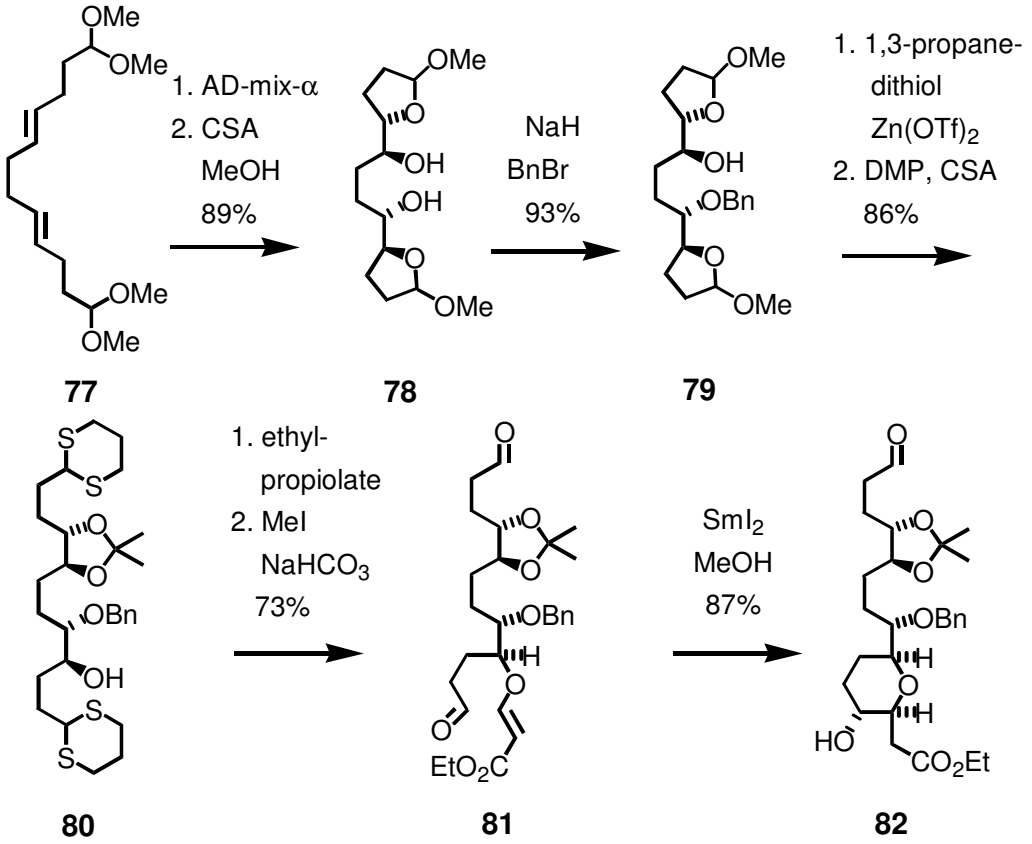
Scheme 17

An aldehyde **73** can be reduced to the ketyl radical **74**. The chair-like ketyl radical is further stabilized by a chelation of the samarium by the ester carbonyl. An intramolecular stereocontrolled addition of the

nucleophilic ketyl radical to the electrondeficient double bond is very favorable and leads to the radical **75** which after H-atom abstraction generates the target THP structure **76**. The relative configuration of the three stereocenters in **76** corresponds to the THP-moiety of mucocin and jimenezin, which makes the SmI_2-induced reductive cyclization a well suited key step for the total synthesis of these natural products.

Two total syntheses have been published which use the SmI_2-induced reductive cyclization for the ring closure of the THP ring **76**: one of mucocin by Takahashi/Nakata[23] and one of jimenezin by Lee.[24] In addition, Takahashi/Nakata applied this methodology for a total synthesis of pyranicin[25] and pyragonicin.[26]

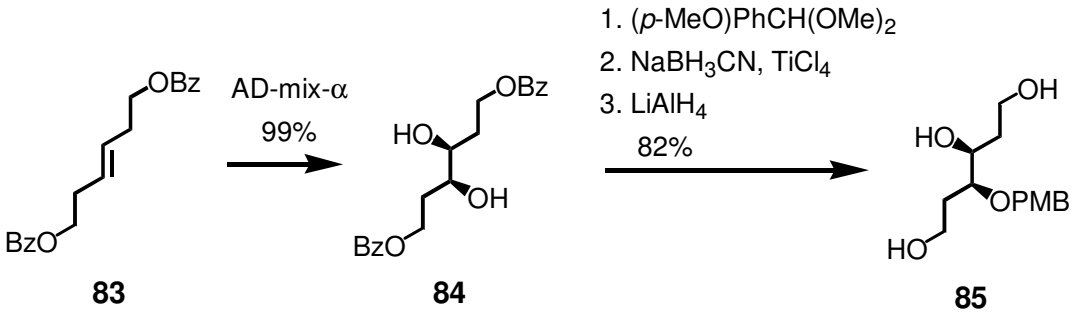
The mucocin synthesis of Takahashi/Nakata[23] used a symmetric bisacetal **77** as entry point for the synthesis of the THP moiety (Scheme 18).



Scheme 18

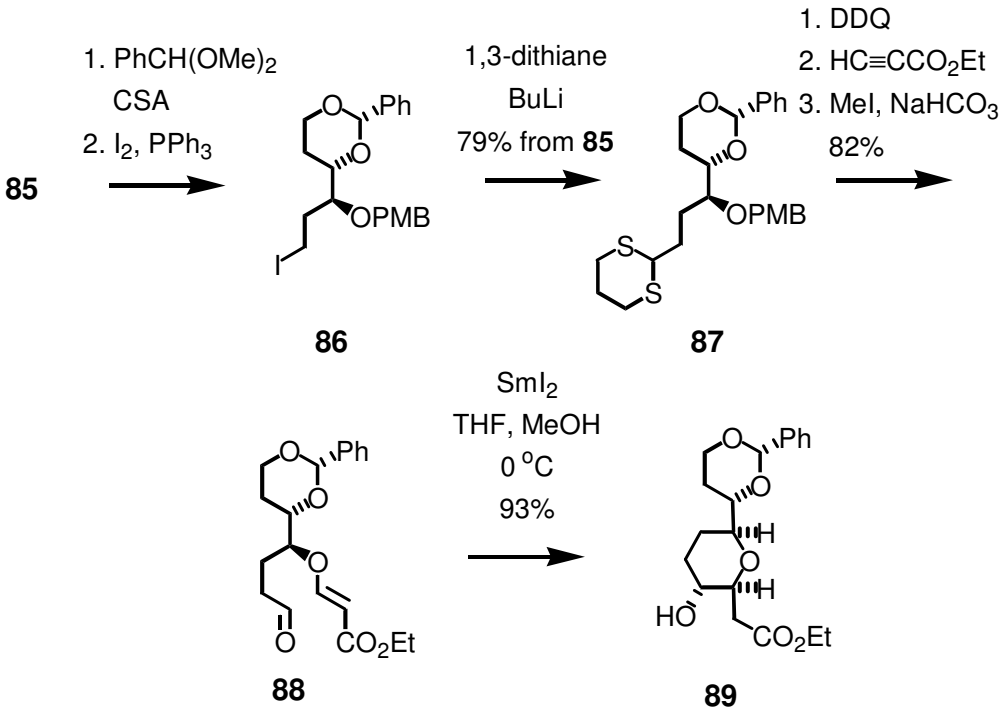
A twofold Sharpless asymmetric dihydroxylation and transacetalization gave the diol **78**. The next step broke the C2-symmetry of **78** with a very high yield to produce the mono-benzyl ether **79**. Both THF acetals were converted into thioacetals and the remaining 1,2-diol was protected as an acetonide (**79** → **80**). The free alcohol in **80** could be transformed into the corresponding *E*-β-alkoxy acrylate which after thioacetal cleavage gave the bis aldehyde **81**. This was used as the precursor for the SmI_2-induced reductive cyclization to produce the THP-derivative **82** in very good yield. The authors point out the remarkable compatibility of the upper aldehyde group under the reaction conditions but notice that a short reaction time is necessary to avoid side reactions like pinacol coupling.

Lee's jimenezin synthesis starts with the Sharpless asymmetric dihydroxylation of the alkene **83** to the diol **84**, which was transformed into the triol **85** (Scheme 19).[24]



Scheme 19

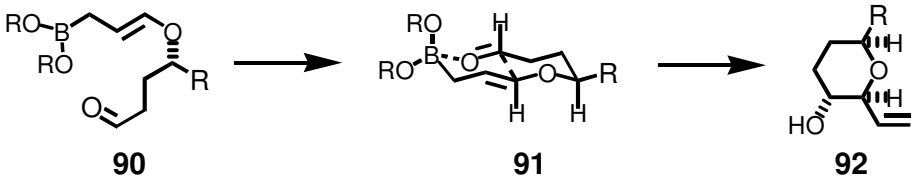
The 1,3-diol in **85** was protected as benzylidene-acetal and the remaining alcohol could be converted into the iodide **86** (Scheme 20). Next the aldehyde group necessary for the radical key step was introduced in form of a 1,3-dithiane (**86** → **87**). After cleavage of the PMB ether the resulting alcohol led to an *E*-β-alkoxy acrylate. Removal of the thioacetal resulted in the aldehyde **88** as the precursor for the SmI_2-induced reductive cyclization. This key step gave the desired THP-moiety **89** of jimenezin in excellent stereoselectivity and yield.[24]



Scheme 20

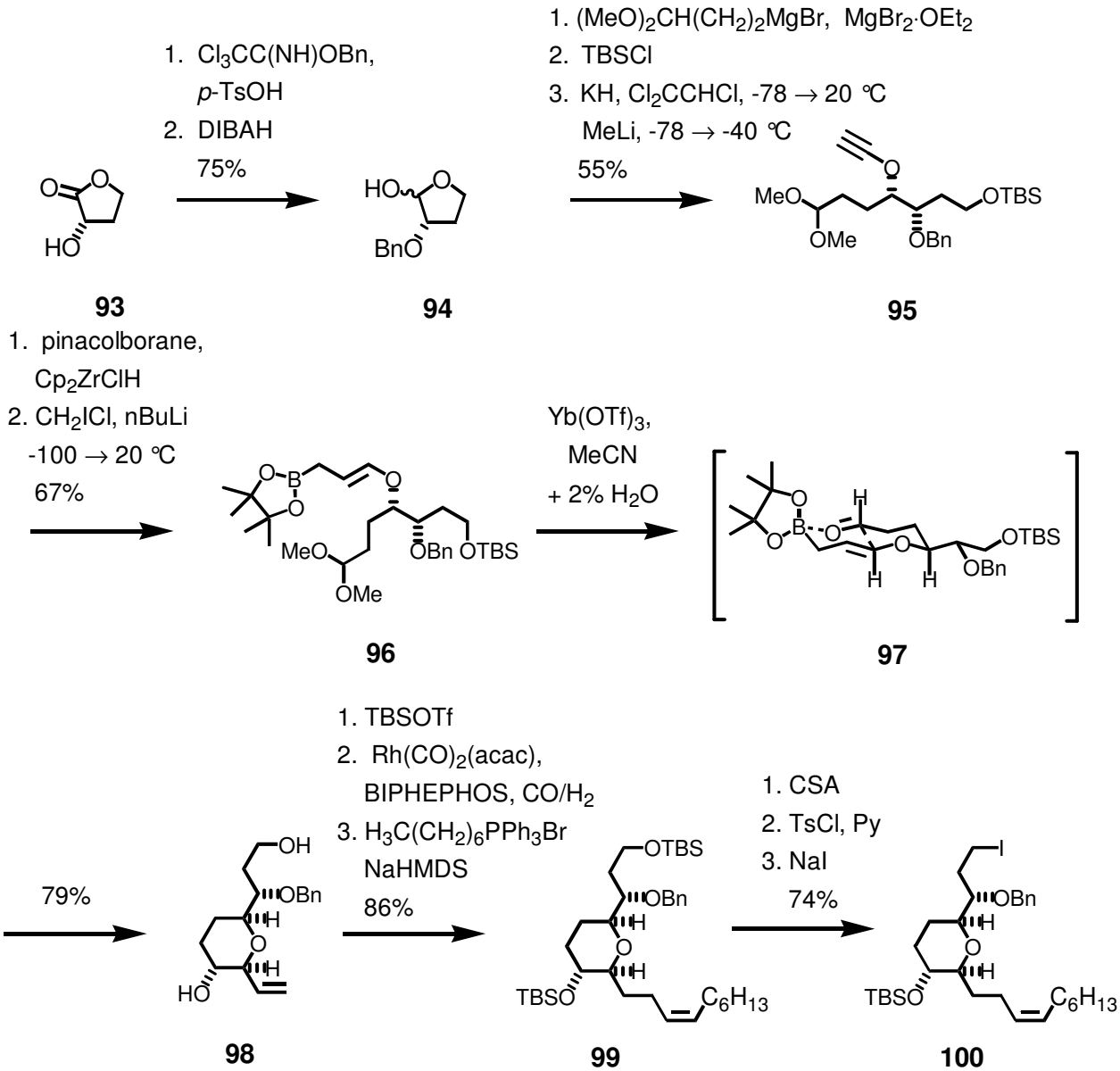
3.2. Allylboration

The intramolecular addition of a *E*-γ-alkoxyallylboronate to an aldehyde as in **90** provides *via* a chair-like transition state **91** a highly stereocontrolled entry into substituted THP rings of type **92** (Scheme 21).[27]



Scheme 21

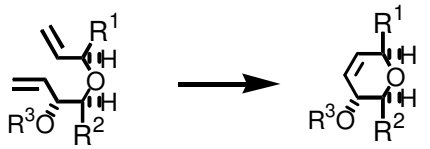
Koert and Hoffmann used the intramolecular allylboration in their total synthesis of jimenezin as key step to construct the THP moiety (Scheme 22).[28] Starting from the hydroxylacton **93** *via* the benzyloxylactol **94** the ynol ether **95** was obtained. The triple bond in **95** was converted by a zirconium-mediated hydroboration into an *E*-vinyl boronate, which was homologized into the *E*-allyl boronate **96**. Treatment with $Yb(OTf)_3$ in acetonitrile with 2% water led to a cleavage of the acetal and gave *via* a transition state **97** the THP **98** as exclusive stereoisomer. A hydroformylation/Wittig sequence served for the introduction of the lower side chain while the upper OH group was transformed into an iodide (**98** → **99** → **100**), the complete THP building block of jimenezin.



Scheme 22

3.3. Ring-closing olefin metathesis

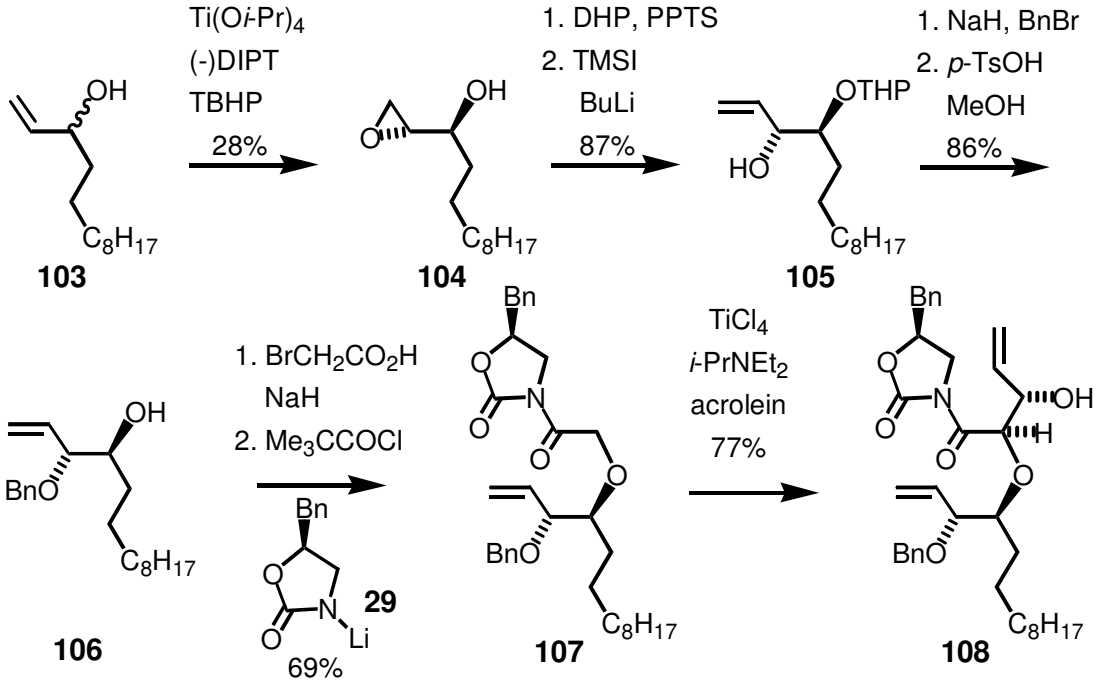
A ring-closing olefin metathesis of the diene **101** using *e.g.* Grubbs second generation catalyst $[Cl_2(PCy_3)(IMes)Ru{=}CHPh]$[29] results in the formation of the THF-moiety **102** (Scheme 23).



101 **102**

Scheme 23

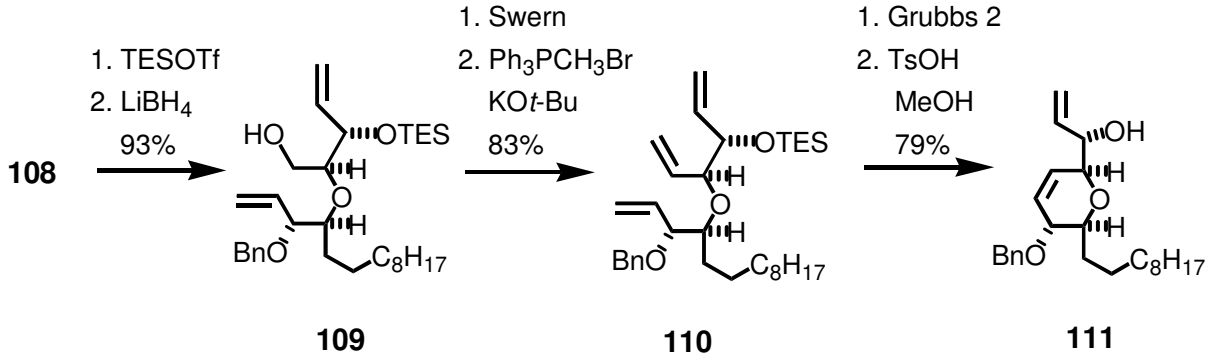
Crimmins applied this method for the THP-ring formation in his total synthesis of mucocin (Scheme 24).[30] A kinetic resolution of the allylic alcohol **103** resulted in the epoxide **104**. After THP-protection, an epoxide opening/Peterson olefination delivered the allylic alcohol **105**. Two protection steps (**105** → **106**) followed by the introduction of an acetate unit with an Evans auxiliary led to compound **107**. A highly stereoselective Evans-aldol reaction of **107** with acrolein produced the aldol **108**.



103 **104** **105** **106** **107** **108** **29**

Scheme 24

Compound **108** could be converted after TES-protection and subsequent removal of the chiral auxiliary into the primary alcohol **109** (Scheme 25).



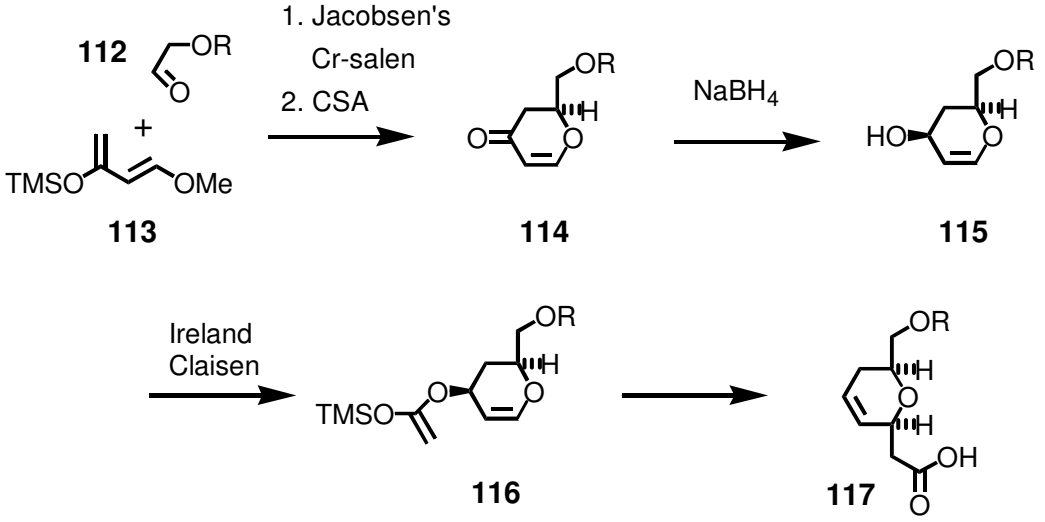
108 **109** **110** **111**

Scheme 25

A Swern-oxidation followed by a Wittig reaction (**109** → **110**) introduced the terminal double bond necessary for the ring-closing olefin metathesis. This key step proceeded very efficiently. Noteworthy is the chemoselectivity of the metathesis in the triene system of **110**. The THP-moiety **111** has the lower side chain of mucocin already in place and was connected to the rest of the molecule by a cross metathesis.[30]

4. Hetero-Diels-Alder reaction

The hetero-Diels-Alder reaction of an aldehyde **112** and the Danishefky diene **113** can lead to enantiomerically pure dihydropyranone **114** (Scheme 26).[31] After a diastereoselective reduction the resulting allylic alcohol is subjected to an Ireland-Claisen rearrangement which gives *via* the silyl ketene acetal **116** the *cis* 2,6-disubstituted THP **117**.[32]

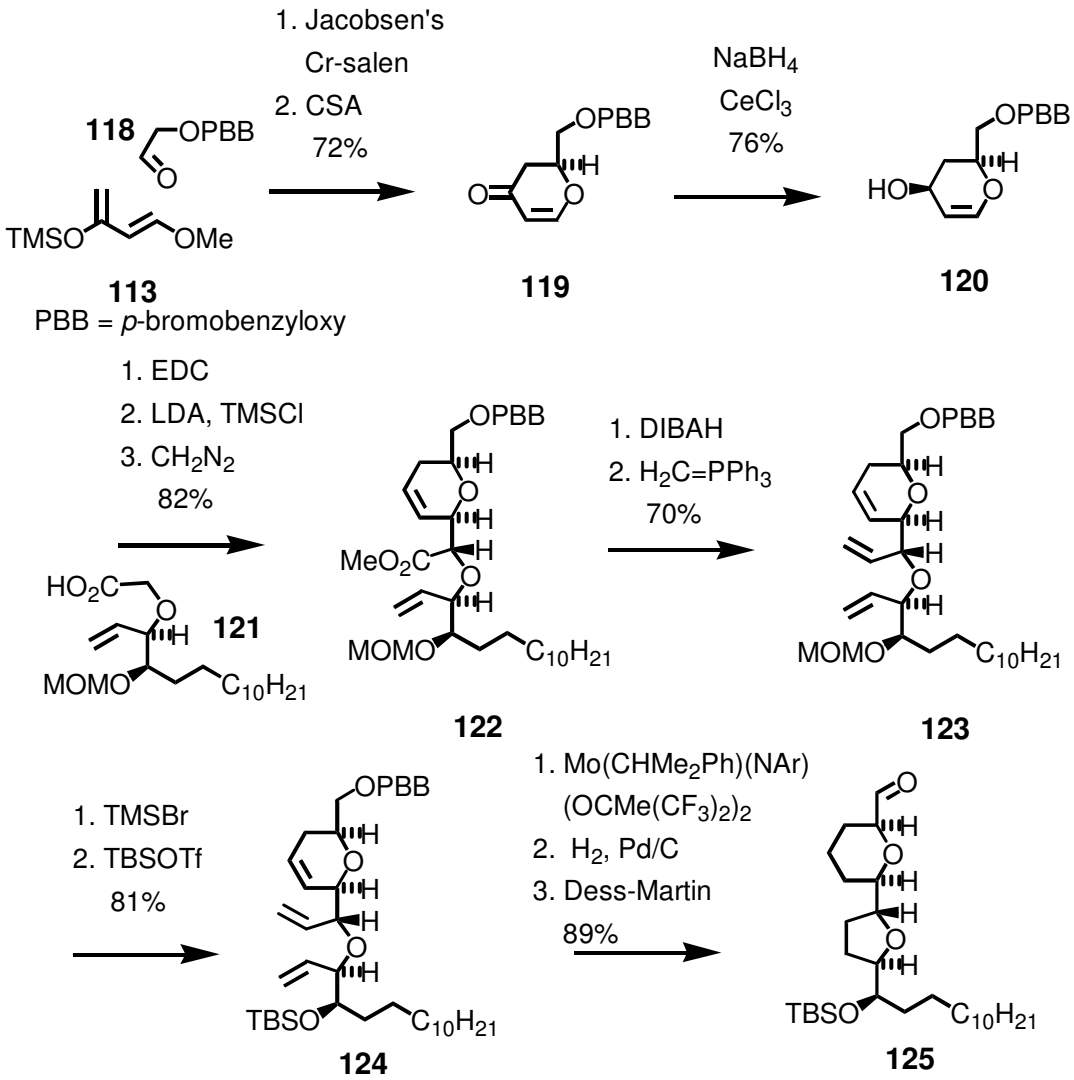


Scheme 26

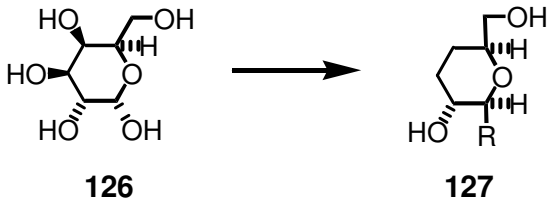
The hetero-Diels-Alder approach was used as a key step for the preparation of the THP-moiety by Jacobsen in his synthesis of muconin (Scheme 27).[32] Starting point was the asymmetric 4+2 cycloaddition of the aldehyde **118** with the diene **113** to produce enantiopure **119**. A stereoselective reduction of the ketone in **119** led to the alcohol **120**. The latter was coupled with the acid **121** and the resulting ester subjected to an Ireland-Claisen rearrangement. The corresponding acid could be converted into the methyl ester **122**. A DIBAH-reduction followed by a Wittig reaction gave the triene **123**. After a protective group change (**123** → **124**) a ring-closing olefin metathesis delivered the THF ring and gave the complete ether core **125** of muconin with the lower alkyl chain already in place.

5. Chiral pool approach

D-Galactose **126** is a suitable source from the chiral pool for the THP-building block **127** as shown in Scheme 28. Takahashi used this chiral pool approach in a mucocin synthesis (Scheme 29).[33] Starting from the protected D-galactose **128** the lactone **129** was prepared. After Grignard addition of the lower side chain the resulting hemiacetal **130** was subjected to a stereoselective cationic reduction to yield **131**. The hydrogenolytic cleavage of the benzyl ethers gave **132**, which *via* derivatisation and subsequent elimination of the *cis*-diol led to **133** and finally to the desired THP-moiety of mucocin **134**. The THP-building block **134** was used by Takahashi in a total synthesis of jimenezin too.[34]



Scheme 27

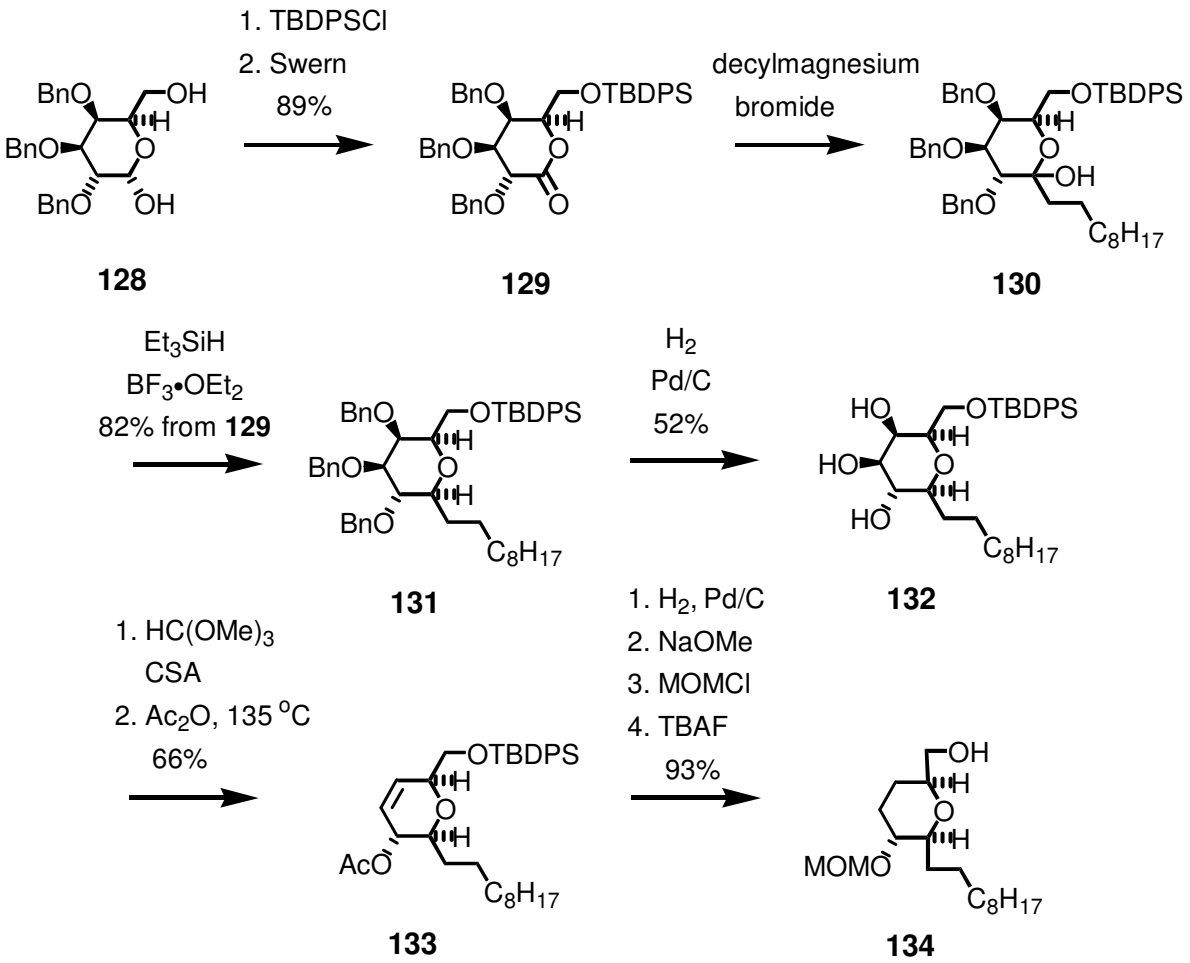


Scheme 28

6. Conclusion

The comparison of the different synthetic solutions allows a few conclusions. All of the reviewed contributions show a very high yielding and selective key step. In most cases this key step fits well into an overall elegant synthesis. In a few cases the use of the key step requires extra steps to adopt to the rest of the synthetic strategy.

The routes that close the THP ring *via* CO bond formation establish the stereocenters before the key step. In contrast, two of the routes for THP ring closure *via* CC-bond formation (SmI_2-induced reductive cyclization, allylboration) form the strategic bond and two stereocenters in just one step. This is a better synthetic performance than creating the strategic bond and the stereocenters in two different steps.



Scheme 29

In conclusion, the broad variety of synthetic solutions for the THP-moieties of the annonaceaous acetogenins are convincing examples for state of the art heterocyclic natural product synthesis.

Acknowledgments

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RECENT DEVELOPMENTS IN THE CHEMISTRY OF 2-THIENYLPYRROLES: SYNTHESIS, REACTIVITY AND APPLICATIONS

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Abstract. *Recent advances concerning the synthesis, reactivity and potential applications of 2-thienyl-pyrroles are reported in the present review. Thienylpyrroles play important roles in natural product chemistry, agriculture, materials science and medicinal chemistry. In materials science, they have found applications as nonlinear optical chromophores, conducting polymers and anion binding agents, while, in medicinal chemistry, they are important building blocks for the synthesis of antitumor agents displaying also antiviral, antibacterial, antifungal, antiinsecticidal and antiherbicidal activities. Therefore the deevelopment of efficient methods for the synthesis of these compounds has become an important and topical area of heterocyclic chemistry. In our laboratories, we have developed a convenient method for the synthesis of 1-alkyl(aryl)-2-thienylpyrroles, through the combination of the Friedel-Crafts and Lawesson reactions. 1-Alkyl(aryl)-2-thienylpyrroles were used as precursors in several type of reactions, allowing the preparation of a variety of new donor-acceptor substituted thienylpyrroles. The characterization of the solvatochromic, optical (linear and nonlinear) and thermal properties of the new π-conjugated push-pull systems are described. The prospects of application of the new compounds are also discussed. Particular attention has been paid to their application as solvatochromic probes and as efficient and thermally stable nonlinear optical materials.*

Contents

1. Introduction

Thiophene and pyrrole moieties play important roles in synthetic and medicinal chemistry, as they are present in a large number of natural products and biologically active compounds.[1] Among five-membered heterocycles, pyrroles possess the highest reactivity and most diverse chemical properties. It is not accidental that it is pyrrole that Nature has "chosen" for constructing the vital pigments chlorophylls and hemoglobin, as well as other vitally important supramolecular structures (various porphyrins, chlorins, prodigiosins, vitamin B_{12}, etc.).

For this reason, amongst all five-membered aromatic heterocycles, molecules containing the pyrrole nucleus have attracted the greatest attention of researchers and have been studied in most detail. Especially, 2-aryl- and 2-heteroaryl-substituted pyrroles are of great interest to the pharmaceutical industry, for instance, as precursors in the synthesis of chemotherapeutics.[2]

Furthermore, synthetic pyrrole containing derivatives (*e.g.* thienylpyrroles and 2,5-dithienylpyrroles) and π-conjugated oligo- and poly-pyrrolic systems are of growing relevance in materials science, supramolecular chemistry and nanotechnology. For example, they have found application in anion binding and cation coordination,[3,4] conducting organic polymers,[5] liquids crystals[6] and nonlinear optics.[7]

The wide array of interesting properties has inspired the development of several procedures for the preparation of differently substituted pyrroles.[8] Methods of synthesis range from the classical Knorr,[9] Paal-Knorr[10] and Hanstzch[11] strategies, transition-metal-catalyzed couplings,[12] 1,3-dipolar cycloadditions procedures[13] and multicomponent protocols.[14] On the other hand, methods for the construction of 2-(2´-thienyl)pyrroles remains limited and the development of new synthesis methods for these heterocycles is an important and challenging objective.

2. Synthesis of 2-thienylpyrroles

2.1. Introduction

The chemistry of thienylpyrroles is a very recent field in the chemistry of heterocyclic compounds. In the last few years, synthetic 2-thienylpyrrole derivatives have come in focus. However, even more than 60 years since the first 2-thienylpyrrole, *bis*-2-[5-(2-thienyl)pyrrole]azametine dihydrochloride (Figure 1) has been reported by Edward Knott[15] at Kodak, Ltd., the synthesis of functionalized thienylpyrroles remains challenging. Conventional methods for the synthesis of pyrroles such as Knorr, Hantzsch, Barton-Zard

(except the Paal-Knorr synthesis) have not found wide use for the preparation of pyrroles bound to thiophene. Often, the yields are low and the regioselectivity is only modest.

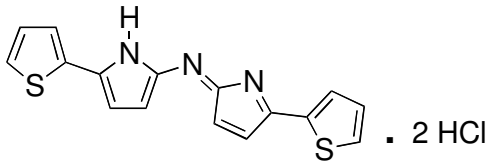


Figure 1

Until recently, no sufficiently efficient and general methods of preparation existed; therefore, although these compounds remained attractive, they were difficult to obtain and were consequently not extensively studied. The development of this field begain in the 1970s, when new methods for pyrrole synthesis (*e.g.* coupling reactions, condensation of heteroarylacetylenes with trimethylsilyl cyanide as well as those with the use of isocyanides, other cyano compounds, azides, etc.) appeared or the existing procedures were modified to allow for linking five-membered aromatic heterocycles. Therefore, 2-thienylpyrroles and their *N*-methyl and *N*-vinyl derivatives have been prepared in a variety of ways. Among the previously reported routes to 2-aryl- and 2-heteroarylpyrroles, the Trofimov reaction of ketoximes with acetylene (or their precursors) is one of the most important. The synthesis of 2-(2-thienyl)-1-vinylpyrroles by this method was first reported in 1977 by Trofimov *et al.* with a yield of 50%.[16a] This procedure allows the synthesis not only of 2-(2´-thienyl)pyrroles unsubstituted on the nitrogen atom but also their 1-vinyl derivatives.[16]

Recent reports on the synthesis of thienylpyrroles include the preparation of those heterocycles through 1,3-dipolar cycloaddition of azomethine ylides with bis-sulfonyl ethylenes,[13b] TMSOTf-mediated reaction of donor-acceptor cyclopropanes with 2-cyanothiophene reactions[17] and a novel version of the Trofimov reaction.[18] However, all these methods have some limitations with respect to the regioselectivity and substitution patterns that can be introduced.

2.2. Synthesis through the combination of the Friedel-Crafts and the Lawesson reactions

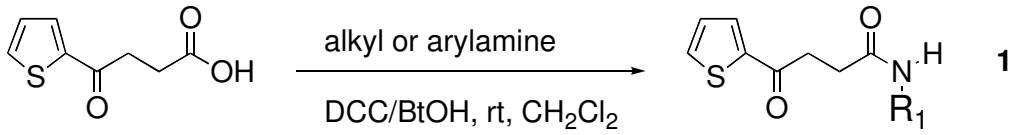
2.2.1. Synthesis of secondary alkyl and aryl-4-(2´-thienyl)-4-oxobutanamides

A common approach to the synthesis of both thiophene and pyrrole groups involves the use of 1,4-dicarbonyl compounds. In the thiophene case, the 1,4-dicarbonyl compound is reacted with a source of sulfur, usually H_2S and HCl, phosphorus(V) sulfide or Lawesson´s reagent (LR).[19] Similarly, pyrroles have traditionally been prepared *via* the condensation of 1,4-dicarbonyl compounds with ammonia or primary amines through the Paal-Knorr synthesis. However, the preparation of the initial 1,4-diketones and/or amines with thienyl substituents remains a challenge: their synthesis includes several stages which do not always result in high yields, a fact which in many circunstances limits the applicability of this method.[10]

Our strategy for the synthesis of 1-(alkyl)aryl-2-thienyl-substituted pyrroles was based on the combination of the Friedel-Crafts and the Lawesson reactions.

Recently, we have reported an efficient synthesis of of *N,N*-dialkyl-4-(2´-thienyl)-4-oxobutanamides by direct amidation of 4-oxo-(2-thienyl)butanoic acid through a DCC/BtOH mediated reaction.[20] We applied this approach to the synthesis of several secondary amides: *N*-propyl-4-(2´-thienyl)-4-oxobutanamide **1a** and aryl-4-(2´-thienyl)-4-oxobutanamides **1b–x**, which embody a number of different substituents on the aryl

moiety donating substituents (Cl, Br, I, CH_3, OH, OMe) or withdrawing substituents (CO_2Me, CN, NO_2) thereby extending our earlier work. Starting from succinic anhydride, we prepared the 3-carbomethoxy-propionyl chloride which, after the Friedel-Crafts reaction with thiophene, yielded methyl 4-(2-thienyl)-4-oxobutanoate. Hydrolysis of the γ-keto ester gave 4-oxo-(2-thienyl)butanoic acid.[20,21] Transformation of 4-oxo-(2-thienyl)butanoic acid to the alkyl and aryl-4-(2´-thienyl)-4-oxobutanamides **1a–x** was carried out by direct amidation of the acid with several commercial alkyl- and arylamines through DCC/BtOH mediated reaction (Scheme 1).[22,23] We found that no secondary products were detected and the yields were fair to good depending on the nucleophilicity of the arylamine (Table 1).



Scheme 1

Table 1. Experimental data obtained in the synthesis of secondary 2-thienyl-4-oxobutanamides **1**.[20,22,23]

Entry	Compound 1	R_1	Yield (%)[a]	δ_H (ppm)[b]
1	**a**	*n*-Pr	80	—
2	**b**	Ph	42	4.54
3	**c**	1-Naphthyl	20	5.23
4	**d**	2-MeOPh	46	4.36
5	**e**	4-MeOPh	62	4.21
6	**f**	2,4-diMeOPh	64	3.99
7	**g**	3,5-diMeOPh	56	4.64
8	**h**	3,4,5-triMeOPh	49	4.44
9	**i**	2-HOPh	54	4.23
10	**j**	2-MePh	51	4.35
11	**l**	2-FPh	73	4.64
12	**m**	4-FPh	41	4.54
13	**n**	2-ClPh	53	4.93
14	**o**	3-ClPh	23	5.15
15	**p**	4-ClPh	22	4.80
16	**q**	2-BrPh	53	4.95
17	**r**	4-BrPh	30	4.83
18	**s**	2,4-diBrPh	26	5.16
19	**t**	2-IPh	55	4.89
20	**u**	3-NO_2Ph	24	5.34
21	**v**	4-CO_2MePh	35	5.45
22	**x**	4-CNPh	31	5.63

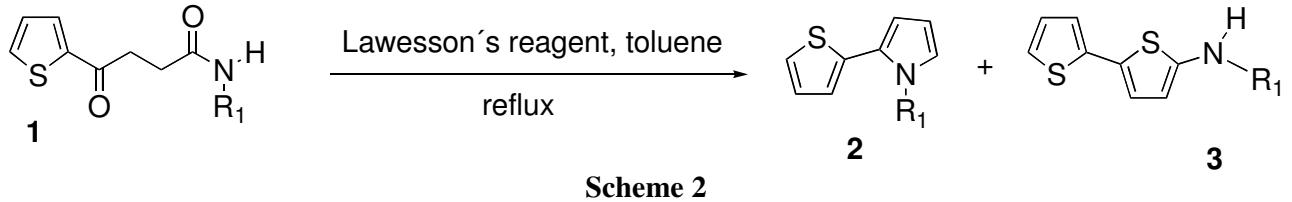
[a]Reaction time: 7 days. [b]For the NH_2 protons of arylamines (300 MHz, acetone-d_6).

A broad correlation could be observed between reaction yields of the synthesis of amides **1** and the chemical shift of the nitrogen protons of the starting arylamines; in fact, from the data in Table 1, it was

possible to infer that an increase in the chemical shift of the NH_2 protons results in a decrease in the basic character of the arylamine and lower yields were obtained for the corresponding aryl-4-(2´-thienyl)-4-oxobutanamides **1b–x**. The effect of different substituents in the anilines used was noteworthy (20–73%). As expected, the amides **1e,f** and **l** (Table 1, entries 5, 6 and 11) obtained from the anilines with electron-donating groups in *ortho* or/and in *para* position (δ_H 3.99–4.64 ppm) were synthesized in better yields: 62–73%. The amides **1u–x** (Table 1, entries 20–22) obtained from anilines with electron-withdrawing groups in *meta* or *para* position (δ_H = 5.34–5.63 ppm) were synthesized in fair yields: 24–35%. 1-Naphthylamine (δ_H = 5.23 ppm) was even less reactive than the other arylamines giving only 20% of amide **1c** (Table 1, entry 4). Arylamides **1c,o,p,r,s,u–x** were obtained in lower yields even after reaction time of seven days. It was possible to detect, by TLC, some unreacted 4-oxo-(2-thienyl)butanoic acid and arylamine starting material. We also examined the effect of reaction time on the synthesis of aryl-4-(2´-thienyl)-4-oxobutanamides **1b–x**. As expected, a longer reaction time was necessary for the synthesis of aryl-4-(2´-thienyl)-4-oxobutanamides **1b–x** (7 days) compared to the analogous reaction to obtain *N,N*-dialkyl-4-(2´-thienyl)-4-oxobutanamides (1 day).[20] We also observed that, in the case of aryl-4-(2´-thienyl)-4-oxobutanamides **1l** and **1s**, the yields improved markedly when the reaction time was increased from one to seven days (**1l**, 14–73%), (**1s**, 8–26%). This new method for the synthesis of secondary alkyl and aryl-4-(2´-thienyl)-4-oxobutanamides is interesting because the experimental procedures described use mild reaction conditions and simple work-up procedures allowing preparation of these derivatives in moderate to good yields.

2.2.2. Reaction of secondary alkyl and aryl-4-(2´-thienyl)-4-oxobutanamides with Lawesson´s reagent

In an earlier study, we have synthesized several 5-alkoxy- and 5-*N,N*-dialkylamino-2,2´-bithiophenes by reaction of *N,N*-dialkyl-4-(2´-thienyl)-4-oxobutanamides with an equimolar amount of Lawesson´s reagent (LR) in toluene at refluxing temperature.[20] When the secondary alkyl- **1a** and aryl-4-(2´-thienyl)-4-oxobutanamides **1b–x** were submitted to the same experimental conditions, we observed that, instead of the expected 5-arylamino-2,2´-bithiophenes, 1-aryl-2-(2´-thienyl)pyrroles **2** and/or 5-arylamino-2,2´-bithiophenes **3** were obtained (Scheme 2, Table 2).[20,22,23]



1 **2** **3**

Scheme 2

Therefore, attempts to convert the secondary alkyl- and aryl-4-(2´-thienyl)-4-oxobutanamides **1a–x** into the corresponding 5-alkyl- or 5-arylamino-2,2´-bithiophenes **3** gave only thienylpyrroles **2** (3–55%), (Table 2, entries 1, 3 and 7–9) or a mixture of thienylpyrroles **2** (16–58%) and bithiophene derivatives **3** (Table 2, entries 2, 4–6, 10–12, 15, 17, 18, 20–22) in low yields (7–32%), pyrroles being the major compounds (Table 2, Scheme 2). Bithiophene derivatives **3n,o,q,t** were obtained as major compounds (21–55%) only when 2- or 3-haloaryl-4-(2´-thienyl)-4-oxobutanamides **1n,o,q,t** were treated with LR under the same experimental conditions described above (Table 2, entries 13, 14, 16 and 19). Treatment of 2´´-hydroxyphenyl-4-(2´-thienyl)-4-oxobutanamide **1i** with LR gave a complex mixture with several products (TLC). After purification by flash chromatography, it was only possible to isolate and identify

traces (3%) of pyrrole **2i**. The very low yield of pyrrole **2i** was probably due to the formation of the corresponding phosphorous-containing heterocycle.[19a,d]

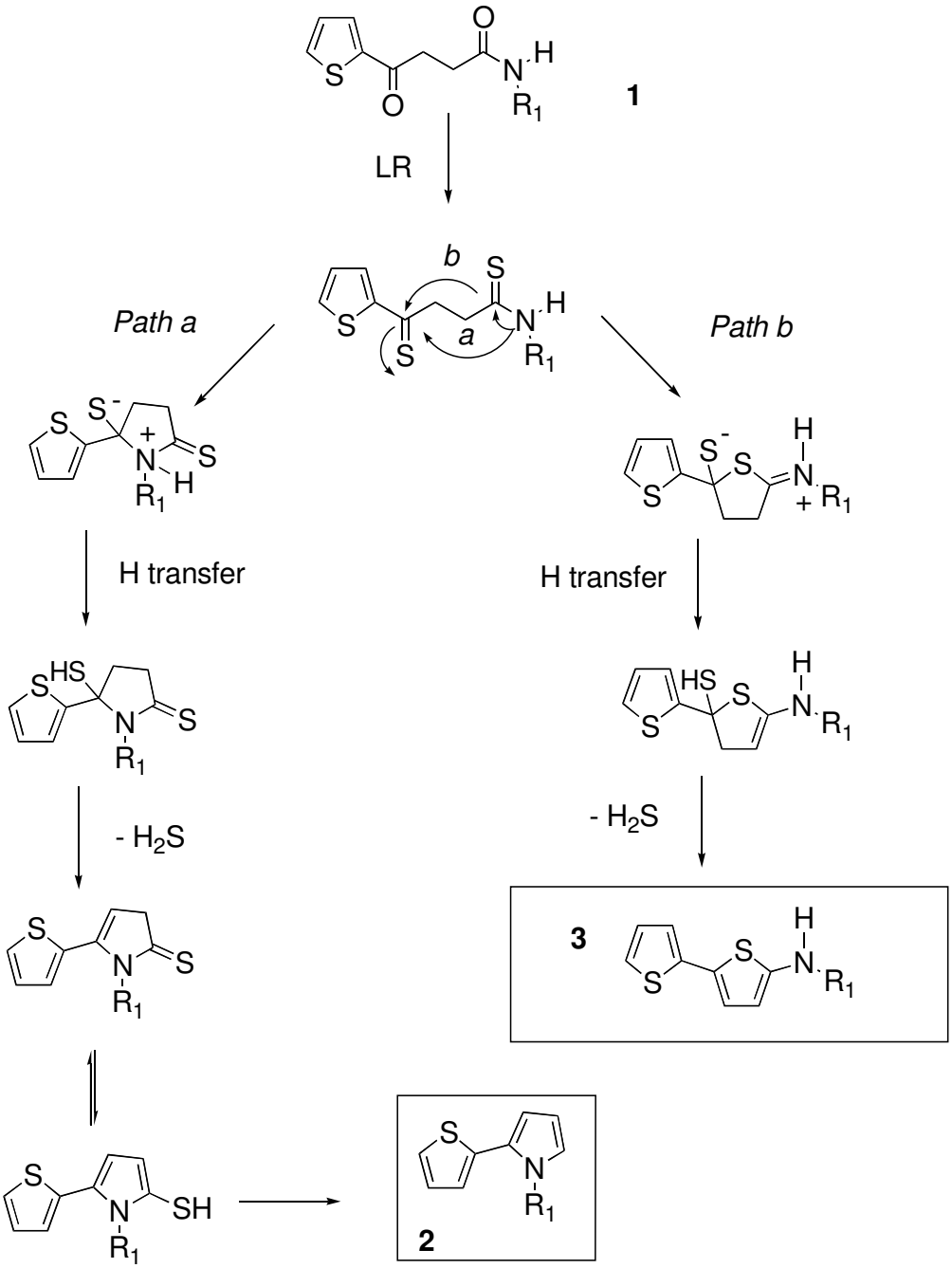
Reactivity studies performed with amides **1m** and **1e**, using different stoichiometric amounts of LR, showed that, the yield of 1-(4´´-fluorophenyl)-2-(2´-thienyl)pyrrole **2m** dropped from 58 to 26% (and no 5-(4´´-fluoroanilino)-2,2´-bithiophene **3m** was isolated), when 0.5 equiv. of LR was used in this reaction. In the case of 4-methoxyphenyl-4-(2´-thienyl)-4-oxobutanamide **1e**, the reflux in toluene during 9 h without LR, resulted in recovery of the unchanged amide **1e**.

Table 2. Experimental data obtained in the synthesis of pyrroles **2** and bithiophenes **3** from secondary alkyl and aryl-4-(2´-thienyl)-4-oxobutanamides **1a–x**.[20,22,23]

Entry	R_1	Reaction time (min.)	Thienylpyrroles 2	Yield (%)	Bithiophenes 3	Yield (%)
1	*n*-Pr	30	**a**	47	**a**	__
2	Ph	15	**b**	58	**b**	9
3	1-naphthyl	20	**c**	55	**c**	__
4	2-MeOPh	15	**d**	16	**d**	14
5	4-MeOPh	15	**e**	33	**e**	14
6	2,4-diMeOPh	15	**f**	32	**f**	12
7	3,5-diMeOPh	15	**g**	24	**g**	__
8	3,4,5-triMeOPh	30	**h**	49	**h**	__
9	2-HOPh	20	**i**	3	**i**	__
10	2-MePh	15	**j**	35	**j**	16
11	2-FPh	20	**l**	30	**l**	17
12	4-FPh	15	**m**	58	**m**	8
13	2-ClPh	30	**n**	16	**n**	21
14	3-ClPh	30	**o**	24	**o**	31
15	4-ClPh	15	**p**	22	**p**	15
16	2-BrPh	15	**q**	6	**q**	46
17	4-BrPh	30	**r**	34	**r**	7
18	2,4-diBrPh	25	**s**	24	**s**	15
19	2-IPh	15	**t**	8	**t**	55
20	3-NO_2Ph	25	**u**	26	**u**	21
21	4-CO_2MePh	15	**v**	37	**v**	32
22	4-CNPh	15	**x**	32	**x**	19

A plausible mechanism for the formation of five membered heterocycles, pyrroles **2** and/or bithiophenes **3** from secondary amides **1** involves an initial thionation of **1** to the corresponding 4-thioxo thioamides followed by further changes shown in Scheme 3. A subsequent intramolecular nucleophilic attack of thioamide N-atom to thiocarbonyl group leads to cyclized produt, which, after elimination of H_2S, suffers desulfurization of thioxo group to 1-(alkyl)aryl-2-(2´-thienyl)pyrroles **2** (*Path a*). On the other hand, the imidothiol form of 4-thioxo thioamides undergoes a ring closure to give 5-amino-2,2´-bithiophenes **3**

(*Path b*). A similar mechanism was proposed earlier by Nisho for the formation of pyrroles and thiophenes from diphenyl-4-oxobutanamides.[24]



Scheme 3[24]

The synthesis of 1-(alkyl)aryl-2-(2´-thienyl)pyrroles **2** and 1-arylamino-2,2´-bithiophenes **3** was reported for the first time by us from aryl-4-(2´-thienyl)-4-oxobutanamides **1a–x** as a combination of the Friedel-Crafts and the Lawesson reaction. If suitable (alkyl)aryl-4-(2´-thienyl)-4-oxobutanamides were synthesized, the synthesis of a large range of 1-(alkyl)aryl-2-(2´-thienyl)pyrroles **2** and 1-amino-2,2´-bithiophenes **3** would be possible. The synthesis of new 1-aryl-substituted thienylpyrroles **2** is an important achievement because this substitution makes it possible to modify the properties of polymers, including the synthesis of chiral conducting polymeric materials with better properties for several optical applications (*e.g.*

NLO).[5b,d,25] The thienylpyrroles **2** described above were used later (see sub-chapter 3.) as precursors in several reactivity studies in order to obtain new donor-acceptor conjugated heterocyclic systems.

3. Synthesis of donor-acceptor substituted 2-thienylpyrrole derivatives

3.1. Introduction

Currently, a variety of synthetic approaches to substituted pyrroles exist although their synthesis, in general, remains challenging. Often, the yields are rather low and a significant number of by-products, such as undesired regioisomers, are obtained. Furthermore, pyrroles are susceptible to chemical degradation as they are rather easily oxidized; this further hampers their synthesis and especially their isolation and purification. Thus, even 150 years after its isolation and synthesis and more than 100 years after the classical pyrrole synthesis was developed, the synthesis of highly substituted pyrroles is anything but straightforward.[8a,f,26] Therefore, the development of effective methods for the regioselective functionalization of the pyrrole or the thiophene rings on thienylpyrrole systems remains an important synthetic challenge, in particular due to the fact thienylpyrrole derivatives are the key building blocks used in the synthesis of important and complex heterocyclic systems.[16d]

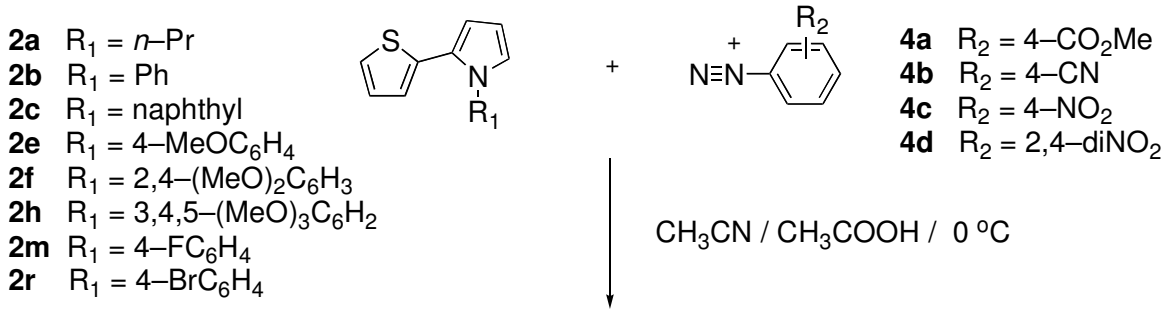
Thiophene and pyrrole are electron-rich heteroaromatic compounds and hence their predominant chemical reactivity is an attack by electrophiles followed by a substitution reaction. The reactivity of pyrrole is comparable to that of an electron-rich benzene derivative such as aniline or phenol. In a typical electrophilic aromatic substitution such as bromination, pyrrole is about 5.9×10^8 times more reactive than thiophene.[27] As a consequence, electrophilic substitution reactions of thienylpyrroles were found to be very selective. According to earlier reports, the pyrrole nitrogen atom has a greater ability to delocalize the positive charge of σ-complexes than the sulfur atom in thiophene; pyrrole is therefore considerably more reactive towards electrophilic substitution than thiophene. Even when both α-positions of the pyrrole ring are occupied, electrophilic substitution will preferentially occur in the β-position of the pyrrole ring rather than the α-position of the thiophene ring.[26,28a,b] The reactivity of these systems has been demonstrated with the use of electrophilic reactions producing derivatives with the electrophile substituted primarily on the pyrrole ring.[16c,d,27-30] Before our recent work, only a few papers were published concerning the regioselectivity studies of 1-alkyl(vinyl)-2-thienypyrrole systems. These studies reported the results concerning essentially electrophilic aromatic substitutions and nucleophilic addition to the triple bond on a few selected examples of simple thienylpyrroles.[7f,16c,d,28a,b,29d] No reports were found concerning the functionalization of 1-aryl-(2-thienyl)pyrroles.

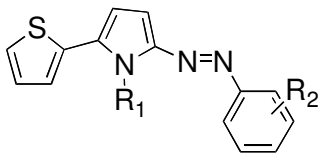
Following our interest in the chemistry of the new thienylpyrroles **2**, we have used these compounds as precursors for the synthesis of functionalyzed thienylpyrrole derivatives. Pyrroles **2** have proved to be versatile substrates in several reactions (aromatic electrophilic substitutions: azo coupling, direct tricyanovinylation reaction, Vilsmeier-Haack formylation), metalation followed by reaction with DMF, conversion of the formyl-pyrroles to dicyanovinyl, benzothiazolyl and benzimidazolyl groups, allowing the preparation of interesting new donor-acceptor substituted thienylpyrroles, selectively functionalized on the pyrrole or on the thiophene rings (see sub-chapters 3.2.–3.6.).

3.2. 2-Thienylpyrrole azo dyes

Our synthesis of 2-thienylpyrroles **2** through the combination of the Friedel-Crafts and Lawesson reactions made these compounds available in reasonable amounts, ready for further applications. Indeed we

are able to use these derivatives with success, as coupling components in azo coupling reactions, allowing the preparation of several new donor-acceptor substituted thienylpyrroles 1-alkyl(aryl)-2-(2´-thienyl)-5-phenylazopyrrole derivatives **5** which have *para* CO_2Me, CN, NO_2 and *ortho-para* NO_2 groups as the electron-withdrawing groups on the phenylazo moiety and the conjugated 1-alkyl(aryl)-2-(2´-thienyl)-pyrrole, as strong π-electron donor systems. The coupling reaction of aryldiazonium salts **4a–d** with 1-alkyl(aryl)-2-(2´-thienyl)pyrroles **2** gave rise to the formation of 1-alkyl(aryl)-2-(2´-thienyl)-5-phenylazo-pyrrole derivatives **5**, by reacting 1-alkyl(aryl)-2-(2´-thienyl)pyrroles with aryldiazonium salts **4a–d** in acetonitrile/acetic acid for 2 h at 0 ºC. As expected, we observed that the diazo coupling was accomplished selectively at the 5-position[31] of pyrrole ring to give compounds **5** in moderate to excellent yields (31–90%), (Scheme 4, Table 3).[32] These results were in agreement with the greater nucleophilicity of the pyrrole ring as compared wit the thiophene ring as has been shown earlier.[28a,b,29d] At the same time, Trofimov *et al.* reported the synthesis of 2-arylazo-1-vinylpyrroles through a modified azo coupling of 1-vinylpyrroles with arenediazonium hydrocarbonates, in which two 2-arylazo-5-thienyl-1-vinylpyrroles were also prepared.[7f]





5a R_1 = *n*–Pr, R_2 = 4–NO_2

5b R_1 = Ph, R_2 = 4–NO_2

5c R_1 = naphthyl, R_2 = 4–NO_2

5e$_1$ R_1 = 4–$MeOC_6H_4$, R_2 = 4–CO_2Me
5e$_2$ R_1 = 4–$MeOC_6H_4$, R_2 = 4–CN
5e$_3$ R_1 = 4–$MeOC_6H_4$, R_2 = 4–NO_2
5e$_4$ R_1 = 4–$MeOC_6H_4$, R_2 = 2,4–diNO_2

5f R_1 = 2,4–$(MeO)_2C_6H_3$, R_2 = 4–NO_2

5h R_1 = 3,4,5–$(MeO)_3C_6H_2$, R_2 = 4–NO_2

5m R_1 = 4–FC_6H_4, R_2 = 4–NO_2

5r R_1 = 4–BrC_6H_4, R_2 = 4–NO_2

Scheme 4

3.3. Tricyanovinyl 2-thienylpyrroles

Three synthetic routes are widely used for the preparation of tricyanovinyl derivatives. Direct reaction of tetracyanoethylene (TCNE) with activated aromatic rings,[33] condensation of an aldehyde with

malononitrile followed by reaction with potassium cyanide and oxidation with lead tetraacetate[33a] or lithiation folowed by quenching with TCNE.[34]

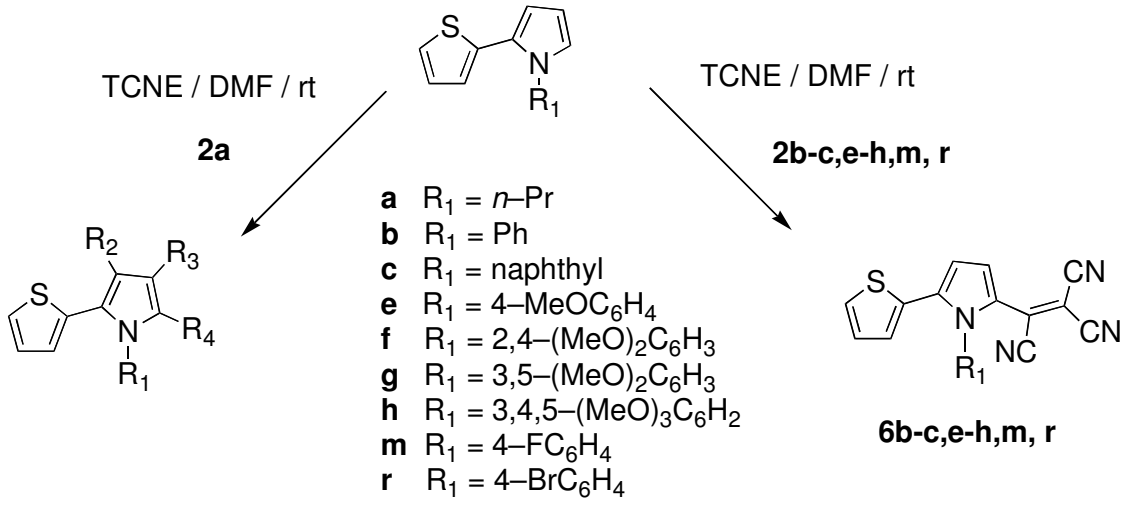
Table 3. Experimental data obtained in the synthesis of azo dyes **5**.[32]

Thienylpyrrole	R_1	λ_{max} (nm)[a]	Thienylpyrrole azo dye	R_2	λ_{max} (nm)[a]	Yield (%)
2a	*n*-Pr	291.0	**5a**	4-NO_2	488.0	63
2b	Ph	294.5	**5b**	4-NO_2	497.0	70
2c	Naphthyl	288.5	**5c**	4-NO_2	498.0	34
2e	4-MeOPh	290.0	**5e$_1$**	4-CO_2Me	473.0	85
2e	4-MeOPh		**5e$_2$**	4-CN	479.0	84
2e	4-MeOPh		**5e$_3$**	4-NO_2	500.0	81
2e	4-MeOPh		**5e$_4$**	2,4-diNO_2	531.0	47
2f	2,4-diMeOPh	286.5	**5f**	4-NO_2	507.0	84
2h	3,4,5-triMeOPh	281.5	**5h**	4-NO_2	499.0	88
2m	4-FPh	293.0	**5m**	4-NO_2	496.0	90
2r	4-BrPh	289.5	**5r**	4-NO_2	492.0	31

[a]All the UV-vis spectra were recorded in ethanol.

Direct tricyanovinylation reactions using 2-thienylpyrroles **2** as substrates gave, as expected, the tricyanovinyl-substituted thienylpyrroles **6–8**, which were selectively functionalized on the pyrrole ring.[29d] The tricyanovinyl- group was introduced in a manner similar to that of a previously reported procedure,[35] that is by reacting the activated thienylpyrroles **2** with TCNE in DMF during 15 min.–3 h at room-temperature (Scheme 5). Under these experimental conditions, we observed that, 1-aryl-2-(2´-thienyl)-pyrroles **2b,c,e–h,m,r** reacted regioselectively forming 1-aryl-2-(2´-thienyl)-5-tricyano-vinylpyrroles **6b,c,e–h,m,r** with yields of 31–73% (Table 4). 1-*n*-Propyl-2-(2´-thienyl)pyrrole **2a** behaved quite differently in this reaction: the main reaction product was **7a** (29%) which results from the substitution at the 3-position of the pyrrole ring; in addition, the 5- and 4-tricyanovinyl-substituted pyrrole derivatives **6a** (12%) and **8a** (8%) were also isolated (Table 4, entries 1–3).[36] In interpreting these results it seems appropriate to take into account the possible steric influence of the *n*-propyl group impeding the substitution at the α-position of the pyrrole ring.[26b]

The tricyanovinyl derivatives synthesized are colored with metallic luster. As for similar 2,5-dithienyl-pyrrole derivatives, the color of the tricyanovinyl-substituted pyrroles **6–8** depends on the substituent on the nitrogen of the pyrrole ring.[5k–o]



6a $R_4 = C(CN)=C(CN)_2$, $R_2 = R_3 = H$
7a $R_2 = C(CN)=C(CN)_2$, $R_3 = R_4 = H$
8a $R_3 = C(CN)=C(CN)_2$, $R_2 = R_4 = H$

Scheme 5

Table 4. Experimental data obtained in the synthesis of tricyanovinyl thienylpyrroles **6–8**.[36]

Thienylpyrrole	R_1	Tricyanovinyl-thienylpyrrole	Yield (%)	IR ν_{CN} (cm^{-1})	λ_{max} (nm)[a]
2a	*n*-Pr	**6a**	12	2215	491.5
2a	*n*-Pr	**7a**	29	2217	408.5
2a	*n*-Pr	**8a**	8	2221	416.0
2b	Ph	**6b**	35	2211	511.5
2c	Naphthyl	**6c**	34	2207	516.5
2e	4-MeOPh	**6e**	50	2212	519.0
2f	2,4-diMeOPh	**6f**	63	2210	525.5
2g	3,5-diMeOPh	**6g**	37	2216	514.5
2h	3,4,5-triMeOPh	**6h**	73	2207	519.0
2m	4-FPh	**6m**	37	2204	510.5
2r	4-BrPh	**6r**	31	2213	509.0

[a]All the UV-vis spectra were recorded in ethanol.

3.4. Formyl thienylpyrroles

3.4.1. Introduction

Formylation is a key process in organic synthesis, with the resulting aldehyde function being a "crossroads" intermediate. Not surprisingly, a large number of methods has been developed for this reaction. Reagents for electrophilic formylation are mostly of the form Y-CH=X^+. Thus the reactions attributed to Vilsmeier ($ClCH=NR_2^+$), Rieche (*e.g.* $MeOCHCl_2 \rightarrow MeO=CHCl^+$), Gatterman ($Zn[CN]_2/HCl \rightarrow HC=NH_2^{2+}$), Gatterman-Koch (CO/HCl/Lewis acid → $HC=O^+$) and even Duff ($CH_2=NH_2^+$ - followed by dehydrogenation of initially formed RCH_2NH_2) all fit this pattern.[37]

Organolithiums, with their unparalleled ability to react with a wide variety of electrophilic compounds, are surely the most versatile of the metalated heterocycles. Usually they are prepared by direct deprotonation of acidic hydrogens using strong bases or, particulary useful in the case of the less acidic sites in aromatic rings, by halogen exchange between a halogenated heterocycle and an organolithium compound or lithium metal. Another frequent alternative is the so-called *ortho*-lithiation or "directed *ortho*-metalation" (DoM) which is the metalation of an aromatic ring adjacent to a heteroatom-containing functional group by providing the lithium base with a coordination point, thus increasing reactivity close to the coordination site. The lithiated species generated by all these methods are able to react with all kinds of electrophiles.[38]

Vilsmeier formylation and metalation followed by quenching with DMF constitute the most significant routes for the preparation of formyl-substituted pyrroles and thiophenes.[27,39]

The formyl-derivatives obtained can further react to produce more complex molecules this has made formyl-thiophenes and formyl-pyrroles some of the most important intermediates and building blocks widely employed in the synthesis of diverse biological active compounds,[40] conducting polymers,[41] anion receptors in biomedical analysis,[42] porphyrins,[43] supramolecular chemistry[44] and molecular electronics.[35,45]

However, until our recent work[23] concerning the formylation of 1-alkyl(aryl)-2-thienylprroles **2** little was known about thienylpyrroles containing an aldehyde moiety. There was only one previous work describing the formylation of thienylpyrroles and this study was performed through the Vilsmeier-Haack reaction on the simple 2-(2´-thienyl)pyrrole and 2-(3´-thienyl)pyrrole. Bouka *et al.* exclusively obtained thienylpyrrole derivatives formylated on the α-position of the pyrrole ring.[28] At the same time that we have reported our work,[23] Trofimov *et al.* communicated the synthesis of 1-vinyl-2-carbaldehydes in which the preparation of a mixture of 1-vinyl-5-formyl-2-(2-thienyl)pyrrole and its vinyl-free 5-formylthienylpyrrole was included.[28c] The development of a general approach to thienylpyrroles containing the aldehyde functionality on the pyrrole or on the thiophene moieties represents an important synthetic challenge.

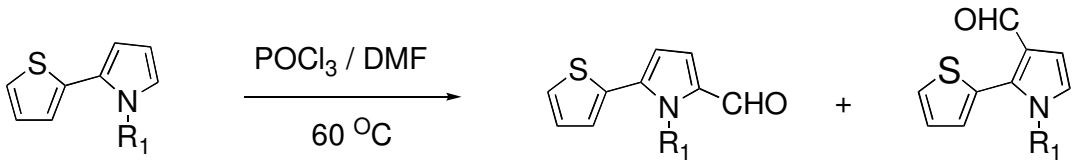
Therefore, we decided to study the reaction behavior of different thienylpyrroles bearing *N*-alkyl or *N*-aryl groups on the pyrrole ring through the Vilsmeier-Haack formylation or through metalation followed by reaction with DMF.

3.4.2. Vilsmeyer formylation

As expected, Vilsmeier formylation of thienylpyrroles **2** proceeded selectively in the pyrrole ring to form the corresponding formyl-substituted thienylpyrroles **9** and **10** (Scheme 6, Table 5).

In our studies of Vilsmeier-Haack formylation of 1-propyl-2-(2´-thienyl)pyrrole **2a**, the 5-position of the pyrrole ring was found to be much more reactive than the 3-position. The Vilsmeier-Haack formylation of **2a**, with $DMF/POCl_3$ at 60 ºC for 2 h produced a mixture of 5-formyl- **9a** (63%) and 3-formyl- derivative

10a, with lower yield (5%) (Table 5, entries 1–2). Under the same experimental conditions, 1-aryl-2-(2´-thienyl)pyrroles **2b** and **2e** behaved quite differently producing a mixture of the 5- and 3-formyl- derivatives in similar yields. Formylation of **2b** gave a mixture of **9b** (19%) and **10b** (22%), (Table 5, entries 3–4) and formylation of **2e** resulted in a mixture of **9e** (12%) and **10e** (10%). In comparison to alkylpyrrole **2a**, the formyl derivatives of 1-aryl-2-(2´-thienyl)pyrroles **2b** and **2e** were obtained in lower yields. In order to interpret the results obtained, we consider several factors: (*i*) an appreciably larger nucleophilicity of the pyrrole ring compared to that of thiophene; (*ii*) a decrease in the electron density in the pyrrole ring due to the competitive conjugation of the *N*-aryl group with the unshared electron pair on nitrogen and also due to its negative inductive effect; (*iii*) possible steric influence due to the *n*-propyl group for attack at the α-position of the pyrrole ring.



2a R_1 = *n*-Pr
2b R_1 = Ph
2e R_1 = 4-$MeOC_6H_4$

9a-b,e **10a-b,e**

Scheme 6

Table 5. Experimental data obtained in the synthesis of formyl-thienylpyrroles **9** and **10**.[23]

Entry	Pyrrole	Formyl-pyrrole	Yield (%)	δ_H (ppm)[a]	IR υ_{CHO} (cm^{-1})	λ_{max} (nm)[c]
1	**2a**	**9a**	63	9.54	1658	321.5
2	**2a**	**10a**	5	9.54	1662	293.5
3	**2b**	**9b**	19	9.39	1660	340.5
4	**2b**	**10b**	22	9.82[b]	1661	325.0
5	**2e**	**9e**	12	9.38	1655	343.0
6	**2e**	**10e**	10	9.81[b]	1661	----

[a]For the C*H*O proton of formyl-thienylpyrroles **9** and **10** (300 MHz, $CDCl_3$). [b]For the C*H*O proton of formyl-thienylpyrroles **9** and **10** (300 MHz, acetone-d_6). [c]All the UV-vis spectra were recorded in ethanol.

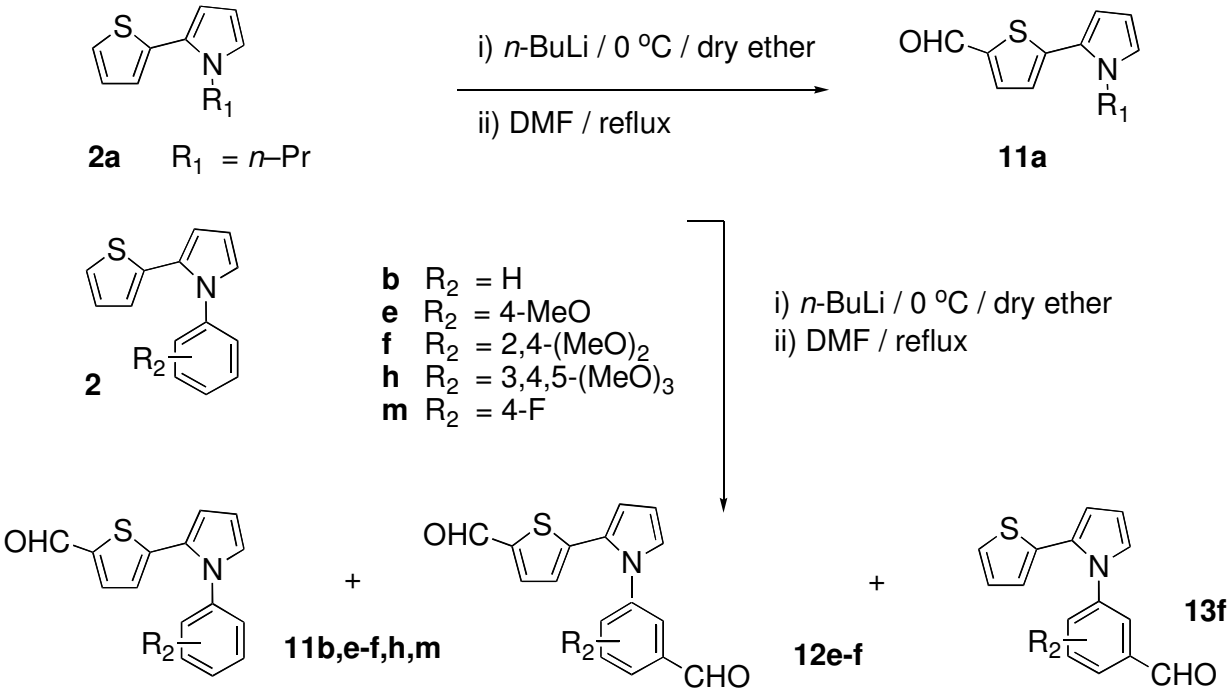
3-Substituted pyrroles are the most difficult to synthesize since most electrophilic aromatic substitution reactions and lithiation reactions of *N*-substituted pyrroles occur at the 2-position and so functionalization at the 3-position of pyrrole is a challenging goal in synthetic research. Bulky substituents on the nitrogen atom promote 3-substitution. This observation led to new approaches to the synthesis of

3-substituted pyrroles, as these are normally found only as by products in reactions leading predominantly to 2-substitution.[46] As 3-formyl *N*-arylpyrroles are key synthetic intermediates to highly active biological compounds, the preparation of new derivatives, even in fair yields, still remains an attractive goal.[16d,30,40a,k]

3.4.3. Metalation followed by reaction with DMF

The electron-rich five membered-aromatic *N*-substituted pyrrole, furan and thiophene are lithiated at C-2 by direct deprotonation with a lithium-containing base. Several authors have reported the α-lithiation of *N*-arylpyrroles using different experimental conditions: *n*-BuLi-TMEDA chelate, *n*-BuLi-*t*BuOK (LiCKOR) superbase, *tert*-BuLi-secondary amides, Na/dry ether/0 °C /*tert*-BuLi, *tert*-BuLi/–78 °C/THF, *n*-BuLi/THF/ –78 °C, *n*-BuLi-TMEDA/THF/–75 °C.[47]

As (5´-formyl-2´-thienyl)pyrroles could not be synthesized solely by the Vilsmeier-Haack reaction, we tried another synthesis strategy to prepare these compounds which involved lithiation followed by treatment with DMF. Therefore, metalation of thienylpyrroles **2** was carried out with *n*-BuLi in dry ether at 0 °C for 1 h. Subsequently, the organolithium derivatives were converted to the corresponding formyl compounds, by addition of DMF followed by refluxing the mixture for 1 h (Scheme 7, Table 6). In order to compare the reactivity of pyrroles **2** under the experimental conditions described above, the reaction time studied for all derivatives (for the metalation and for the reaction with DMF) was 1 h. We observed that, as a consequence of the limited reaction time, in some cases, unreacted starting materials remained in the reaction mixtures.



Scheme 7

Through this method, we were able to lithiate selectively thienylpyrroles **2a,b,h–m** at the α-position of the thiophene ring giving formyl-derivatives **11a,b,h–m**.

The methoxy group is known as a moderately strong *ortho* directing substituent with electron withdrawal and electron donor properties.[38a,48] At the same time, for compounds **2e,f**, the 4-methoxy and the

2,4-dimethoxy group(s) have an α-directing effect on the aromatic ring. Consequently, the formylation of the aromatic ring was also observed for thienylpyrroles **2e,f** (Table 6, entries 4, 6 and 7, compounds **12e,f**, **13f**) due to the *ortho* directing effect of the methoxy groups, giving a mixture of several formylated derivatives with (5´-formyl-2´-thienyl)pyrroles **11e,f** being the major products. For compound **2f**, we studied also the effect of the reaction time for the metalation step and for the reaction with DMF. Metalation of thienylpyrrole **2f** for 2 h followed by 2 h of reflux with DMF gave a mixture of four compounds: thienylpyrrole **2f** (18%), 1-(2´´,4´´-dimethoxyphenyl)-2-(5´-formyl-2´-thienyl)pyrrole **11f** (34%), 1-(3´´-formyl-2´´,4´´-dimethoxyphenyl)-2-(2'-thienyl)pyrrole **13f** (14%) and 1-(3´´-formyl-2´´,4´´-dimethoxyphenyl)-2-(5´-formyl-2'-thienyl)pyrrole **12f** (18%) (Table 6, entries 5–7). The experiment showed that, instead of improving the yield of compound **11f**, we obtained the diformylated compound **12f** and a higher yield for the formyl-aryl derivative **13f** as a result of the increased reaction time. Compounds **11h** and **11m** were obtained but in lower yields. It should be noted also that we could not isolate any benzylic formyl product from these reactions.

The synthesis of 5´-formyl-2-(2´-thienyl)pyrroles **11** selectively formylated on the thiophene ring of a thienylpyrrole system was reported for the first time by us[23] and this achievement opens the way to a new range of formyl functionalized thienylpyrroles. The formyl-thienylpyrroles selectively formylated on the pyrrole or on the thiophene rings were used later, as versatile building blocks in the synthesis of new donor-acceptor substituted thienylpyrroles through conversion of the formyl functionality to dicyanovinyl-, benzothiazolyl and benzimidazolyl groups (sub-chapters 3.5.–3.7.).

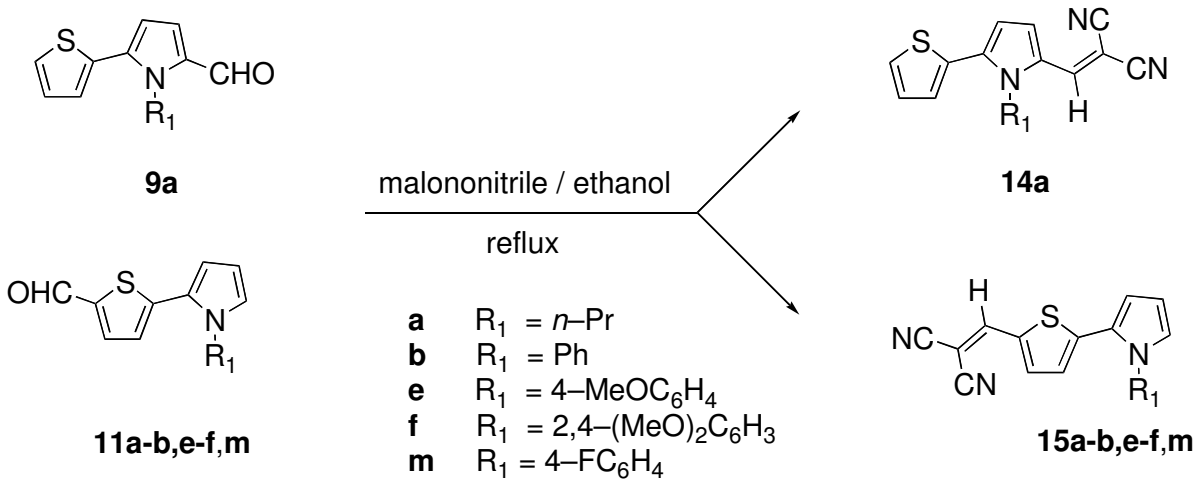
Table 6. Experimental data obtained in the synthesis of formyl-thienylpyrroles **11–13**.[23]

Entry	Pyrrole	Formyl-pyrrole	Yield (%)	δ_H (ppm)[b]	IR υ_{CHO} (cm^{-1})	λ_{max} (nm)[d]
1	**2a**	**11a**	68	9.87	1659	374.0
2	**2b**	**11b**	78	9.75	1659	374.0
3	**2e**	**11e**	63	9.74	1659	379.0
4	**2e**	**12e**	5	9.81[c], 10.48[c]	1659, 1684	374.0
5	**2f**	**11f**	48, 34[a]	9.73	1652	384.5
6	**2f**	**12f**	18[a]	9.75, 10.45	1657, 1690	377.0
7	**2f**	**13f**	8, 14[a]	10.45	1693	-----
8	**2h**	**11h**	12	9.77	1659	377.0
9	**2m**	**11m**	25	9.75	1659	373.5

[a]Yields for compounds **11f–13f** obtained for 2 h of lithiation followed by 2 h of reaction with DMF. [b]For the C*H*O proton of formyl-thienylpyrroles **11–13** (300 MHz, $CDCl_3$). [c]For the C*H*O proton of formyl-thienylpyrroles **11–13** (300 MHz, acetone-d_6). [d]All the UV-vis spectra were recorded in ethanol.

3.5. Dicyanovinyl 2-thienylpyrroles

Thienylpyrroles containing the formyl group in either the pyrrole (**9a**) or on the thiophene rings (**11a,b,e,f,m**) were condensed with malononitrile in refluxing ethanol producing dicyanovinyl- derivatives **14** and **15**, (Scheme 8, Table 7) in moderate to quantitative yields (36–100%).[49]



Scheme 8

Table 7. Experimental data obtained in the synthesis of dicyanovinyl thienylpyrroles **14** and **15**.[49]

Entry	Formyl-pyrrole	Dicyanovinyl-pyrrole	Yield (%)	δ_H (ppm)[a]	IR υ_{CN} (cm^{-1})	λ_{max} (nm)[b]
1	**9a**	**14a**	100	7.46	2217	415.0
2	**11a**	**15a**	93	7.75	2215	454.5
3	**11b**	**15b**	47	7.61	2219	455.0
4	**11e**	**15e**	100	7.59	2215	462.0
5	**11f**	**15f**	90	7.57	2217	473.5
6	**11m**	**15m**	36	7.62	2217	454.5

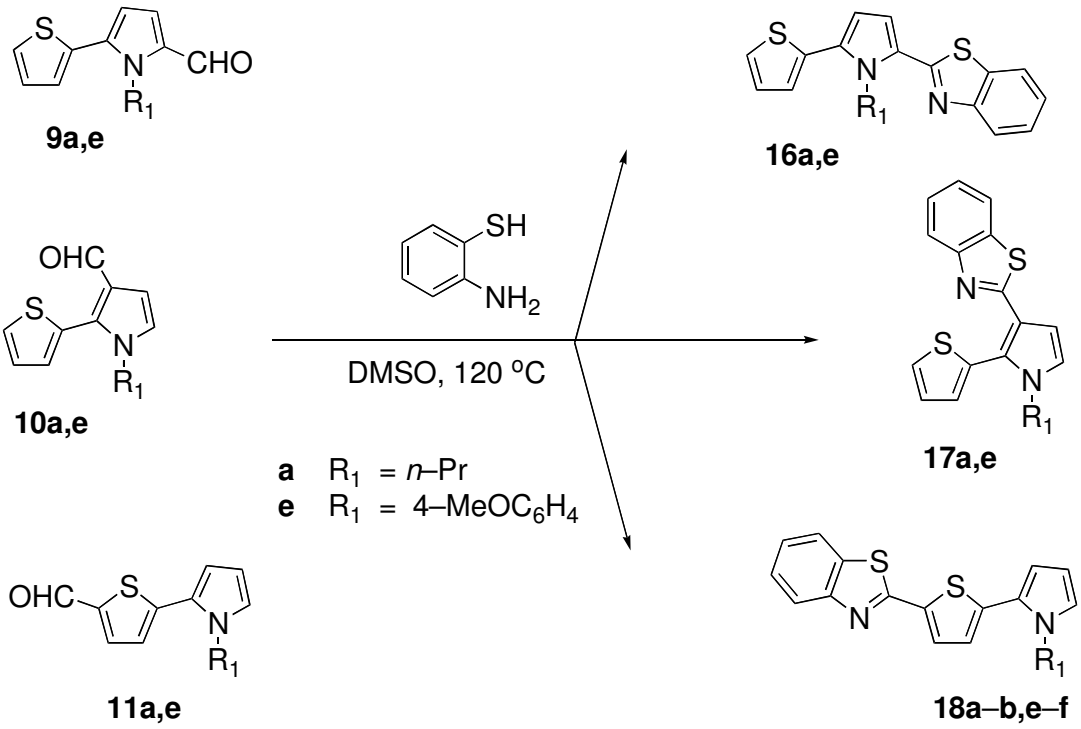
[a]For the C*H*=C(CN)$_2$ proton of dicyanovinyl-thienylpyrroles **14** and **15** (300 MHz, $CDCl_3$). [b]All the UV-vis spectra were recorded in ethanol.

3.6. Thienylpyrrolyl-benzothiazoles

Compounds **9–11** with the formyl group at 5-position or 3- and 5´-position of the pyrrole or thiophene ring, respectively, were used as precursors of the benzothiazoles **4–6** in order to evaluate the effect of the position of benzothiazole group on the optical properties of these chromophores.

Benzothiazoles **16–18** with either alkyl or aryl groups substituted on 1-position of the thienylpyrrolyl system were obtained by reaction of *o*-aminobenzenethiol with formyl derivatives **9–11**, in DMSO at 120 °C[50] for 2–3 h (Scheme 9, Table 8), generating thienylpyrrolyl-benzothiazoles **16–18** in fair to excellent yields (34–93%).[51]

The reaction is initiated by the formation of the corresponding imine that cyclises spontaneously, yielding the benzothiazoline, which is oxidised to the benzothiazole, aided by the oxidizing character of DMSO.



Scheme 9

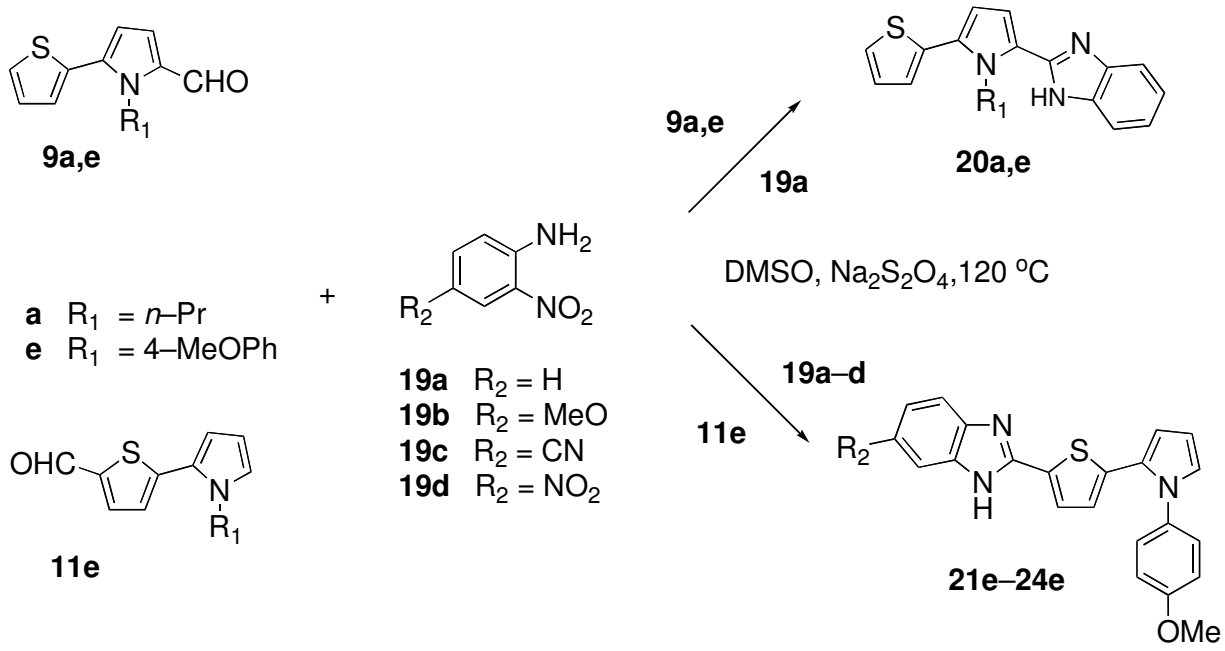
Table 8. Experimental data obtained in the synthesis of thienylpyrrolyl-benzothiazoles **16–18**.[51]

Entry	Formyl-pyrrole	Thienylpyrrolyl-benzothiazole	Yield (%)	λ_{max} (nm)[a]
1	**9a**	**16a**	75	353.0
2	**9e**	**16e**	35	366.0
3	**10a**	**17a**	34	318.0
4	**10e**	**17e**	48	319.0
5	**11a**	**18a**	36	377.5
6	**11b**	**18b**	48	374.5
7	**11e**	**18e**	93	386.5
8	**11f**	**18f**	67	390.0

[a]All the UV-vis spectra were recorded in ethanol.

3.7. Thienylpyrrolyl-benzimidazoles

The most popular synthetic approaches for the synthesis of benzimidazoles generally involve the condensation of an arylenediamine with a carbonyl equivalent.[52]



Scheme 10

Table 9. Experimental data obtained in the synthesis of thienylpyrrolyl-benzimidazoles **20–24**.[54]

Entry	Formyl-pyrrole	Thienylpyrrolyl-benzimidazole	Yield (%)	δ_H (ppm)[a]	IR υ (cm^{-1})	λ_{max} (nm)[b]
1	**9a**	**20a**	95	9.40-9.45	3430 (NH)	327.0
2	**9e**	**20e**	74	----	3435 (NH)	328.0
3	**11e**	**21e**	40	----	3480 (NH)	369.0
4	**11e**	**22e**	76	----	3489 (NH)	367.0
5	**11e**	**23a**	85	12.47	3412 (NH) 2213 (CN)	375.0
6	**11e**	**24e**	64	12.45	3362 (NH)	391.0

[a]For the N*H* proton of the imidazole ring of thienylpyrrolyl-benzimidazoles **20–24** (300 MHz, acetone-d_6). [b]All the UV-vis spectra were recorded in ethanol.

These methods usually use strong acid or alternatively harsh dehydratation conditions often at elevated temperatures, in order to produce benzimidazoles. These conditions are not fully compatible with a broad range of functional groups and desirable substrates. Therefore, we used a new method of synthesis reported recently by Yang[53] *et al.* for the preparation of 2-substituted benzimidazoles by a one step reaction through the $Na_2S_2O_4$ reduction of *o*-nitroanilines in the presence of aryl or heteroaryl (pyridyl and quinolyl) aldehydes. Applying this mild and versatile method of synthesis, we were able to prepare the new

benzimidazoles **20–24** using as precursors formyl-thienylpyrroles **9** and **11** with the formyl group at 5-position or 5´-position of the pyrrole or thiophene ring, respectively, in order to evaluate the effect of the position of benzimidazole group on the optical properties of these chromophores. Therefore, compounds **9** and **11** with either alkyl or aryl donors on the thienylpyrrolyl system and H, OMe, CN or NO_2 groups on the benzimidazole moiety, were prepared by a one step reaction through the $Na_2S_2O_4$ reduction of several *o*-nitroanilines **19** in the presence of formyl-thienylpyroles **9** and **11** in DMSO at 120 °C for 15 h. Under these conditions, compounds **20–24** were obtained in moderate to excellent yields (40–95%) (Scheme 10, Table 9).[54] Although compound **24e** was obtained from the dinitro precursor **19d**, no reduction was observed for the second nitro group. A broad correlation could be observed between the donor or acceptor properties of the group attached to 6-position of the benzimidazole nucleus and the chemical shift of the nitrogen proton of the benzimidazole ring in compounds **20–24** (Table 9). In fact, from the data in Table 9, one may infer that an increase in the chemical shift of the NH proton in the ^{1}H NMR spectra results in a decrease in the basic character of the benzimidazole. The NH was also identified by IR spectroscopy as a sharp band at about 3362–3435 cm^{-1}.

4. Applications

4.1. Introduction

The design and synthesis of organic chromophores as nonlinear optical (NLO) materials has attracted much attention in recent years. They have great and as yet largely unrealized potential especially for use in optical communications, information processing, frequency doubling and integrated optics.[55] One commonly used strategy to design π-electron chromophores for second-order NLO applications is to end-cap a suitable conjugated bridge with donor (D) and acceptor (A) substituents. In the 1990s, several authors pointed out that the strength of the electron-donor and -acceptor must be optimized for the specific π-conjugated system and the loss of aromaticity between the neutral form and the charge separated zwitterionic form of the chromophore is believed to be responsible for the reduced or saturated β (first molecular hyperpolarisability) values. Therefore, attempts have been made to design chromophores with less aromatic characteristics in the ground state, by replacing the benzene ring in stilbene derivatives by easily delocalisable five-membered heteroaromatic rings. It has also been demonstrated that the electron density of the π-conjugated system plays a major role in determining second-order NLO response. The electron excessive/deficient heterocycles act as auxiliary donors/acceptors while connected to donating/withdrawing groups and the increase of donor/acceptor ability leads to substantial increases in the measured β values.[56]

Having in mind this idea, several investigators pursued the synthesis and characterization of conjugated heterocyclic systems in which the donor moiety was represented by a π-excessive five-membered heterocycle (pyrrole or thiophene)[7g,35,57] and the acceptor group was a deficient heterocyclic ring (azine or benz-X-azole).[58] These new heterocyclic derivatives exhibited improved solvatochromic, electrochromic, fluorescent and nonlinear optical properties.[5] For the practical application of second-order NLO materials, not only a high hyperpolarisability but also good thermal stability is required. In this respect, promising candidates are benz-X-azole derivatives,[58] as well as conjugated thiophene and pyrrole heterocycles acting as auxiliary donors, substituted with appropriate acceptor groups. In contrast, the benz-X-azole heterocycles act as an electron-withdrawing group and also as an auxiliary acceptor. Moreover, they extend the conjugation length of the π-electron bridge.

Our research on new organic[35,57,58a,d,e] and organometallic[59] materials includes an interest in new molecules with potential applications in optical and electronic devices. In particular, oligothiophene[35,57] and benz-X-azole[58a,d,e] derivatives which typically exhibit favorable fluorescence, solvatochromic, electrochemical and NLO properties could be used in the manufacture of organic light-emitting diodes (OLEDs), semiconductor materials, in optical data storage devices and second-harmonic generators. We were therefore motivated to explore the potential of conjugated 1-(alkyl)aryl-2-(2'-thienyl)pyrroles **2** as strong π-electron donor moieties and their donor-acceptor substituted phenylazo- (**5**), tricyanovinyl- (**6–8**), formyl- (**9–13**), dicyanovinyl- (**14** and **15**), benzothiazole (**16–18**), and benzimidazole derivatives (**20–24**) in order to study their potential application as monomers for the synthesis of conducting heterocyclic materials, solvatochromic probes, photochromic and nonlinear optical materials.

4.2. Conducting polymers

Low band gap polyconjugated polymers are exceptionally attractive materials for applications in high performance optical and electronic devices. In particular, polythiophene and polypyrrole have been widely investigated as potential materials in the field of molecular electronics.[5g,57b] However, polypyrrole, although highly conducting, is not stable in the dedoped state towards oxygen. On the other hand, polythiophene, although stable, requires high potentials to be cycled between the doped and dedoped states. A tailoring of the electroactive properties could be reached by the preparation of hybrid polymers including pyrrole and thiophene units. Therefore, 2-(2´-thienyl)pyrroles have been identified as prospective monomers for organic conductive polymers. The latter combine high electroconductivity as well as thermal and environmental stability.[5a–g,w,60]

Table 10. Electrochemical data for thienylpyrroles **2** and thienylpyrrole azo dyes **5**.[32]

Thienylpyrroles 2		**Thienylpyrrole azo dyes 5**				
	Oxidation[a]		**Reduction[a]**		**Oxidation[a]**	
Compound	**E_{pa} / V**	**Compound**	**$-\ ^1E_{1/2}$ / V**	**$-\ ^2E_{1/2}$ / V**	**$^1E_{pa}$ / V**	**$^2E_{pa}$ / V**
2a	0.57	**5a**	1.23	1.70	0.78	0.96
2b	0.53	**5b**	1.29	1.76	0.72	0.93
2c	0.54	**5c**	1.31	1.80	0.72	0.92
2e	0.48	**5e$_1$**	1.71	__	0.57	0.87
2e	__	**5e$_2$**	1.74	__	0.59	0.88
2e	__	**5e$_3$**	1.35	1.83	0.62	0.90
2e	__	**5e$_4$**	1.40	1.76	0.68	0.93
2f	0.45	**5f**	1.36	1.77	0.61	0.90
2h	0.46	**5h**	1.35	1.81	0.63	0.91
2m	0.55	**5m**	1.27	1.73	0.80	0.96
2r	0.54	**5r**	1.25	1.72	0.79	0.97

[a]Measurements were carried out in *N,N*-dimethylformamide containing 0.1 mol dm^{-3} $[NBu_4][BF_4]$ as base electrolyte with a carbon working electrode at scan rate of 0.1 V s^{-1}. Ferrocene was added as an internal standard at the end of each measurement and all E values are quoted in volts *versus* the ferrocinium/ferrocene-couple.

Table 11. Electrochemical data for thienylpyrroles **2** and tricyanovinyl-thienylpyrrole **6–8**.[36]

Thienylpyrroles 2		Tricyanovinyl-thienylpyrroles 6–8				
Compound	**Oxidation[a]**	**Compound**	**Oxidation[a]**	**Reduction[a]**		**Band gap[b]**
	E_{pa} (V)		**E_{pa} (V)**	**$-^1E_{1/2}$ / (V)**	**$-^2E_{pc}$ / (V)**	**(eV)**
2a	0.57	**6a**	1.11	0.92	1.61	2.03
2b	0.53	**6b**	0.95	1.00	1.70	1.95
2c	0.54	**6c**	0.96	1.02	1.73	1.98
2e	0.48	**6e**	0.94	1.14	1.80	2.08
2f	0.45	**6f**	0.92	1.05	1.75	1.97
2g	0.48	**6g**	0.95	1.01	1.78	1.96
2h	0.46	**6h**	0.94	1.06	1.72	2.00
2m	0.55	**6m**	0.97	0.94	1.78	1.91
2r	0.54	**6r**	0.98	0.99	1.70	1.97

[a]Solution approximately 1-2 mM in each of the tested compounds in acetonitrile 0.10 $[NBu_4][BF_4]$ was used, and the scan rate was 100 mV s^{-1}, potentials *versus* the ferrocinium-ferrocene-couple.

[b] E_{HOMO} = 4.39 + E_{ox} (eV) and E_{LUMO} = E_{red} + 4.39 (eV).

Table 12. Electrochemical data for dicyanovinyl-thienylpyrroles **14** and **15**.[49]

Compound	**Oxidation[a]**		**Reduction[a]**	**Band gap[b]**
	$E_{1/2}$ (V)	**E_{pa} (V)**	**$-E_{1/2}$ (V)**	**(eV)**
14a	0.80	1.20	1.46	2.26
15a	0.46	0.96	1.56	2.02
15b	0.68	1.10	1.42	2.10
15e	0.59	1.06	1.44	2.03
15f	0.50	0.93	1.49	1.99
15m	0.56	1.00	1.47	2.03

[a]Measurements made in dry acetonitrile containing 1.5 mM of each of the quoted compounds and 0.10 M $[NBu_4][BF_4]$ as base electrolyte with a carbon working electrode at a scan rate of 0.1 V s^{-1}. Ferrocene was added as an internal standart at the end of each measurement, and all E values are quoted in volts *versus* the ferrocinium/ferrocene-couple.

[b] E_{HOMO} = 4.39 + E_{ox} (eV) and E_{LUMO} = E_{red} + 4.39 (eV)

The synthesis of thienylpyrroles containing substituents at the nitrogen atom has attracted considerable attention because the substitution makes it possible to modify the properties of polymers, including the synthesis of conducting polymeric materials with better properties for NLO applications. Therefore, our attention was focused on 1-aryl-2-(2´-thienyl)pyrroles. These new systems are expected to show some beneficial features: *i*) the aryl group is perpendicular to the π-system such that the coplanarity is affected to a lesser extent while resulting in a bathochromic shift in its UV-vis absorption spectrum; *ii*) the perpendicular aryl group prevents the stacking of the π-system and as a result increases its solubility; *iii*) various aryl groups can be employed in order to modify the physical properties of 1-aryl-2-(2´-thienyl)pyrroles.[5a,d,i,25]

The redox properties of the phenylazo- (**5**, Table 10), tricyanovinyl- (**6–8**, Table 11) and dicyanovinyl-thienylpyrroles (**14** and **15**, Table 12) were studied by cyclic voltammetry. All the functionalized derivatives displayed oxidations at more positive potentials compared to 2-thienylpyrroles **2**, as a consequence of the destabilizing effect of the electron-withdrawing groups substituted on the pyrrole (**5** and **6–8**) or on the thiophene (**14** and **15)**, rings. The results showed also that the extent of the interaction between the electron donanting and accepting termini is dependent on the substituents on the nitrogen of the pyrrole ring and also by the electronic nature and position of substitution (pyrrole or thiophene ring) of the different acceptor groups.[32,36,49] Electrochemical band gaps, (Tables 11 and 12) were calculated as previously described[61] from the potentials of the anodic and cathodic processes and agree well with the calculated optical band gaps. To our knowledge, these are among the lowest band-gap materials based on thienylpyrrole derivatives and they should be attractive potential monomers for the fabrication of conducting polymers.

4.3. Solvatochromic probes

All the donor-acceptor substituted thienylpyrroles synthesized are deeply colored compounds which exhibit intense absorptions in the UV-visible range. The position of these absorptions is influenced by the structure of the compounds, for example by the substituent on the nitrogen atom of the pyrrole ring and by the position of substitution of the acceptor group on the pyrrole or on the thiophene ring and also by the strengh of the acceptor group. The electronic spectra of donor-acceptor substituted thienylpyrroles were recorded in ethanol (Tables 3–9). Dramatic differences in energy occur upon functionalization of thienylpyrroles **2** with acceptor groups. These effects have been attributed to the stabilization of LUMO by the electron-withdrawing groups.[57c]

Several studies have demonstrated that the replacement of a benzene ring by a less aromatic heterocycle in typical donor-acceptor chromogens of the same chain length and bearing the same D-A pair, results in a significant bathochromic shift (in a given solvent) of the visible absorption spectra. Accordingly to theorectical NLO studies, this red shift, obtained for example with thiophene and thiazole rings, should be acompanied by an increase in the molecular hyperpolarisability. Experimental data confirmed this positive effect, in particular, for the five-membered heterocycles mentioned above. It is widely recognized that low energy bands in the UV-vis spectra and large solvatochromism are good indicators of potential NLO properties.[57a,c,d,58a,d]

In order to investigate if phenylazo- (**5**),[32] tricyanovinyl- (**6–8**),[36] dicyanovinyl-thienylpyrroles (**14** and **15**),[49] thienylpyrrolyl-benzothiazole (**16–18**)[51] and thienylpyrrolyl-benzimidazoles (**20–24**)[54] could act as suitable probes for the determination of solvent polarity, we carried out a study of the absorption spectra of above mentioned chromophores in 13 or 15 solvents with different polarities from *n*-hexane (–0.08 π* value by Kamlet and Taft) to DMSO (1.00 π* value by Kamlet and Taft).[62] All the compounds exhibited positive solvatochromism with respect to their CT absorption band, that is, the position of the absorption maximum shifts to longer wavelengths as the polarity of the solvent increases due to a greater stabilization of the excited state relative to the ground state with increasing polarity of the solvent. In view of the pronounced solvatochromism and the good correlation with π* values for the solvents investigated, compounds **5e$_3$** ($\Delta\nu$ = +2088 cm^{-1}), **6a** ($\Delta\nu$ = +1228 cm^{-1}), **6h** ($\Delta\nu$ = +804 cm^{-1}), **7a** ($\Delta\nu$ = +1260 cm^{-1}), **15a** ($\Delta\nu$ = +1130 cm^{-1}), **15f** ($\Delta\nu$ = +1263 cm^{-1}), **18a** ($\Delta\nu$ = +1121 cm^{-1}), **18f** ($\Delta\nu$ = +924 cm^{-1}), **21e** ($\Delta\nu$ = + 685 cm^{-1}), **22e** ($\Delta\nu$ = +807 cm^{-1}) and **24e** ($\Delta\nu$ = +1277 cm^{-1}) seem to be very appropriate solvent polarity indicating dyes.

4.4. Nonlinear optical (NLO) materials

We have used the hyper-Rayleigh scattering (HRS) method[63] to measure the first hyperpolarizability β of tricyanovinyl- (**6–8**, Table 13),[36] dicyanovinyl- (**14** and **15**, Table 13),[49] benzothiazole (**16–18**, Table 14)[51] and benzimidazole-thienylpyrroles (**20–24**, Table 14)[54] at an incident wavelength of 1064nm. *p*-Nitroaniline (*p*NA) was used as standard[64] in order to obtain quantitative values, while care was taken to properly account for possible fluorescence of the dyes. The static hyperpolarisability β_0 values were calculated using a very simple two-level model neglecting damping. They are therefore only indicative and should be treated with caution.

The results obtained for the first hyperpolarisability β, of tricyanovinyl derivatives (**6–8**, Table 13), showed that β varies with the substituent on the pyrrole ring (alkyl or aryl) and with the position of substitution (3, 4 or 5) of the acceptor group on the pyrrole ring. Therefore, compounds **6e,f** (having one or two methoxy- groups at *ortho* or *ortho-para* position on the aromatic ring) and compounds **6m** and **6r** (having one halogen, F or Br, at *para* position on the aromatic ring) show higher β values. Compound **7a** having a propyl group at the 1-position of the pyrrole ring and the tricyanovinyl acceptor group at 3-position exhibit the largest β and β_0 values. The β value of **7a** is 19 times that of *p*NA while the corresponding β_0 is 13 times greater. Comparison of the β values for compounds **6a** and **8a** shows that the substitution of the tricyanovinyl- group at the 3-position on the pyrrole ring leads to a larger nonlinearity than the same acceptor group at 4- (**8a**) or at 5-position (**6a**). The compounds with high molecular nonlinearities have a response at 1064 nm that are 10–20 times greater that the well known *p*NA molecule which is often used as standart.

The study of the nonlinear optical properties of dicyanovinyl-thienylpyrroles (**14** and **15**, Table 13), showed that the β values for compounds with the dicyanovinyl- group on the thiophene ring are 22–38 times greater than that of *p*NA, whereas the corresponding β_0 values are 4–14 times of *p*NA. As expected, the β values for pyrroles **15b,e,f** increased with the donor effect of the substituent on the nitrogen atom of the pyrrole ring along the series phenyl < 4-MeO-phenyl < 2,4-diMeO-phenyl. Compound **14a** having a propyl group at the 1-position of the pyrrole ring and the dicyanovinyl acceptor group on the pyrrole moiety exhibit the lowest β and β_0 values. Comparison of the β values for **14a** (85 $\times 10^{-30}$ esu) and **15a**, (526 $\times 10^{-30}$ esu) showed that the substitution of the dicyanovinyl- group at the 5´-position on the thiophene ring leads to a larger nonlinearity than the same acceptor group at 5-position on the pyrrole ring (**14a**). These results are in accordance with the theoretical studies of Varanasi *et al.* who concluded that an increase or decrease of the molecular nonlinear activity of heteroaromatic systems depends on the nature of the aromatic rings as well as the location of these heteroaromatic rings in the systems.[56a] The results obtained showed that, even with a stronger acceptor group, tricyanovinyl derivatives **6a,b,e,f,m** exhibit lower hyperpolarisability values compared with dicyanovinyl compounds **15a,b,e,f,m**. Thus, the location of the dicyanovinyl group on the pyrrole or on the thiophene ring alone can either dramatically enhance or decrease the overall molecular nonlinearity of the system.

These studies showed that the thienylpyrrole moiety should not simply be viewed as a conjugated segment but also as significant role as structural unit, which affects the overall electron transfer properties of the system. Pyrrole, being the most electron-rich five-member heteroaromatic ring, counteracts the electron withdrawing effect of the dicyanovinyl group (in **14a**), resulting in a decrease in β. The same explanation could be used to account for the lower β values observed in tricyanovinyl-pyrroles (**6–8**) as discussed earlier.

As expected, the dycianovinyl-pyrrole **14a** exhibits a lower value of β (85 x10^{-30} esu) compared to the corresponding tricyanovinylpyrrole **6a** (254 x10^{-30} esu).

Table 13. UV-vis absorptions, β and β_0 values for *p*NA and for compounds **6–8** and **14** and **15**.[a36,49]

Tricyanovinyl-thienylpyrroles	λ_{max} (nm)	$\beta^b/10^{-30}$ esu	$\beta_0^c/10^{-30}$ esu	Dicyanovinyl-thienylpyrroles	λ_{max} (nm)	$\beta^b/10^{-30}$ esu	$\beta_0^c/10^{-30}$ esu
6a	486	254	—	**14a**	414	85	28
—	—	—	30	**15a**	458	526	111
6b	504	244	19	**15b**	450	364	85
6c	506	234	17				
6e	510	253	17	**15e**	458	439	93
6f	514	263	13	**15f**	514	651	33
6g	508	221	15	—	—	—	—
6h	512	225	13	—	—	—	—
6m	506	290	21	**15m**	449	439	104
6r	504	280	22	—	—	—	—
7a	408	317	105	—	—	—	—
8a	414	240	80	—	—	—	—
***p*NA**	352	16.9[64]	8.5	—	—	—	—

[a]Experimental hyperpolarisabilities and spectroscopic data measured in dioxane solutions. [b]All the compounds are transparent at the 1064 nm fundamental wavelength. [c]Data corrected for resonance enhancement at 532 nm using the two-level model with $\beta_0 = \beta\,[1-(\lambda_{max}/1064)^2][1-(\lambda_{max}/532)^2]$; damping factors were not included.[63]

In accordance with the results discussed above for tricyano- (**6–8**) and dicyanovinyl-thienylpyrroles (**14** and **15**), the data for thienylpyrrolyl-benzothiazoles (**16–18**) and thienylpyrrolyl-benzimidazoles (**20–24**) showed that β is dependent on the substituent on the pyrrole ring (alkyl or aryl) and on the position of the substitution (3 or 5) of the benzothiazole or benzimidazole group on the pyrrole or on the thiophene ring.

It has also been shown that the benzothiazoles have high molecular nonlinearities especially derivatives **18** in which the benzothiazole group is substituted on the thiophene ring, as their values are 20–33 times higher that the well known *p*NA molecule. The effect of the electronic nature of the group that substitutes the benzimidazole heterocycle at 6-position is also noteworthy. It was obvious that the increase of the acceptor strength of the groups mentioned above, along the series H < CN < NO_2, results both in red-shifted absorption maxima and enhanced β values for benzimidazoles **21e**, **23e** and **24e**.

It was also observed that, smaller nonlinearities were obtained for benzimidazoles **20a,e** and **21e** compared to thienylpyrrolyl-benzothiazoles **16a** and **16e** with similar structures, due to the different electronic nature of benzimidazole heterocycle compared to benzothiazole.[65] The thermal stability of thienyl-benzothiazoles (**16–18**) and thienyl-benzimidazoles (**20–24**) were also estimated by thermogravimetric analysis (TGA), measured at a heating rate of 20 ºC min^{-1} under a nitrogen atmosphere (Table 14). The results obtained revealed an excellent thermal stability for all compounds, which could be heated up to T_d= 330–375 ºC for **16–18** or to T_d = 326–401 ºC for **20–24**.

In agreement with the thermal stability properties and the solvatochromic, electrochemical and nonlinear optical studies, the new compounds prepared could be used on the manufacture of semiconductor materials, as solvatochromic probes or materials with strong nonlinear (NLO) properties.

Table 14. UV-vis absorptions, β and β_0 values for *p*NA and for compounds **17,18** and **20–24** and T_d values for compounds **17,18** and **20–24**.[a,51,54]

Thiazoles	λ_{max} (nm)	$\beta^b/10^{-30}$ esu	$\beta_0^c/10^{-30}$ esu	T_d (^oC)[e]	Imidazoles	λ_{max} (nm)	$\beta^b/10^{-30}$ esu	$\beta_0^c/10^{-30}$ esu	T_d (^oC)[e]
16a	353.0	64	32	—	**20a**	332.5	42	23	326
16e	366.0	85	39	336	**20e**	336.0	58	31	363
17a	318.0	75	44	—	—	—	—	—	—
17e	319.0	73	43	369	—	—	—	—	—
18a	377.5	—[d]	—[d]	302	—	—	—	—	—
18b	374.5	330	150	330	—	—	—	—	—
18e	386.5	450	180	357	**21e**	361.0	60	29	380
—	—	—	—	—	**22e**	364.0	—[f]	—[f]	401
—	—	—	—	—	**23e**	366.5	114	53	390
—	—	—	—	—	**24e**	363.0	121	57	365
18f	390.0	550	220	375	—	—	—	—	—
***p*NA**	352.0	16.9[64]	8.5	—	—	—	—	—	—

[a]Experimental hyperpolarisabilities and spectroscopic data measured in dioxane solutions. [b]All the compounds are transparent at the 1064 nm fundamental wavelength. [c]Data corrected for resonance enhancement at 532 nm using the two-level model with $\beta_0 = \beta\,[1-(\lambda_{max}/1064)^2][1-(\lambda_{max}/532)^2]$; damping factors were not included.[63] [d]The hyperpolarisability for compound **18a** proved to be extraordinarily large, possibly due to a two photon resonance enhancement effect, so no value is given. [e]Decomposition temperature (T_d) measured at a heating rate of 20 ºC min^{-1} under a nitrogen atmosphere, obtained by TGA. [f]The hyperpolarisability for compound **22e** proved to be abnormally large, possibly due to a two photon resonance enhancement effect, so no value is given.

4.5. Photochromic systems

Azo dyes with heterocyclic components have been intensively investigated to produce bright and strong colour shades ranging from red to greenish blue on synthetic fabrics. These results led to the development of commercial products which have replaced the conventional azobenzene disperse dyes. Besides their classic applications in synthetic dyes and pigments, heteroaryl azo chromophores could act also as organic second-order nonlinear optical (NLO) materials suitable for applications such as second harmonic generation and optical switching.[66]

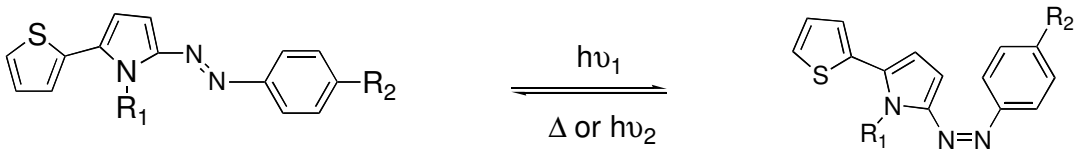
Usually, azo compounds are chemically stable molecules that display intense absorption bands whose position can be tailored, by appropriate ring substitution, to fall anywhere from UV to near-IR spectrum.[67] One of the most interesting properties of these chromophores is the readily induced and reversible isomerization about the azo bond between the *E*- and *Z*-isomers, which can be photo or thermally interconverted. The reversible structural change is a space-demanding process and brings important reversible modifications not only on physico-chemical properties of the molecules but also on a variety of compatible matrices, such as solutions, liquid crystals, sol-gel systems, monolayer films or polymers, where they can be incorporated.[68] This opens a wide field of potential applications for systems incorporating azo-chromophores. In fact, these systems can be used as photoswitches to control a variety of chemical and

physical (*e.g.* mechanical, electronic and optical) properties. The principal requirements for photonic devices includes thermal stability of both isomers, fatigue resistant character, high sensitivity, rapid response and reactivity when incorporated in solid matrices.

The photoisomerisation of azoaromatic dyes is an extensively studied phenomenon. Generally, the two isomers exhibit different absorption spectra and are therefore distinguishable. The thermodynamically more stable *E*-isomer is normally highly coloured due to the allowed extension of the π-electronic system while the *Z*-isomer is an uncoloured or weakly coloured species due to an out-of-plane configuration of the aromatic groups attached to the azo group.[69] Upon continuous irradiation with visible light, a coloured solution of an azo dye (normally constituted mainly by the *E*-isomer) exhibits a fast decrease of the absorbance measured at the longer wavelengths due to the conversion to the *Z*-isomer. A photostationary equilibrium between the two isomers is attained and when the irradiation source is removed, the *Z*-isomer thermally (or photochemically) converts back to the highly coloured *E*-isomer following a monoexponential kinetic. This isomerization is completely reversible, free from side reactions and one of the cleanest photoreactions known. Both the spectra of the photoactive molecules and the reaction kinetics are strongly dependent on the nature of the matrix in which the photochromic substances are incorporated.[68a]

The mechanism of the *E-Z* interconversion remains unclear and it seems that there may not be one general mechanism, but a competition between rotational (about the –N=N– double bond axis) and inversional (through a transition state where one of the nitrogen atoms is *sp*-hibridized) mechanisms, depending on the particular molecular structure and the local environment.[70]

Very few reports concerning the photochromic properties of heteroaromatic azo dyes can be found in the literature.[71] Therefore, we decided to investigate the photochromic behaviour of thienylpyrrole azo dyes **5** (Scheme 11), in THF solutions (Table 15).[72]



5 *E* -isomer

R_1 = alkyl, aryl
R_2 = NO_2, CN, CO_2Me

5 *Z* -isomer

Scheme 11

It was observed that the photochromic properties were strongly dependent on the substitution pattern of the dyes. Nitro-substituted thienylpyrrole azo dyes are particular interesting since they exhibit very fast colouration/decolouration processes. These compounds showed also aggregation phenomena in freshly prepared solutions of THF, which led to variable photochromic behaviours. Only after 1–5 hours the solutions reached equilibrium and only then reproducible photochromic behaviour could be observed. The activation energy calculated for compound **5c** was 56 kJ/mol which is considerably lower than the value for azobenzene (94 kJ/mol) or other heteroaromatic azo dyes like 2-(phenylazo)imidazoles (79 kJ/mol) or phenylazopyridines (90 kJ/mol). To our knowledge, these are among the lowest values of the activation energy reported for heterocyclic azo dyes. The photochromic properties described for thienylpyrroles **5** makes them good candidates for optical data storage devices where it is desirable to use excitation energies

of lasers with longer wavelengths (which are easier to manufacture) and to obtain fast photochromic systems.

Table 15. Spectrokinetic properties under continuous irradiation: maxima wavelength of absorption (λ_{max}), colourability (A_{eq}), absorbance variation (Δ Abs) and thermal bleaching rate (k_Δ) of azo dyes **5**.[72]

Thienylpyrrole Azo Dye	R_1	R_2	λ_{max} (nm)	A_{eq}	Δ Abs	Δ Abs (%)	k_Δ (s^{-1})
5a	*n*-Pr	4-NO_2	490	0.58	0.13	22	0.32
5b	Ph	4-NO_2	498	0.59	0.16	27	0.21
5c	naphthyl	4-NO_2	497	0.66	0.22	34	0.17
5e$_1$	4-MeOPh	4-CO_2Me	464	0.40	0.19	48	0.0011
5e$_2$	4-MeOPh	4-CN	477	0.66	0.37	56	0.011
5e$_3$	4-MeOPh	4-NO_2	500	0.42	0.11	26	0.33
5f	2,4-diMeOPh	4-NO_2	508	0.68	0.10	15	0.71
5h	3,4,5-MeOPh	4-NO_2	501	0.69	0.14	20	0.41
5m	4-FPh	4-NO_2	495	0.49	0.18	37	0.13

4.6. Organic light-emmiting devices (OLED´s)

The benzothiazole nucleus appears in many fluorescent compounds that have useful applications such as polidentate ligands, in laser technology as laser dyes, organic luminophores, thermo- and LTV-stabilizers for polymer materials, diazotype materials, materials with nonlinear optical (NLO) properties, as fluorescence sensors. Recently benzothiazole derivatives as well their metal complexes were widely investigated as electron transporting and emmiting layers for organic light-emmiting devices (OLED´s).[45e,73] Thienylpyrrole derivatives are also characterised by important electroluminescent properties.[74] Therefore, some preliminary studies have been made concerning the fluorescence properties of thienylpyrrolyl-benzothiazoles **18a,b,e,f**.[75] Absorption and emission spectra of 5 x 10^{-6} M solutions of compounds **18a,b,e,f** were run in degassed absolute ethanol and fluorescence relative quantum yields were determined using 9,10-diphenylanthracene as fluorescence standard. This preliminary study showed that the fluorescence relative quantum yields of thienylpyrrolyl-benzothiazole derivatives **18a,b,e,f** in absolute ethanol were found to be in the range 0.56 to 0.80, emitting in the 482–486 nm region and they exhibit also large Stokes' shifts. An absorption and emission solvatochromic study in eight solvents was carried out for all derivatives, showing that solvent polarity influences the position of the absorption and the emission band, as well as the fluorescence quantum yield. Due to their strong fluorescence, benzothiazole derivatives **18a,b,e,f** can find use as fluorescent markers or as light emitters in organic light emitting devices (OLEDs), among other applications. More complete studies concerning the photophysical properties of benzothiazoles in solution and in solid state are currently underway.

5. Conclusions

A convenient and practical method for the synthesis of 1-alkyl(aryl)-2-(2´-thienyl)pyrroles has been developed in our laboratories from secondary alkyl(aryl)-4-(2´-thienyl)-4-oxobutanamides in the presence of Lawesson´s reagent. The method can be applied to several secondary alkyl or aryl 4-(2´-thienyl)-4-oxobutanamides. 1-Alkyl(aryl)-2-(2´-thienyl)pyrroles were versatile building blocks allowing the preparation of a large variety of donor-acceptor substituted thienylpyrroles. Thus, 1-alkyl(aryl)-2-(2´-thienyl)pyrroles were used as precursors in several electrophilic reactions permitting the synthesis of 5-phenylazo-, 5-tricyanovinyl- and 5-formyl-thienylpyrroles. Through metalation followed by reaction with DMF, it was possible to obtain for the first time new formyl-thienylpyrroles selectively functionalized on the thiophene ring. The formyl-thienylpyrroles functionalized on the thiophene or on the pyrole ring were also used as versatile synthons to prepare several new derivatives such as: dicyanovinyl-thienylpyrroles, thienylpyrrolyl-benzothiazoles and thienylpyrrolyl-benzimidazoles. Our recent work shows that 1-alkyl(aryl)-2-(2´-thienyl)pyrroles and their corresponding formyl-derivatives constitute excellent precursors for the synthesis of a wide range of new interesting push-pull substituted thienylpyrroles. Moreover, the thermal stability and the electrochemical, optical (linear and nonlinear), solvatochromic and photochromic properties of the new π-conjugated heterocyclic systems were studied, showing that these fascinating compounds have a wide range of potential applications namely as conducting materials, solvatochromic probes, OLED´s, nonlinear optical and photochromic materials. Therefore, the data presented in this review demonstrate the considerable recent progress that has been achieved concerning the synthesis and exploration of potential applications of 2-thienylpyrrole derivatives. Nevertheless the potential of 2-thienylpyrroles and their derivatives are still far from being fully revealed. We hope that this review will entice others researchers to join us as we continue to explore the promise latent in these intriguing molecules.

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QUINOLINE FUNCTIONALIZATION BY DEPROTONATIVE METALATION

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Abstract. *Metalation of quinolines and isoquinolines generally requires more chemoselective bases than metalation of pyridines due to facile nucleophilic addition (often observed at the 2- and 1-position, respectively) in relation to lower energy levels of the LUMOs of these substrates. Whereas classical lithium bases are still capable of performing deprotonation reactions of quinolines carrying heterosubstituents provided that elaborated procedures are designed, recourse to other classes of deprotonating agents is required for bare heterocycles. Subsequent reactions with electrophiles open access to a wealth of building blocks for various applications such as synthesis of biologically active compounds, material science or supramolecular chemistry.*

Contents

1. Introduction

Quinolines and isoquinolines belong to the most important heterocycles. Natural products such as alkaloids of the cinchona bark are derived from quinoline. Examples are the diastereoisomeric pairs quinine-quinidine and cinchonidine-cinchonine (bare quinoline was first obtained by alkaline degradation of the alkaloid cinchonine). Another example is camptothecin, a highly toxic polycyclic quinoline alkaloid isolated from the stem wood of a Chinese tree.[1]

The quinoline core is present in many important biologically active agents such as 8-hydroxyquinoline and some halogenated derivatives (used as antiseptics) and chloroquine (one of the older antimalarial). *N*-Alkyl-4-quinolone-3-carboxylic acids such as ciprofloxazin and moxifloxazin are constituents of antibacterials. Quinmerac is a quinoline-8-carboxylic acid employed as a herbicide.[1]

Isoquinoline occurs in coal tar and bone oil. Derivatives are widely present in nature. Most of the quinoline alkaloids derive from 1-benzylisoquinoline.[1]

The main approaches used to build the ring system of quinolines are: (1) reduction and subsequent cyclization of 2-nitrocinnamoyl compounds, (2) Pd-catalyzed transfer hydrogenation/heterocyclization of (2-aminophenyl)ynones, (3) cyclocondensation of 2-aminoaryl ketones or aldehydes with ketones possessing an α-CH_2 group (*Friedländer synthesis*) or reaction of methylene ketones with isatin (*Pfitzinger synthesis)*, (4) intramolecular S_EAr processes such as cyclocondensation of primary arylamines with a free *ortho* position with β-diketones or with β-keto aldehydes (*Combes synthesis*), or β-keto esters (*Knorr* and *Konrad-Limpach synthesis*), and (5) reaction of primary arylamines possessing an unsubstituted *ortho* position with α,β-unsaturated carbonyl compounds (*Skraup* and *Doebner-Miller synthesis*).[1]

To build the isoquinoline ring system, the main approaches are: (1) cyclization of (2-formyl-phenyl)ethanal and analogous dicarbonyl compounds with ammonia, (2) cyclization of *N*-(2-aryl-ethyl)amides and subsequent oxidation (*Bischler-Napieralski synthesis*), (3) reaction of arylaldehydes with aminoacetaldehyde (*Pomeranz-Fritsch synthesis*), (4) cyclocondensation of 2-arylethylamines with aldehydes, and (5) intramolecular aza-Wittig reaction of azidocinnamic esters.[1]

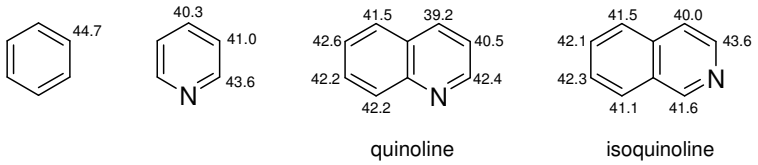
Addition and substitution processes can be used to functionalize quinolines. Whereas S_EAr reactions occur on the more activated benzene moiety, nucleophilic addition and substitution reactions take place at the hetero ring, as a rule in the 2- or 4-position for quinoline and 1-position for isoquinoline.[1]

Site selectivity could be easily achieved of course if the electrophile could react with a specific quinolylmetal rather than with the unmodified heterocycle. Non-deprotonative accesses to quinolylmetals such as halogen/metal exchange have been developed,[2] but the problem is only deferred since the preparation of bromo- and polybromoquinolines that could be used as substrates is generally not trivial. The metalation (hydrogen/metal permutation) avoids the use of heavy halogen-substituted quinolines.

The acidities of hydrogens in quinolines are related to less highly-conjugated p orbitals (decrease in aromaticity) in the ring when compared to naphthalene. The pK_a values for C-H bonds of numerous aromatic heterocyclic compounds including quinoline and isoquinoline have been recently calculated (Scheme 1).[3]

The strongest acidities on quinolines were estimated to be the 4-positions (39.2 and 40.0 for quinoline and isoquinoline, respectively). When metallic bases are employed to deprotonate these π-deficient aza-

heterocycles, the regioselectivity of the reaction is generally different because of additional effects.[4] Coordination of the ring nitrogen to the metal (particularly in the absence of a chelating solvent such as THF) causes the disaggregation of the base (which becomes more reactive), increases the electron-withdrawing effect of the nitrogen, and (thus) favors the deprotonation at an adjacent position. In addition, it should be noted that the lithiated compound at the nitrogen adjacent position is on the one hand stabilized by the electron-withdrawing effect of the nitrogen(s), but on the other hand destabilized by electronic repulsion between the carbanion and the lone pair of the nitrogen.



Scheme 1. Estimated pK_a values for C-H bonds.

The electron-withdrawing effect of the azine nitrogen decreases the energy level of the LUMO of these substrates and makes them more sensitive to nucleophilic addition.[4a] As a consequence, "soft" alkyllithiums, which are strong bases (pK_a ~ 40–50), have to be avoided since they easily add nucleophilically to the quinoline ring, even at low temperatures. It is often advisable to rely upon the "harder", though less basic lithium diisopropylamide (LDA, pK_a = 35.7) and lithium 2,2,6,6-tetramethylpiperidide (LTMP, pK_a = 37.3) to effect deprotonation. Nevertheless, this still happens to be difficult with bare heterocycles, for which formation of dimeric products -either by addition of lithiated substrate to another molecule or by dimerization of "radical anions"- can hardly be avoided.

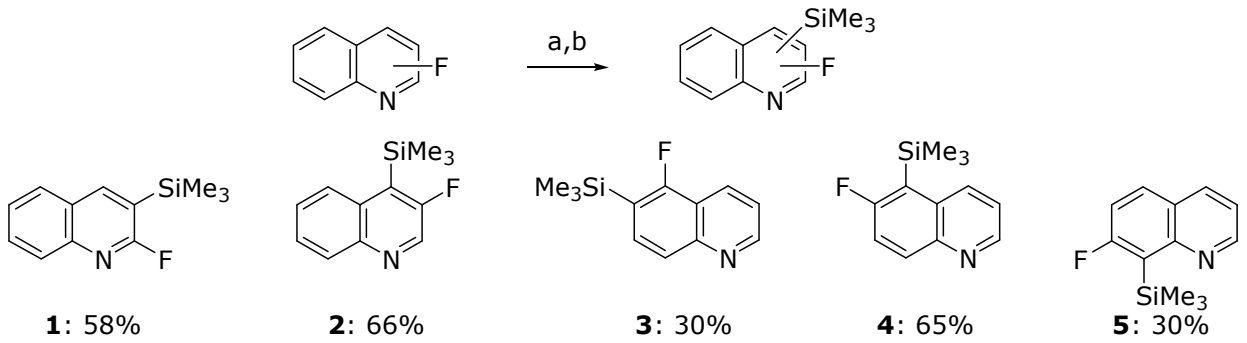
Using lithium amides as bases, the reaction is usually under thermodynamic control, and the regioselectivity observed is the result of different effects such as stabilization by the electron-withdrawing effect of the ring nitrogen and destabilization by electronic repulsion between the carbanion and the lone pair of the adjacent ring nitrogen. These effects are modulated by the aggregation state of the lithium species, which largely depends on solvent, for example. A rationalization of the regioselectivity becomes more complicated when substituted quinolines are concerned. As the ring nitrogen, the substituent can stabilize by inductive electron-withdrawing effect. It can also chelate the Lewis acidic metal of the base, an effect that is important for the few reactions carried out under kinetic control using alkyllithiums since it allows the disaggregation of the base, reinforces the electron-withdrawing effect of the substituent and increases the proximity effect of the complexed base. Under thermodynamic control, unlike the ring nitrogen the substituent can stabilize the metalated substrate by chelation, which reinforces the electron-withdrawing effect. Steric hindrance caused by the substituent has an impact on the outcome of the reaction too.

2. Functionalization of halogen- and trifluoromethyl-substituted quinolines

2.1. Fluoroquinolines

Owing to their low LUMO levels, quinolines are subjected to nucleophilic addition. When treated with the BuLi-TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) chelate in diethyl ether (DEE), fluoroquinolines are easily converted into products of 1,2-addition.[5] Using the same base in tetrahydrofuran (THF), which is a more basic solvent than DEE, both deprotonation of fluoroquinolines and nucleophilic addition of the base to the substrates were evidenced by trapping with chlorotrimethylsilane.[5] On the other hand, using lithium diisopropylamide (LDA) at low temperatures allows to avoid competitive nucleophilic

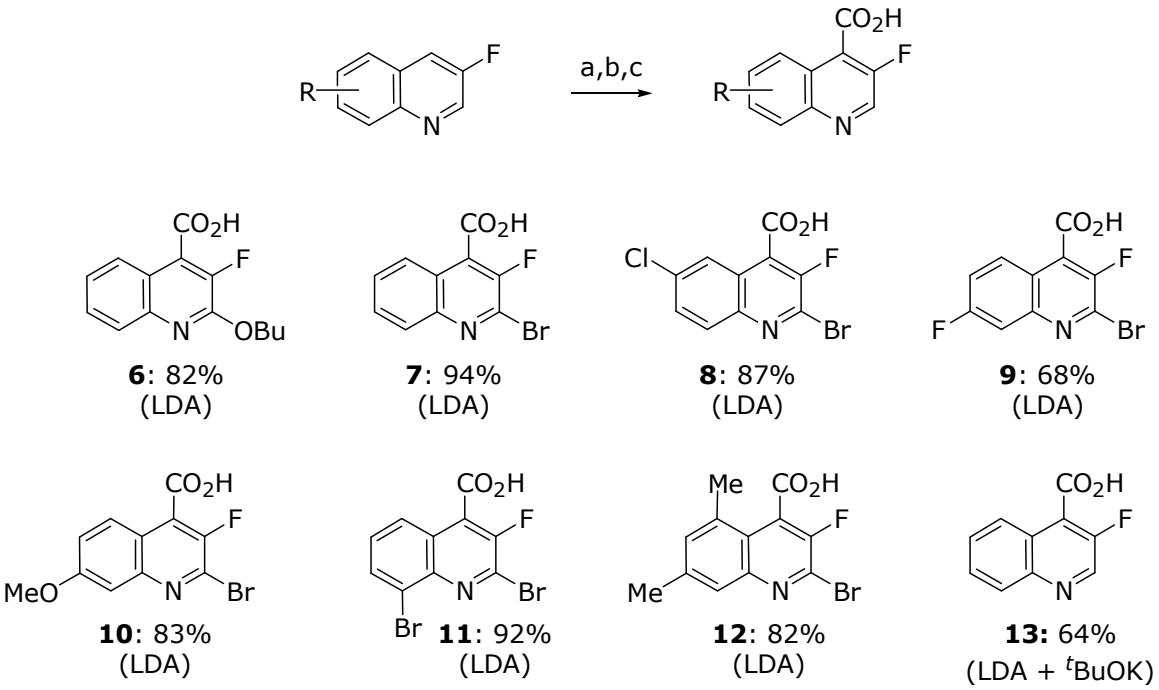
addition reactions and gives chemo- and regioselectively (adjacent to fluorine) the functionalized 2-, 3-, 5-, 6- and 7-fluoroquinoline **1–5** after quenching with chlorotrimethylsilane (Scheme 2).[5]



a. LDA, THF, –75 °C; b. $ClSiMe_3$.

Scheme 2

Metalation using LDA in THF at low temperatures (–75 °C) has been extended to substituted fluoroquinolines such as 2-butoxy-3-fluoroquinoline[6] and various 2-bromo-3-fluoroquinolines[7] to furnish the corresponding carboxylic acids **6–12** after carboxylation/neutralization. Whereas LDA suffices to deprotonate 2-bromo-3-fluoroquinolines owing to the long-range assistance of the bromo group, 3-fluoroquinoline undergoes metalation more efficaceously when mixed-metal reagents are used. It is readily deprotonated with LDA in the presence of potassium *tert*-butoxide in order to be carboxylated subsequently (compound **13**) (Scheme 3).[6]

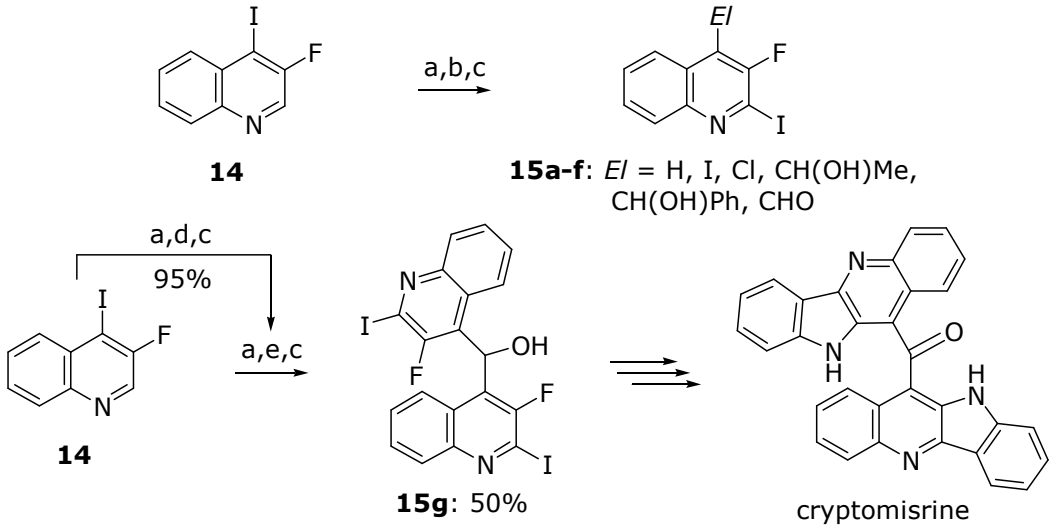


a. LDA or LDA + ^{t}BuOK, THF, –75 °C, 2 h; b. CO_2; c. H^+.

Scheme 3

When 3-fluoro-4-iodoquinoline (**14**) is submitted to LDA in THF at –75 °C, the 4-substituted 3-fluoro-2-iodoquinolines **15** are obtained after interception with electrophiles. This result is presumably a consequence of a rapid isomerization of first formed 3-fluoro-4-iodo-2-lithioquinoline to more stable

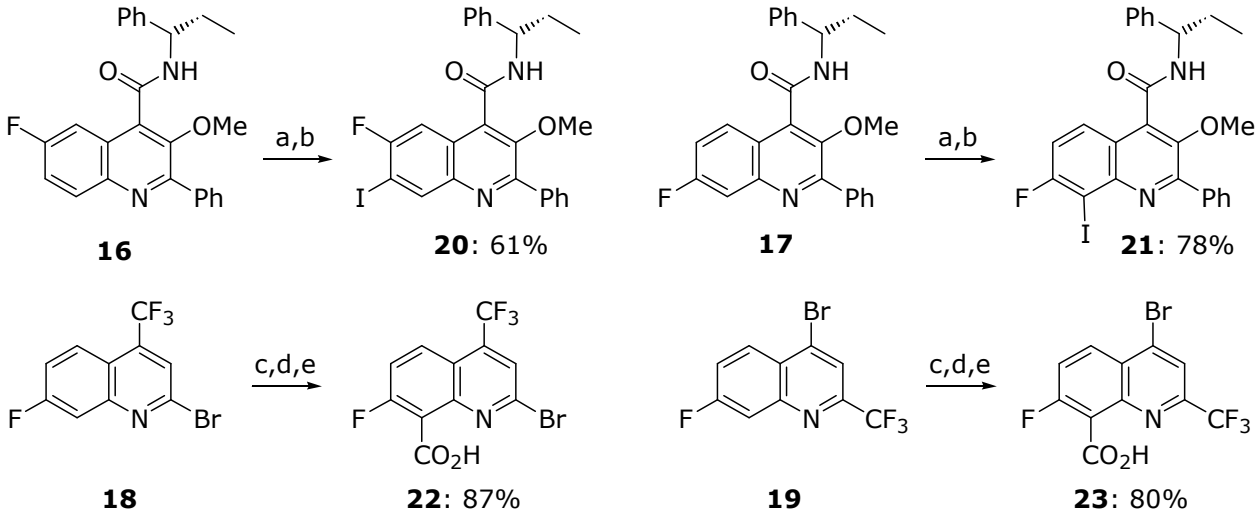
3-fluoro-2-iodo-4-lithioquinoline (migration of the iodine atom from the 4- to the 2-position) during the deprotonation step.[8] Such a metalation-isomerization process was applied twice in the course of the synthesis of cryptomisrine, an indolo[3,2-*b*]quinoline dimer (Scheme 4).[8b]



a. LDA, THF, −75 °C, 2 h; b. *Electrophile*; c. hydrolysis; d. HCO_2Et, −75 °C, 2 h; e. **15f**, −75 °C, 2 h.

Scheme 4

Hydrogen-metal permutations of functionalized 6- and 7-fluoroquinolines have also been described using hindered lithium dialkylamides in THF at –75 °C. Lithiations of (*S*)-*N*-(1-phenylpropyl)-6- and -7-fluoro-3-methoxy-2-phenyl-4-quinolinecarboxamide (**16–17**),[9] 2-bromo-7-fluoro-4-(trifluoromethyl)-quinoline (**18**)[10] and 4-bromo-7-fluoro-2-(trifluoromethyl)quinoline (**19**)[11] afford in this way the corresponding iodides **20–21** and carboxylic acids **22–23**, respectively, in good yields (Scheme 5).

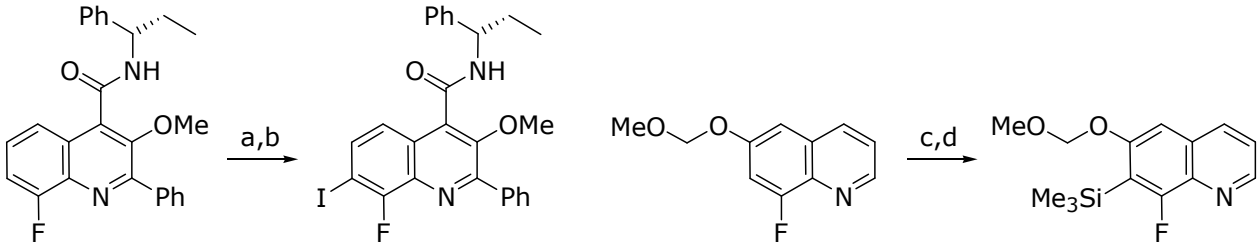


a. 3 equiv LTMP, 1 equiv BuLi, THF, −75 °C, 5 h; b. I_2; c. LDA, THF, −75 °C, 2 h; d. CO_2; e. H^+.

Scheme 5

Deprotonation of 8-fluoroquinoline has never been observed using LDA in THF at low temperatures, a result explained by the presence of a strong cation chelating site in the vicinity of the fluorine and nitrogen atoms.[5] Using lithium 2,2,6,6-tetramethylpiperidide (LTMP) in excess at –75 °C, the conversion of the

secondary 2,3-disubstituted 8-fluoro-4-quinolinecarboxamide **24** (amide function protected as its lithium salt) to the corresponding 7-iodo derivative **25** proves possible passing through the 7-lithio compound, but in a low 28% yield.[9] 8-Fluoro-6-methoxymethoxyquinoline (**26**) is successfully lithiated at the location flanked by the two activating groups with methyllithium at –75 °C, as demonstrated by interception with chlorotrimethylsilane (compound **27**, 83% yield), whereas 1,2-addition compounds are concomitantly formed using butyllithium or *tert*-butyllithium (Scheme 6).[12]



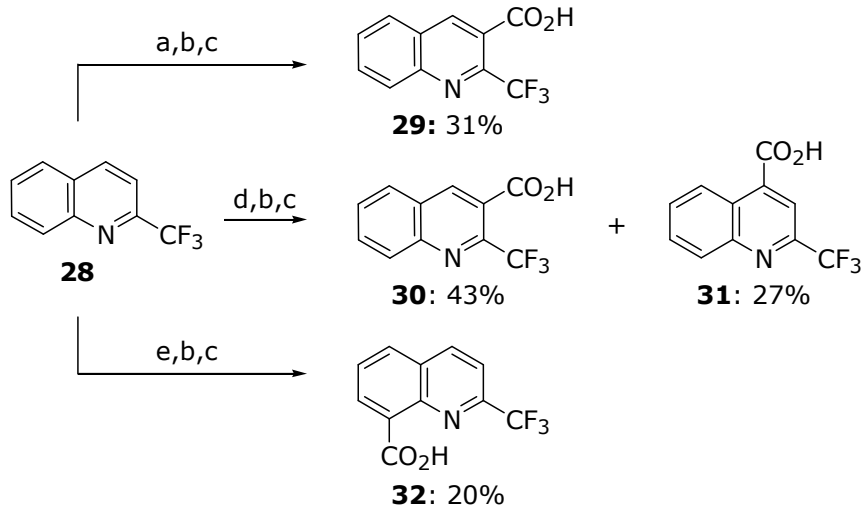
24 **25**: 28% **26** **27**: 83%

a. 3 equiv LTMP, 1 equiv BuLi, THF, –75 °C, 5 h; b. I_2; c. MeLi, THF, –75 °C, 6 h; d. $ClSiMe_3$.

Scheme 6

2.2. (Trifluoromethyl)quinolines

Trifluoromethyl-substituted building blocks attract more and more attention. Unlike the fluoro group, which only acidifies the adjacent hydrogen, the trifluoromethyl group exerts a strong electron-withdrawing effect, but this inductive activation is counterbalanced by the steric hindrance caused by the bulky substituent.[13] An optional site-selective hydrogen/metal interconversion reaction can be performed with 2-(trifluoromethyl)quinoline (**28**) (Scheme 7).[14]



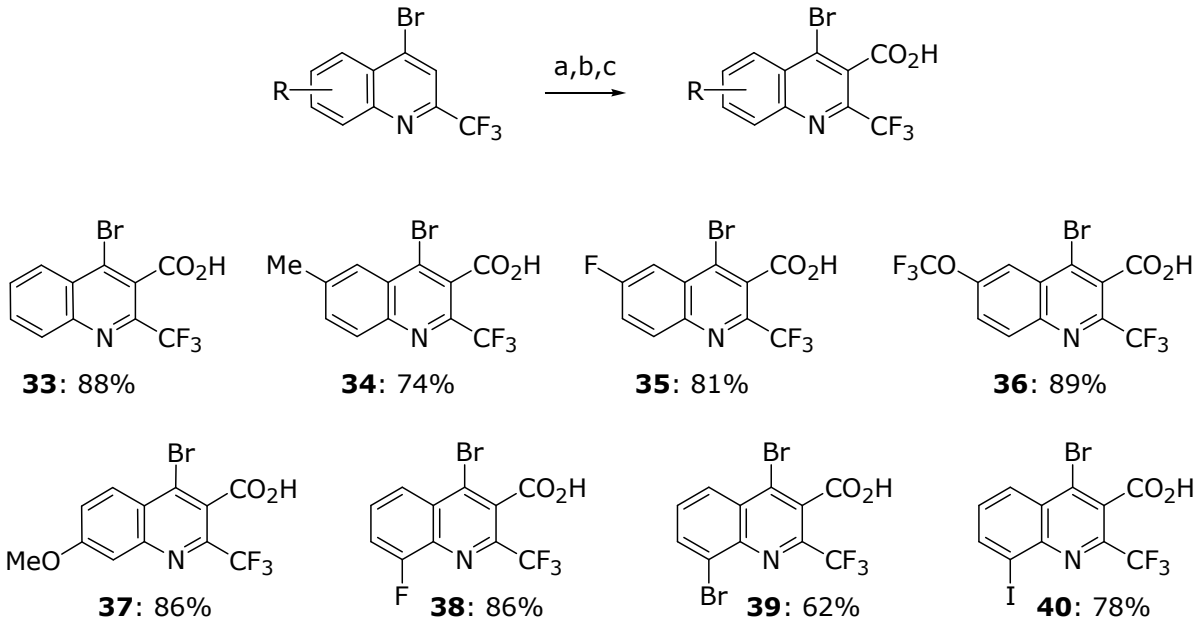
a. LDA, THF, –75 °C, 2 h; b. CO_2; c. H^+; d. LTMP, THF, –75 °C, 2 h; e. LTMP, DEE, –75 °C, 6 h.

Scheme 7

Deprotonation occurs solely at the 3-position when LDA is used in THF at –75 °C, generating 2-(trifluoromethyl)-3-quinolinecarboxylic acid (**29**) in 31% yield after trapping with dry ice. The bulkier LTMP does not behave regioselectively, attacking both the activated 3- and the sterically less hindered 4-position when employed in THF to afford a 3:2 mixture of 2-(trifluoromethyl)-3- and

-4-quinolinecarboxylic acid (**30–31**) in 43 and 27% yield, respectively, after carboxylation and neutralization. When DEE is used instead of THF, the metalation is regioselectively rerouted to the 8-position, probably due to coordination of the reagent by the nitrogen lone pair, opening the entry to 2-(trifluoromethyl)-8-quinolinecarboxylic acid (**32**) in 20% yield after trapping with dry ice.

The presence of a bromo group, which acts as a second activating substituent, is probably at the origin of the better yields obtained when 4-bromo-2-(trifluoromethyl)quinoline and its 6-, 7- or 8-substituted congeners are transformed into the corresponding 3-quinolinecarboxylic acids **33–40** using LDA as the base (Scheme 8).[11] In contrast, 5-methoxy-, 5-fluoro- and 5,7-dimethyl-substituted 4-bromo-2-(trifluoromethyl)quinolines prove to be unaffected by exposure to LDA or LTMP. Since 4-chloro-5-fluoro-2-(trifluoromethyl)quinoline reacts in this way to afford 4-chloro-5-fluoro-2-(trifluoromethyl)-3-quinolinecarboxylic acid in 61% yield upon standard carboxylation/neutralization procedure, the operation of a buttressing effect[15] was suggested on the basis of crystallographic studies to explain the inertness of the more congested 4-bromo derivatives.[16]



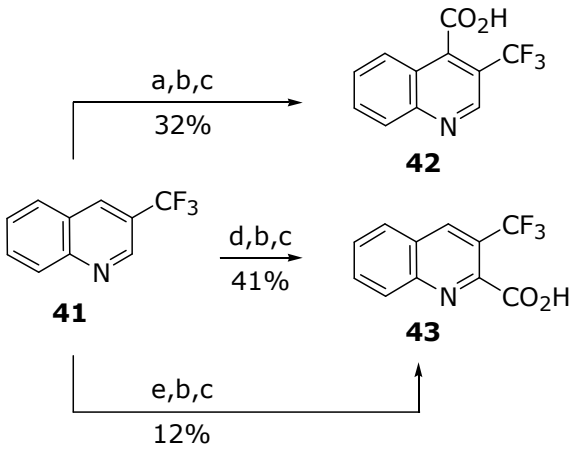
a. LDA, THF, –75 °C, 2 h; b. CO_2; c. H^+.

Scheme 8

The case of 3-(trifluoromethyl)quinoline (**41**) illustrates again the concept of "optional site selectivity" (Scheme 9).[14] Whereas LDA attacks the more acidic 4-position (when compared to the 2-position)[17] when used in THF at –75 °C to give 3-(trifluoromethyl)-4-quinolinecarboxylic acid (**42**) in 32% yield after trapping with dry ice, LTMP is effective at lithiating exclusively the less congested 2-position (absence of *peri*-hydrogen atom) under the same reaction conditions to produce 3-(trifluoromethyl)-2-quinolinecarboxylic acid (**43**) in 41% yield. The latter was also obtained using butyllithium in the presence of lithium 2-(dimethylamino)ethoxide (Caubère's base) in DEE, but in a low 12% yield.

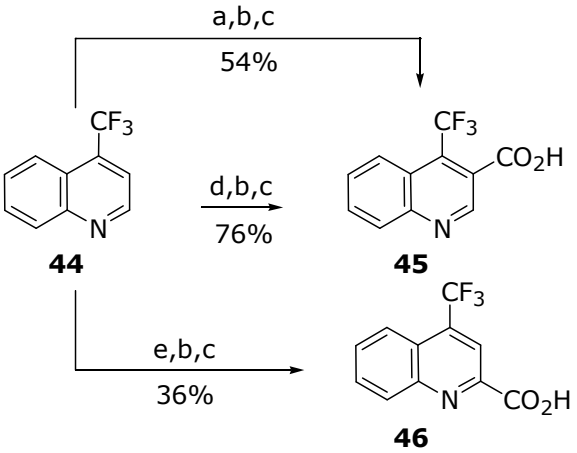
4-(Trifluoromethyl)pyridine (**44**) is converted into 4-(trifluoromethyl)-3-quinolinecarboxylic (**45**) in 54 and 76% yield, respectively, using LDA or LTMP in THF at –75 °C. In contrast, Caubère's base deflects the reaction from the 4- to the 2-position to give 4-(trifluoromethyl)-2-quinolinecarboxylic (**46**) in 36% yield

after carboxylation/neutralization, an orientation attributed to the assistance of the quinoline nitrogen (Scheme 10).[14]



a. LDA, THF, −75 °C, 2 h; b. CO_2; c. H^+; d. LTMP, THF, −75 °C, 2 h; e. BuLi-LDMAE, DEE, −75 °C, 2 h.

Scheme 9



a. LDA, THF, −75 °C, 2 h; b. CO_2; c. H^+; d. LTMP, THF, −75 °C, 2 h; e. BuLi-LDMAE, DEE, −75 °C, 2 h.

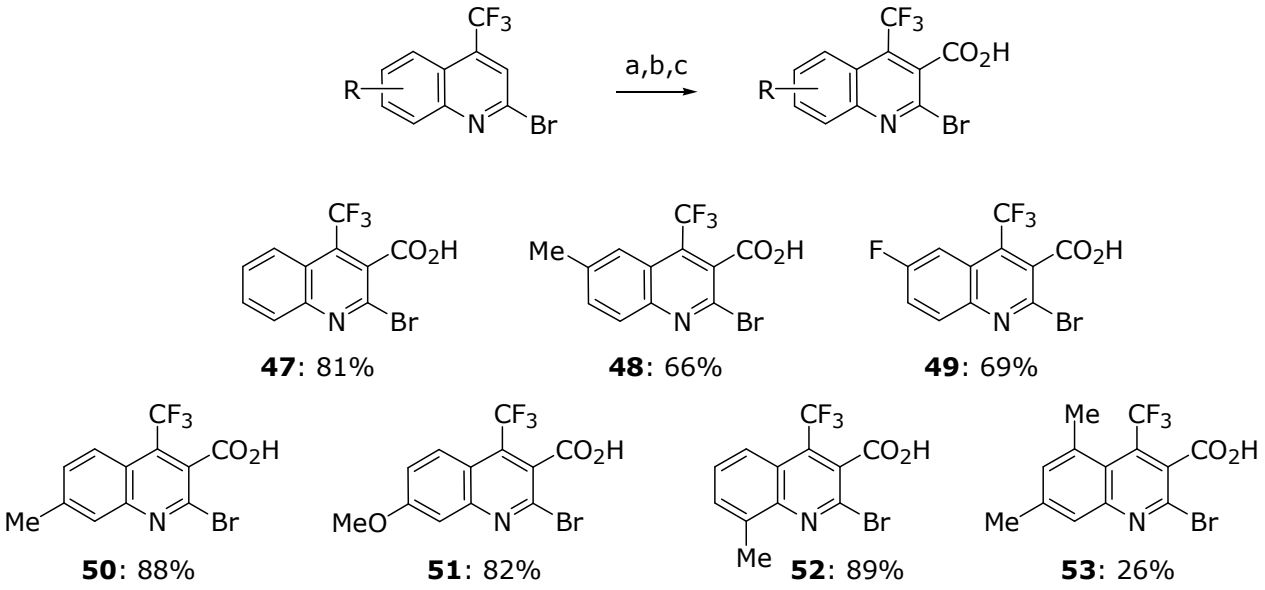
Scheme 10

A systematic investigation has revealed that the presence of a second activating substituent (a bromo group) favors the reaction using LDA, ensuring higher yields for the 3-quinolinecarboxylic acid derivatives **47–53**.[10] 2-Bromo-5,7-dimethyl-4-(trifluoromethyl)quinoline hardly reacts under these conditions whereas 2-bromo-5,7-dimethoxy-4-(trifluoromethyl)quinoline is inert toward LDA or LTMP;[16] buttressing effect were again advanced to rationalize these results (Scheme 11).

2.3. Chloroquinolines

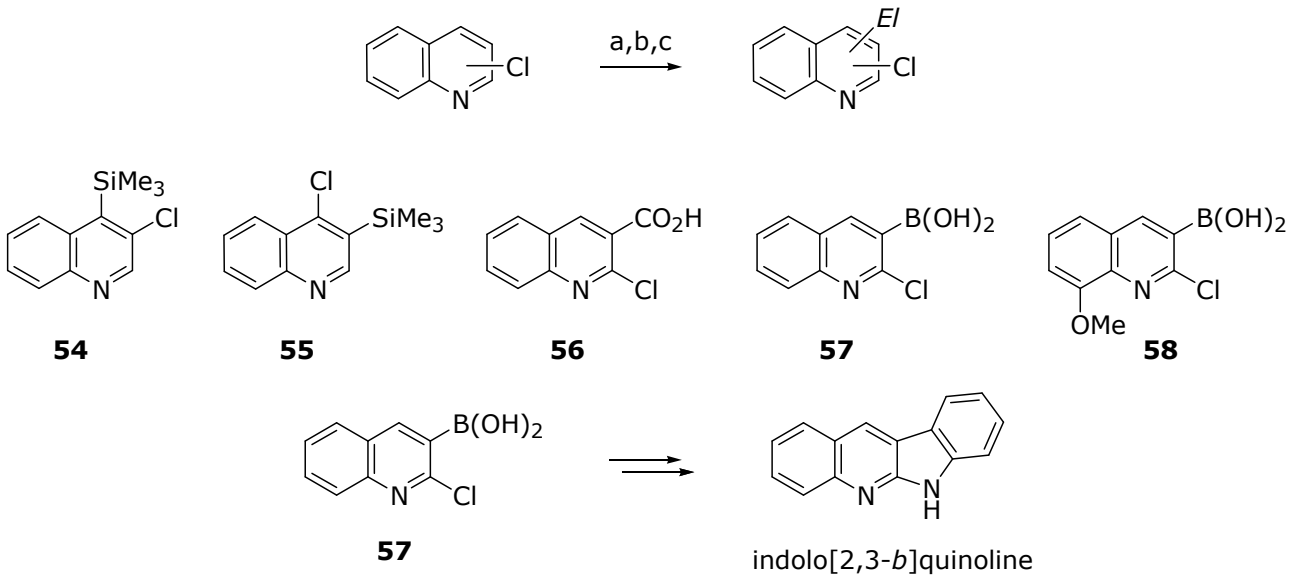
As observed with 3-fluoroquinoline, LDA-mediated deprotonation of 3-chloroquinoline occurs at the 4-position using LDA in THF at –75 °C, leading to the 4-trimethylsilyl derivative **54**.[5] 4-Chloroquinoline is similarly deprotonated at the 3-position, without formation of *peri*-functionalized products as observed with naphthalenes (compound **55**).[18] The reaction can be extended to 2-chloroquinoline, giving 2-chloro-3-quinolinecarboxylic acid (**56**) and 2-chloro-3-quinolineboronic acid (**57**) in 67 and 85% yield, respectively.[18] For 2-chloro-8-methoxyquinoline, and using the more hindered and basic LTMP, 2-chloro-8-methoxy-3-

quinolineboronic acid (**58**) was obtained in 82% yield.[19] 2-Chloro-3-quinolineboronic acid (**57**) acted as starting material for the synthesis of indolo[2,3-*b*]quinoline by palladium-catalyzed cross-coupling with 2-iodoaniline and acid catalysis steps in 35% overall yield (Scheme 12).[18]



a. LDA, THF, –75 °C, 2 h; b. CO_2; c. H^+.

Scheme 11

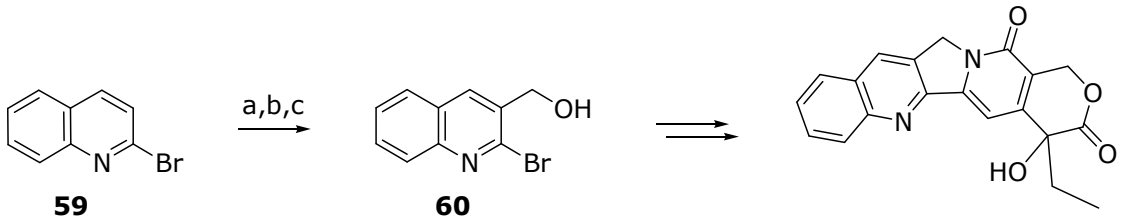


a. LDA or LTMP, THF, –75 °C, 2 h; b. *Electrophile*; c. hydrolysis.

Scheme 12

2.4. Bromoquinolines

The metalation of bromoquinolines has been only scarcely examined up to now because of the unavailability of the substrates. The deprotonation of 2-bromoquinoline (**59**) has been reported using LDA in THF at –75 °C. After trapping either with formaldehyde or with *N*,*N*-dimethylformamide followed by sodium borohydride, the expected 3-quinolinemethanol **60** is isolated in 58 and 78% yield, respectively.[20] It served in a synthesis of camptothecin, an alkaloid endowed with antitumoral properties (Scheme 13).[20]

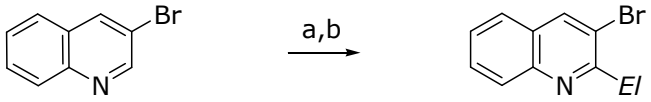


59 **60** (±)-camptothecin

a. LDA, THF, –75 °C; b. CH_2O or DMF then $NaBH_4$; c. hydrolysis.

Scheme 13

Metalation of the isomers is a challenging problem because of the propensity of these heterocycles to undergo 1,2-addition reactions with organometallic reagents. A chemoselective method using a mixed Mg/Li amide of type $R_2NMgCl{\cdot}LiCl$ was developed in 2006 for the deprotonation of sensitive substrates.[21] Using TMPMgCl·LiCl at –25 °C, the 2-magnesiated derivative of 3-bromoquinoline (**61**) is generated, as demonstrated by trapping with iodine and *N*,*N*-dimethylformamide to provide the functionalized quinolines **62** in 87 and 91% yield, respectively (Scheme 14).



61 **62**: *El* = I, CHO

a. TMPMgCl·LiCl, THF, –25 °C, 30 min; b. *Electrophile*.

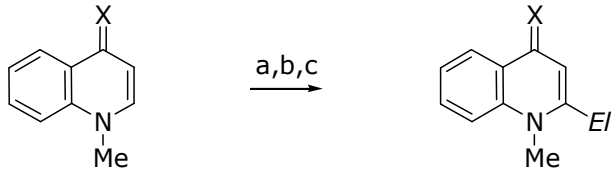
Scheme 14

In the aforementioned examples, 1,2-addition reactions to the quinoline ring are circumvented employing hindered lithium dialkylamides, and elimination of lithium halide is avoided by using low reaction temperatures.

3. Functionalization of quinolines bearing oxygen-based substituents

3.1. Hydroxyquinolines and quinolones

It was showed in 1992 that lithiation of *N*-methyl-4-quinolone or -quinolinethione (**63–64**) occurs at the 2-position.[22] The reverse addition of the substrates to an excess of LDA in THF at –75 °C can be efficiently used for the synthesis of a large range of 2-substituted derivatives (compounds **65–66**) (Scheme 15).



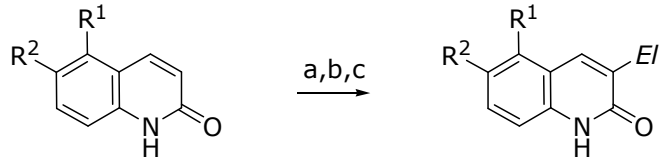
63-64 **65-66**

65: X = O, *El* = D, Et, CH(OH)Ph, CH(OH)(4-(NO_2)Ph), CH(OH)(4-(OMe)Ph) CH(OH)(3-py), COPh, CO(3-py), CH_2OH, C(OH)PhMe, $C(OH)Ph_2$: 14-71%
66: X = S, *El* = CH(OH)Ph, CH(OH)(3-py), CH(OH)(4-(OMe)Ph): 40-82%

a. 3 equiv LDA, THF, –75 °C, 30 min; b. *Electrophile*; c. hydrolysis.

Scheme 15

In contrast to *N*-methyl-2-quinolone, which gives a complex mixture of products when the BuLi-TMEDA chelate is used in THF at room temperature, 2-quinolone (**67**, $R^1 = R^2 = H$) is cleanly deprotonated at the 3-position when treated similarly.[23] Metalation at the 3-position is also observed from –75 °C when a methoxy group is present at the 5- or 6-position (Scheme 16).[24]



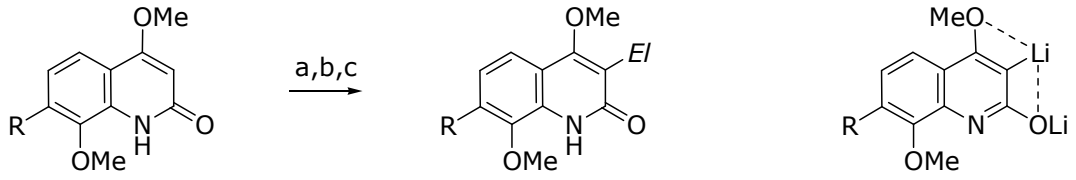
67

$R^1 = R^2 = H$, *El* = Me, CH(OH)Ph, CH(OH)(4-(OMe)Ph), CH(OH)(4-FPh), CH(OH)(2-FPh), CH(OH)(4-ClPh), CH(OH)(2-ClPh), $C(OH)Ph_2$, $SiMe_3$, SMe, CHO, CO_2H: 18-96%
$R^1 = H$, $R^2 = OMe$, *El* = $SiMe_3$, Me: 38-47%
$R^1 = OMe$, $R^2 = H$, *El* = $SiMe_3$, Me: 25%

a. 2 equiv BuLi-TMEDA, THF; b. *Electrophile*; c. hydrolysis.

Scheme 16

In the presence of a methoxy group at the 8-position, the addition of the base to the 2-quinolone ring is favored against deprotonation,[24] unless a second methoxy group at the 4-position contributes with the phenoxide anion to stabilize a lithio derivative at the 3-position (substrates **68**).[25] This was suggested since the *N*-methylated derivative of 4,8-dimethoxy-2-quinolone cannot be deprotonated under the same reaction conditions (Scheme 17).



68

R = H, *El* = CHO, SMe, CH(OH)Ph, $C(OH)Ph_2$, $SiMe_3$, I, $CH_2CH{=}CH_2$, $B(OH)_2$, Me: 10-93%
R = OMe, *El* = CHO: 54%

a. 4 equiv BuLi-TMEDA, THF, 55 °C, 1 h; b. *Electrophile*; c. hydrolysis.

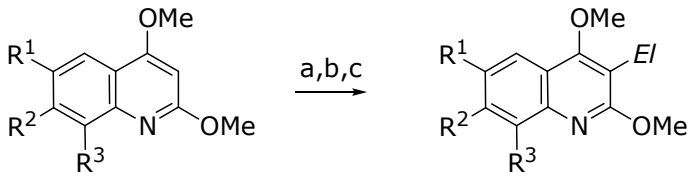
Scheme 17

3.2. Alkoxyquinolines

It was showed in 1951 that butyllithium is not the best base to promote the metalation of 2-ethoxyquinoline since 2-ethoxy-3-quinolinecarboxylic acid is isolated in a low 7% yield after reaction of the base in DEE at room temperature and subsequent trapping with dry ice.[26] This was explained by the competitive 1,2-addition of the base to the substrate, giving after rearomatization 2-butylquinoline in 60% yield.

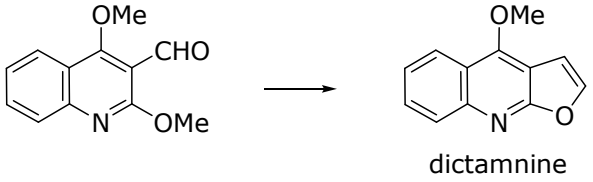
Higher yields of 3-substituted products are observed after metalation of 2,4-dimethoxy-, 2,4,6-trimethoxy-, 2,4,7-trimethoxy-, 2,4,8-trimethoxy- and 2,4,6,7-tetramethoxyquinoline (substrates **69**). Interception of the intermediate lithio compounds with *N*-methylformanilide[27] or 3,3-dimethylallyl bromide[28]

furnishes the expected 3-substituted derivatives **70** in good yields. The 3-functionalized derivatives led for example to dictamnine[27] and skimmianine,[28] two furoquinoline alkaloids (Scheme 18).

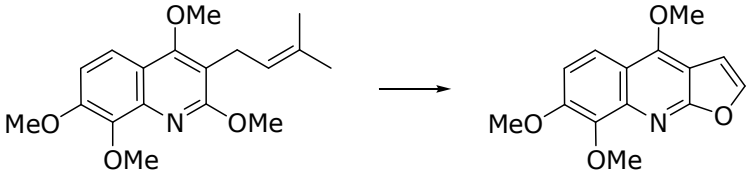


69 **70**

70: R^1, R^2, R^3 = H or OMe, *El* = CHO, $CH_2CH=CMe_2$: 69-76%



dictamnine

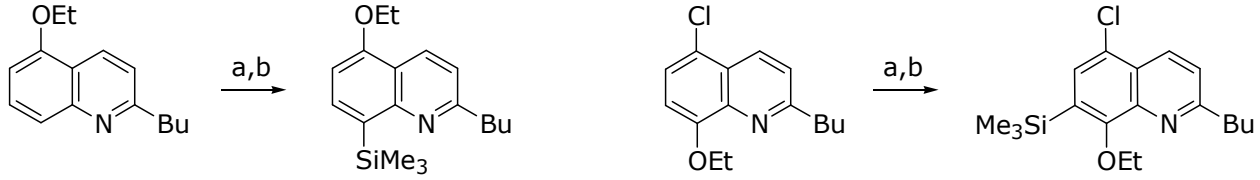


skimmianine

a. BuLi, DEE, 0 °C; b. *Electrophile*; c. hydrolysis.

Scheme 18

Metalation of 5- and 8-ethoxyquinoline furnishes the substituted benzo ring derivated provided that the C2 site is occupied. Indeed, treatment of 2-butyl-5-ethoxyquinoline (**71**) and 2-butyl-5-chloro-8-ethoxyquinoline (**72**) with TMEDA-activated BuLi in cyclohexane at 20 °C results in the deprotonation at the adjacent position to the nitrogen- and oxygen-containing group, respectively, as evidenced by trapping with chlorotrimethylsilane (Scheme 19).[29]



71 60% **72** 13%

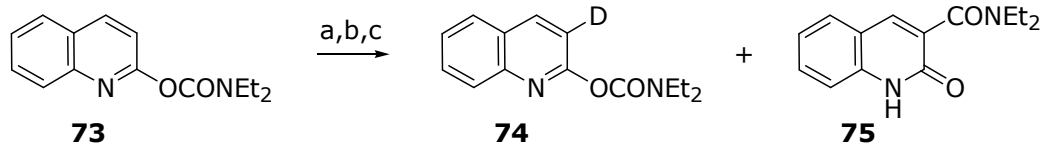
a. BuLi-TMEDA, C_6H_{12}, 20 °C; b. $ClSiMe_3$.

Scheme 19

3.3. *O*-(Quinolyl)carbamates

Deprotonation of all isomeric *O*-(quinolyl)carbamates has been studied.[30] When *N*,*N*-diethyl-2-quinolinecarbamate (**73**) is involved in a deprotonation procedure, the lithio derivative can either survive until the trapping step or stabilize itself by anionic Fries rearrangement. Using LDA in THF at –75 °C with *N*,*N*-diethyl-2-quinolinecarbamate, the expected 3-deuterated derivative **74** is obtained (40% yield after quenching with deuterated water) together with the anionic Fries rearrangement product **75**. Employing the

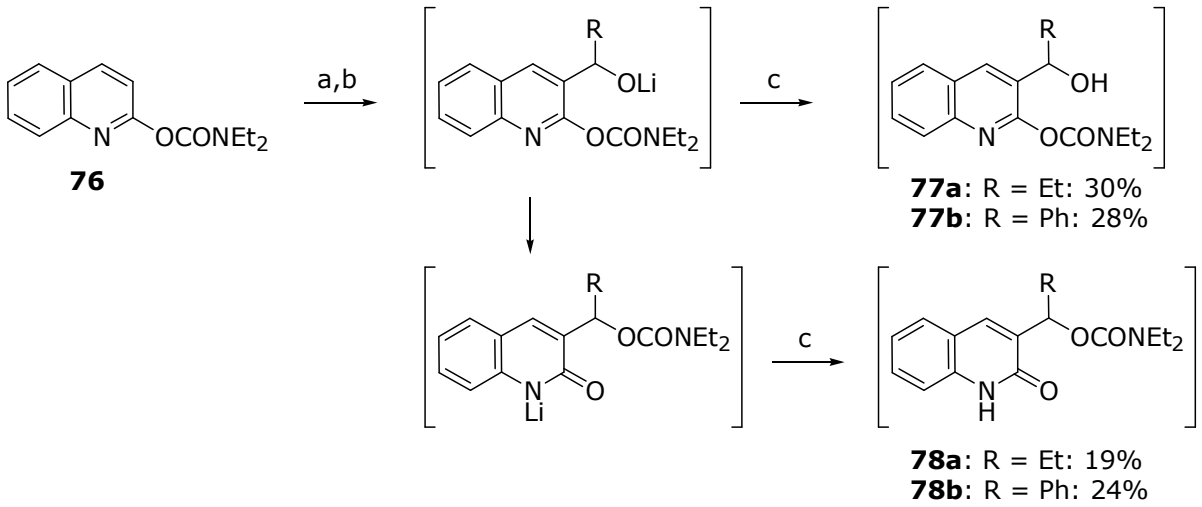
^{s}BuLi-TMEDA chelate at –105 °C, the anionic Fries rearrangement is avoided, and *N*,*N*-diethyl-2-(3-D)quinolinecarbamate (**74**) is formed (80% conversion) (Scheme 20).[30b]



a. base, THF, 1 h; b. MeOD; c. hydrolysis.

Scheme 20

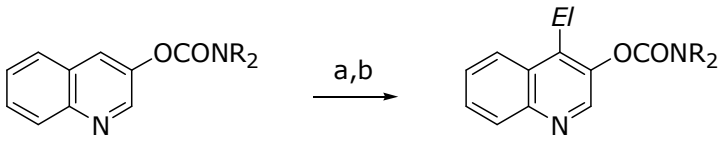
When the lithio derivative coming from deprotonation of *N*,*N*-diethyl-2-quinolinecarbamate (**76**) is intercepted with aldehydes, the expected 3-quinolinemethanols **77** are obtained together with an isomeric compound **78**. The latter could result from a nucleophilic attack of the intermediate lithium alkoxide to the carbamate function (Scheme 21).[30b]



a. ^{s}BuLi, THF, –105 °C, 1 h; b. RCHO; c. hydrolysis.

Scheme 21

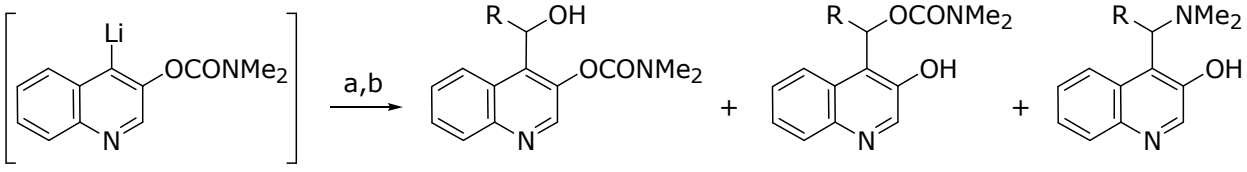
Using LDA in THF at –75 °C with *N*,*N*-diethyl- and *N*,*N*-dimethyl-3-quinolinecarbamate **79** results in a regioselective deprotonation at the 4-position; stabilization through anionic Fries rearrangement does not take place before interception with deuterated methanol or chlorotrimethylsilane (Scheme 22).[30] 4-Lithio-*N*,*N*-diethyl- and even -*N*,*N*-dimethyl-3-quinolinecarbamate prove more stable than 3-lithio-*N*,*N*-diethyl-2-quinolinecarbamate.



a. LDA, THF, –75 °C; b. *Electrophile*.

Scheme 22

When 4-lithio-*N*,*N*-dimethyl-3-quinolinecarbamate (**80**) is trapped with aldehydes, complications arise: the expected α-substituted 4-quinolinemethanols **81** are again obtained together with the isomeric compound **82** resulting from a nucleophilic attack of the intermediate lithium alkoxide to the carbamate function. In addition, an unexpected loss of carbon dioxide from the latter to give α-substituted *N*,*N*-dimethyl-3-hydroxy-4-quinolinemethylamines **83** in unreproducible yields is observed during the reaction work-up (Scheme 23).[30]

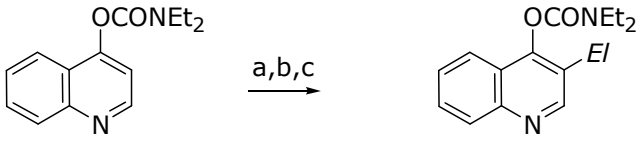


80 **81** **82** **83**

a. RCHO; b. work-up.

Scheme 23

When used in THF at –75 °C, LDA is able to deprotonate *N*,*N*-dialkyl-4-quinolinecarbamates. The anionic Fries rearrangement takes place with the *N*,*N*-dimethyl lithio compound to afford 3-(*N*,*N*-dimethylcarbamoyl)-4-quinolinone in 80% yield, whereas the corresponding *N*,*N*-diethyl lithio compound survives intact until trapping to furnish the 3-functionalized compounds **84** in high yields (Scheme 24).[30b]

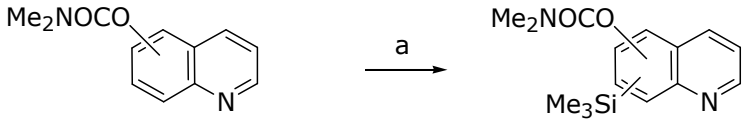


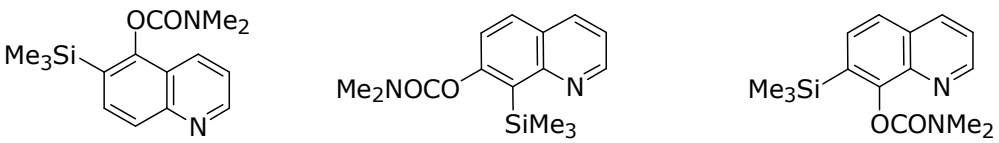
84: *El* = D, Me, $SiMe_3$, CH(OH)Et: 75-95%

a. LDA, THF, –75 °C, 1 h; b. *Electrophile*; c. hydrolysis.

Scheme 24

N,*N*-Dimethyl-5-, -7- and -8-quinolinecarbamate are regioselectively transformed into the 6-, 8- and 7-functionalized derivatives **85–87**, respectively, when simultaneously treated with LDA and chlorotrimethylsilane (*in situ* trapping conditions) in THF at –75 °C (Scheme 25).[31] Under these conditions, *N*,*N*-dimethyl-6-quinolinecarbamate gives a mixture of 5- and 7-silylated together with 5,7-disilylated derivatives in a 2:2:1 ratio.[31]



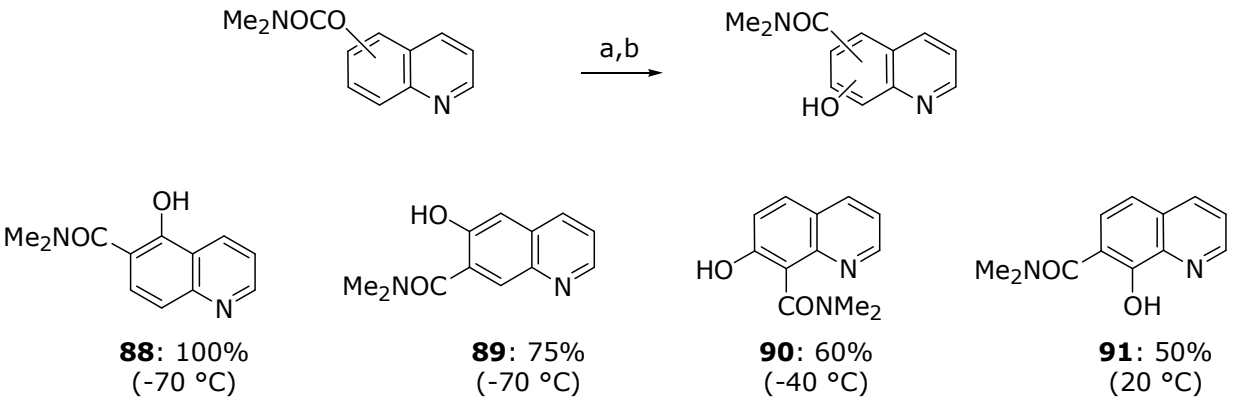


85: 70% **86**: 90% **87**: 40%

a. LDA, $ClSiMe_3$, THF, –75 °C.

Scheme 25

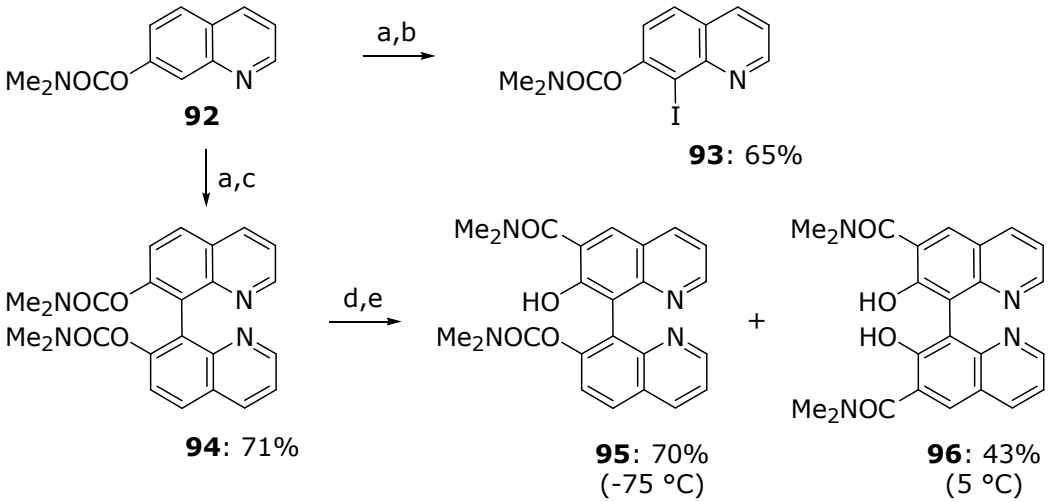
In the absence of electrophile, the lithiated *N*,*N*-dimethyl-5-, -6-, -7- and -8-quinolinecarbamate decompose by anionic Fries rearrangement. The latter occurs regioselectively using LDA in THF, at specific temperatures for each isomer, to give compounds **88–91** (Scheme 26).[31]



a. LDA, THF; b. hydrolysis.

Scheme 26

It is possible to functionalize *N*,*N*-dimethyl-7-quinolinecarbamate (**92**) at the 8 position by accumulation of the lithio intermediate at –75 °C (decomposition occurred from –40 °C) followed by electrophilic trapping (iodination or oxidation with ferric chloride, to give compounds **93** and **94**, respectively). Exposure of the 8,8'-biquinoline **94** to LDA in THF results in a single (compound **95**) or double (compound **96**) anionic Fries rearrangement, depending on the reaction temperature (Scheme 27).[32]

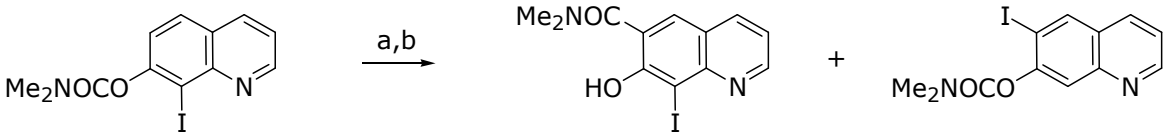


a. LDA, THF, –75 °C; b. I_2, THF, –75 °C; c. $FeCl_3$, THF, –75 to 0 °C;
d. LDA, THF, –75 °C or –75 to 5 °C; e. aq. NH_4Cl.

Scheme 27

Whereas lithiation of 8-iodo-*N*,*N*-dimethyl-7-quinolinecarbamate (**93**) using LDA in THF at 0 °C followed by protonolysis leads to the carbamoyl transfer product **97**, the reaction surprisingly furnishes 6-iodo-*N*,*N*-dimethyl-7-quinolinecarbamate (**98**) when carried out at –75 °C. Such a halogen-dance reaction could proceed by (1) initial metalation at the C6 site and (2) migration of the iodine atom from the 8- to the 6-position, giving the thermodynamically more stable 8-lithio isomer. At higher temperatures, the anionic

Fries rearrangement is less likely for 6-iodo-8-lithio-*N*,*N*-dimethyl-7-quinolinecarbamate (owing to its relative stability) than for 8-iodo-6-lithio-*N*,*N*-dimethyl-7-quinolinecarbamate. The equilibrium between both species could be shifted toward the latter, consumed to give the 6-quinolinecarboxamide **97** (Scheme 28).[32]

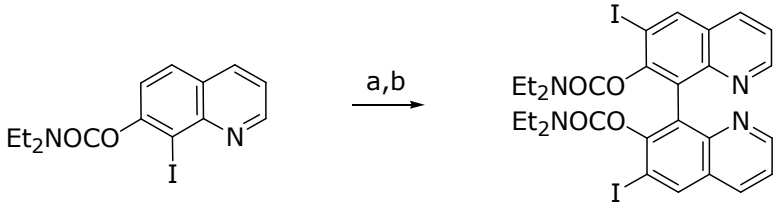


93 **97**: 76% (0 °C) **98**: 62% (-75 °C)

a. LDA, THF, −75 °C or −75 to 0 °C; b. aq. NH_4Cl.

Scheme 28

6-Iodo-8-lithio-*N*,*N*-diethyl-7-quinolinecarbamate generated by treatment of 8-iodo-*N*,*N*-diethyl-7-quinolinecarbamate (**99**) using LDA at –75 °C in THF can be remarkably converted into the corresponding 8,8'-biquinoline **100** by treatment with ferric chloride (Scheme 29).[32]



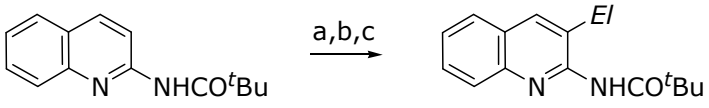
99 **100**: 54%

a. LDA, THF, −75 °C, 10 min; b. $FeCl_3$, −75 to 0 °C, 24 h.

Scheme 29

4. Functionalization of quinolines bearing nitrogen-based substituents

The unavailability of the nitrogen lone pair of nitrogen-based substituents for coordination with metalating agents due to resonance effects[33] makes less accessible the deprotonation of these substrates. In addition, the acidifying effect exerted by these groups on adjacent hydrogens is weak compared to other non-coordinating functions such as heavy halogens, and lithium dialkylamides can hardly be used. It is thus advisable to employ weakly nucleophilic bases as common alkyllithiums tend to add nucleophilically to the ring 2- or, when occupied, 4-position.



101

102: *El* = D, I, $SiMe_3$, SMe, CO_2Et, CH(OH)Ph, $CH(OH)CH_3$, $C(OH)Et_2$, $CH_2CH(OH)CH_3$: 11-95%

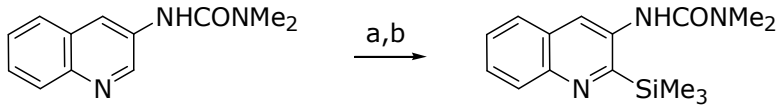
a. 3 equiv BuLi, DEE, 0 °C, 3 h; b. *Electrophile*; c. hydrolysis.

Scheme 30

As quinoline is prone to nucleophilic addition of 1,2-type, deprotonation of 2-substituted isomers is expected to be more facile. Indeed, 2-(pivaloylamino)quinoline (**101**) is amenable to lithiation at C3 when treated with an excess of neat butyllithium in DEE at 0 °C. The 3-iodo derivative **102** (*El* = I) was for

instance isolated in a good 90% yield after trapping with iodine (Scheme 30).[34] On the other hand, butyllithium combined with TMEDA proves inappropriate, giving a mixture of the 3-iodo and 4-butyl derivatives when used in DEE at 0 °C.

3-(Pivaloylamino)quinoline is a challenging model to test the scope of the method. As expected in the absence of substituent at the C2 site, the deprotonation with alkyllithiums (butyllithium, *tert*-butyllithium or the BuLi-TMEDA chelate) in THF leads to the corresponding 2-alkylquinolines after subsequent oxidation.[35] Admittedly, the 2-substituted derivatives **103** were obtained starting from the corresponding *N*,*N*-dimethyl urea **104** in THF at –75 °C, but only upon simultaneous treatment with LDA and chlorotrimethylsilane (*in situ* trapping conditions) (Scheme 31).[35]

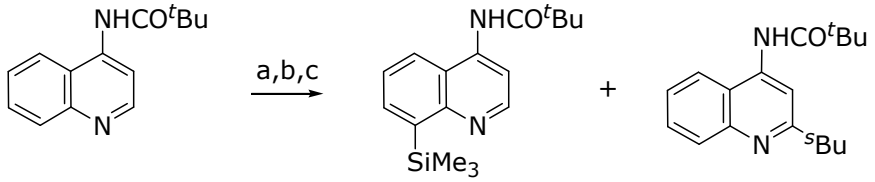


104 **103**: 93%

a. LDA, $ClSiMe_3$, THF, –75 °C; b. hydrolysis.

Scheme 31

1,2-Addition is similarly observed when 4-(pivaloylamino)quinoline (**105**) is treated with the BuLi-TMEDA chelate at –50 °C.[35] Addition is however reduced when more basic *sec*-butyllithium is employed at –90 °C, as evidenced by trapping with chlorotrimethylsilane to generate a mixture of the 8-silylated compound **106** and the 2-(*sec*-butyl) derivative **107** (Scheme 32). This unexpected regioselectivity suggests a coordinative interaction between the ring nitrogen and the base. Unfortunately, the lithiated intermediate was unable to react with carbonyl electrophiles.[35]



105 **106**: 45% **107**: 45%

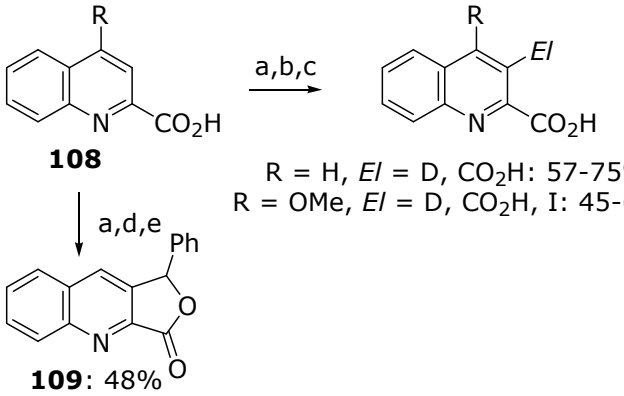
a. ^{s}BuLi, THF, –90 °C; b. $ClSiMe_3$; hydrolysis.

Scheme 32

5. Functionalization of quinolines bearing carbon-based substituents

5.1. Quinolinecarboxylic acids

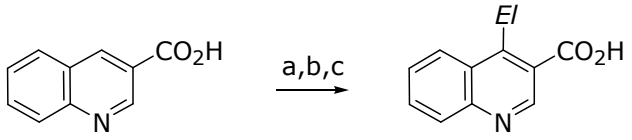
The metalation of free carboxylic acids avoids protection and deprotection step. The use of butyllithium to generate the lithium salts of quinolinecarboxylic acids, as established for the pyridine series,[36] was first considered but without success due to competitive addition to the quinoline ring. LTMP in THF was therefore used both to form the lithium salts and to deprotonate them. The metalation of quinaldic acid (**108**, R = H) is achieved at –25 °C, as evidenced by trapping the dilithio derivative with heavy water, dry ice and benzaldehyde (in the latter case, a subsequent cyclization to lactone **109** is achieved under acidic conditions). From 4-methoxyquinaldic acid (**108**, R = OMe), deprotonation can be performed at 0 °C, owing to the substituents present at both the 2- and 4-position (Scheme 33).[37]



a. 3 equiv LTMP, THF, −25 °C (R = H) or 0 °C (R = OMe), 30 min;
b. *Electrophile*; c. H^+; d. PhCHO; e. CH_3CO_2H, EtOH, reflux.

Scheme 33

From 3-quinolinecarboxylic acid (**110**), it is difficult to avoid the 1,2- and 1,4-addition of the 4-lithio derivative to the starting lithium quinolinecarboxylate. Nevertheless, working at –50 °C allows to minimize it to afford regioselectively the 4-functionalized products **111** (Scheme 34).[37]



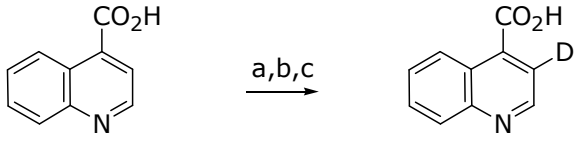
110

111a: *El* = D: 59%
111b: *El* = CO_2H: 80%

a. 3 equiv LTMP, THF, −50 °C, 30 min; b. *Electrophile*; c. H^+.

Scheme 34

Concerning lithium 4-quinolinecarboxylate (generated from **112**), no lithiation is observed using less than 5 equiv of LTMP in THF at –50 °C (Scheme 35). The decreased efficiency of the directing power of the lithium carboxylate could be attributed to the non-coplanarity between the C=O and C-Li bonds, a consequence of the steric hindrance caused by the *peri* hydrogen at C5.[37]



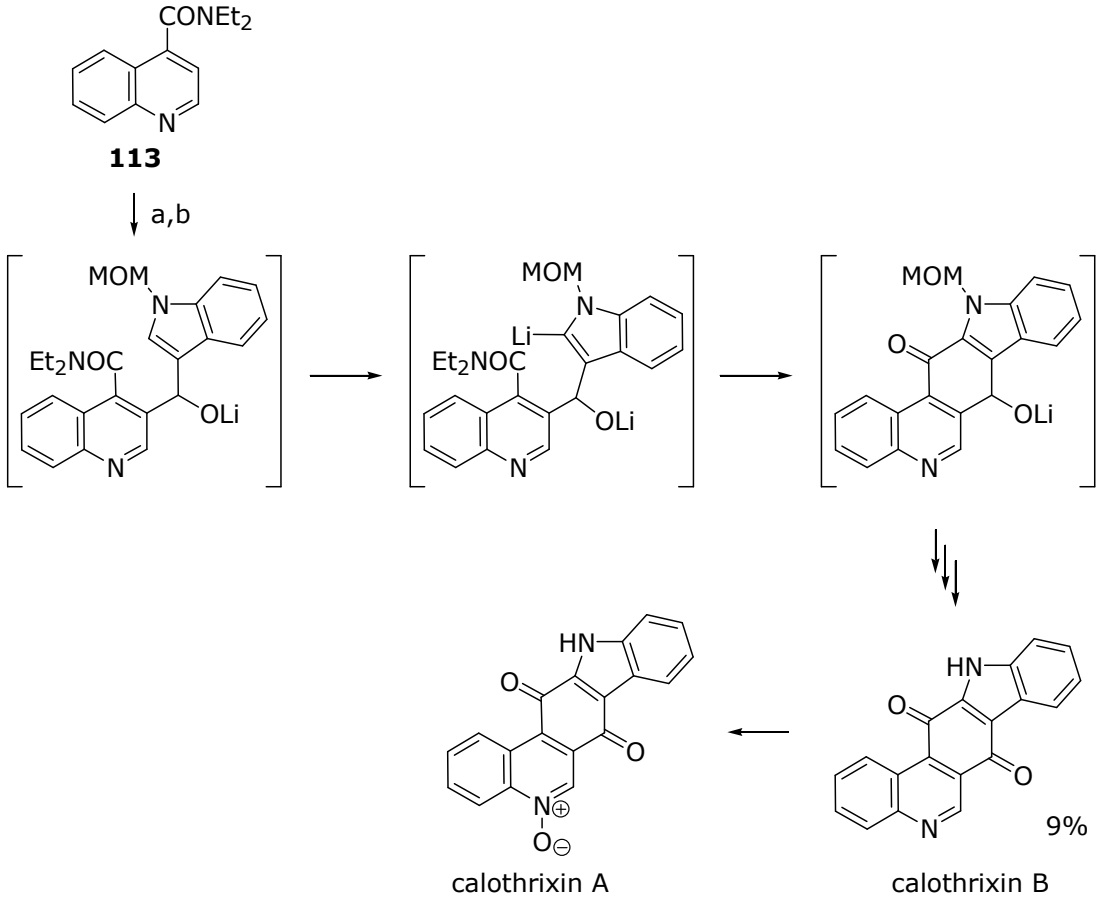
112 33%

a. 6 equiv LTMP, THF, -50 °C, 30 min; b. D_2O; c. H^+.

Scheme 35

5.2. Quinolinecarboxamides

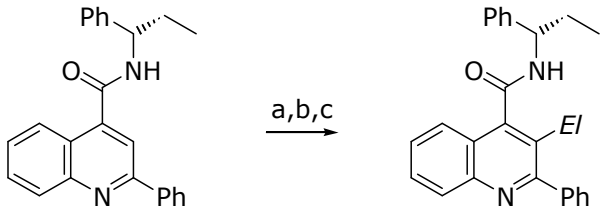
As observed with lithium 4-quinolinecarboxylate, metalation of *N*,*N*-diethyl-4-quinolinecarboxamide (**113**) requires an excess of LTMP in THF. The reaction was exploited as a key step during the course of the synthesis of calothrixin A and B (Scheme 36). The choice of LTMP is crucial. Indeed, *sec*-butyllithium, *tert*-butyllithium and lithium hexamethyldisilazide are useless whereas LDA only gives small amounts of the expected product.[38]



a. 4 equiv LTMP, THF, –90 °C, 35 min; b. *N*-MOM-3-indolecarboxaldehyde, –90 °C to rt, 2 h.

Scheme 36

The functionalization of (*S*)-*N*-(1-phenylpropyl)-2-phenyl-4-quinolinecarboxamide (**114**) through the lithiated derivative was studied in order to label with carbon-11 NK-3 receptor antagonist SB 222200.[39] Lithiation is first studied using deuterated methanol as an electrophile. Using hindered lithium amides LDA or LTMP, even in large excess (10 equiv), and *tert*-butyllithium, no reaction is detected. The BuLi-TMEDA chelate gives better yields than butyllithium alone; when 10 equiv are used in THF at low temperature, the expected 3-functionalized quinolines **115** are isolated in satisfying yields after interception with electrophiles (Scheme 37). In spite of the drastic conditions used, the sequence does not lead to racemization of the stereogenic center.



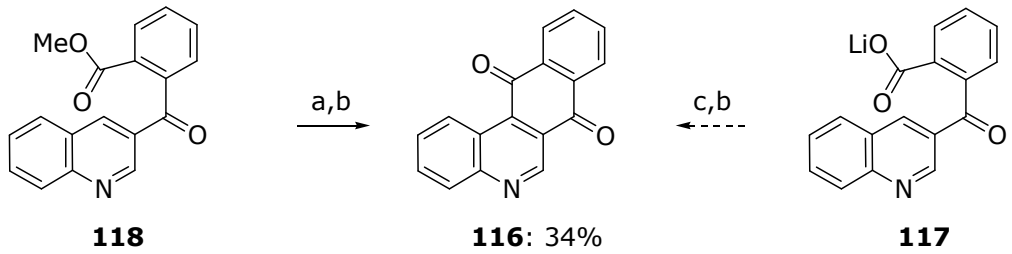
114 **115**: *El* = D, I, Br, Cl, $SnMe_3$, $SiMe_3$: 59-74%

a. 10 equiv BuLi-TMEDA, THF, –60 °C, 5 h; b. *Electrophile*, –60 °C, 1 h; c. H^+.

Scheme 37

5.3. Other quinolines bearing carbon-based substituents

In order to reach heterocyclic quinones, a deprotonation-condensation sequence involving quinolines bearing an alkyl carboxylate or a lithium carboxylate group remote from the quinoline ring was investigated.[40] Benzo[*j*]phenanthridine-7,12-dione (**116**) is regioselectively obtained in 10 and 34% yields, respectively, when lithium 2-(3-quinolylcarbonyl)benzoate (**117**) and methyl 2-(3-quinolylcarbonyl)benzoate (**118**) are exposed to LTMP in THF (Scheme 38). A better result is obtained with the latter since it intercepts the lithio intermediate at a lower temperature.

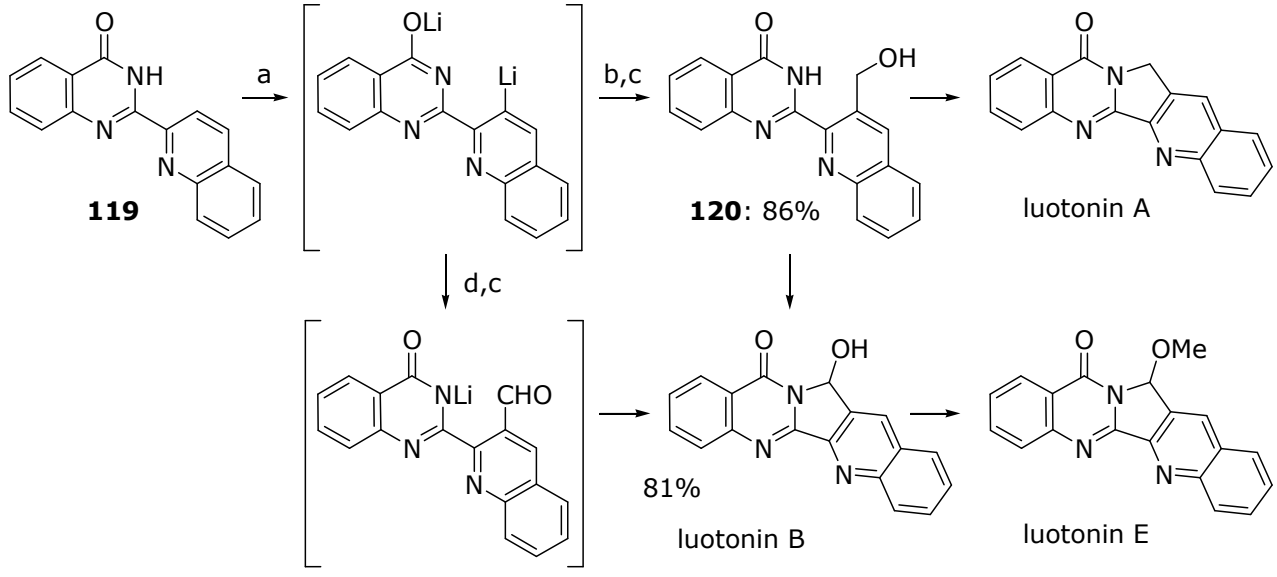


118 **116**: 34% **117**

a. 3 equiv LTMP, THF, −75 °C, 2 h; b. hydrolysis; c. 3 equiv LTMP, THF, rt, 2 h.

Scheme 38

A regioselective lithiation of a quinoline moiety at the position adjacent to a quinazolinone was used as a key step for a synthesis of the human DNA topoisomerase I poison luotonin A and luotonins B and E.[41]



119 **120**: 86% luotonin A

121 luotonin B luotonin E

a. 2 equiv mesityllithium, THF, −75 °C, 30 min to −20 °C; b. THF solution of HCHO (5 equiv), −30 °C, 20 min; c. saturated aq. solution of NH_4Cl; d. DMF (5 equiv), −20 °C, 30 min.

Scheme 39

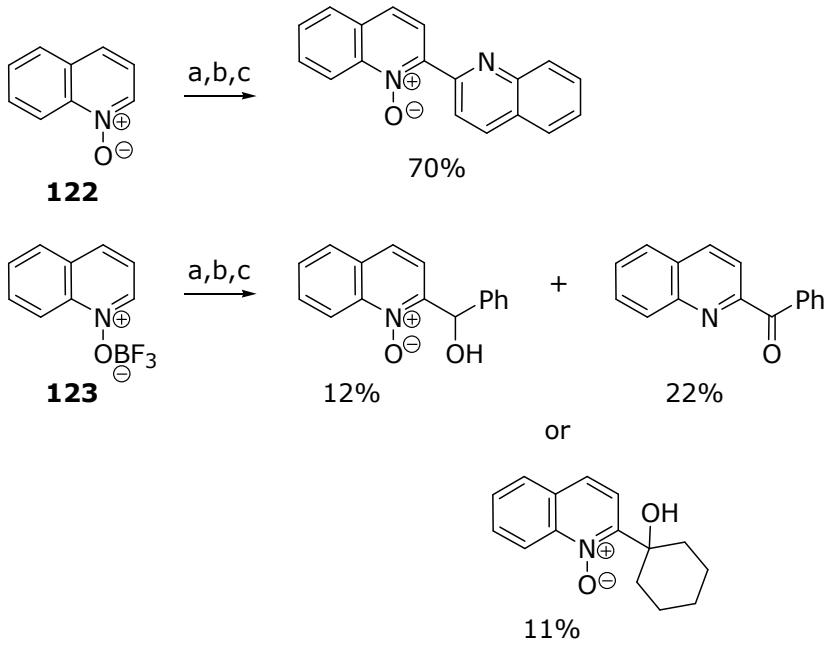
The strategy is based on the ability of the amide unit in quinazolinone to direct metalation reactions on an adjacent 2-aryl group (in this case, 3-quinolyl). Whereas the reaction of the 2-quinolylquinazolinone **119** with alkyllithiums (butyllithium, *sec*-butyllithium and *tert*-butyllithium) combined or not with TMEDA, at 0 to –75 °C, or even with LDA, leads to the formation of worthless complex mixtures, the use of non-nucleophilic mesityllithium at –20 °C furnishes the desired dilithiated species as follows: (1) deprotonation

of the quinazolinone amide and (2) deprotonation at the proximal 3'-position of the quinoline ring. Subsequent reaction with formaldehyde or *N*,*N*-dimethylformamide yields expected quinazolinone **120** or **121**, respectively. The former is transformed either into luotonin A using a Mitsunobu cyclization, or into luotonin B by PCC oxidation. The latter directly cyclizes to give luotonin B, which is next converted into luotonin E on treatment with *p*-TSA/methanol (Scheme 39).

6. Functionalization of *N*-activated quinolines and isoquinolines

6.1. *N*-Activated quinolines

In quinoline *N*-oxide, the acidity of the hydrogen at the 2-position is enhanced by the inductive effect of the oxide and by the complexing ability of the lone pair on oxygen with lithium. Therefore, 2-lithiation becomes feasible. The deprotonation of quinoline *N*-oxide (**122**) and its BF_3 complex **123** has been examined.[42] Deprotonation turns out less useful in the quinoline *N*-oxide than the pyridine *N*-oxide series[43] since addition giving 2,2'-dimers cannot be avoided. Starting from the corresponding BF_3 complex **123** gives mixtures including the desired products (Scheme 40).



a. LTMP, TMEDA, DEE, −75 °C, 1.5 h; b. PhCHO or cyclohexanone; c. hydrolysis.

Scheme 40

6.2. *N*-Activated isoquinolines

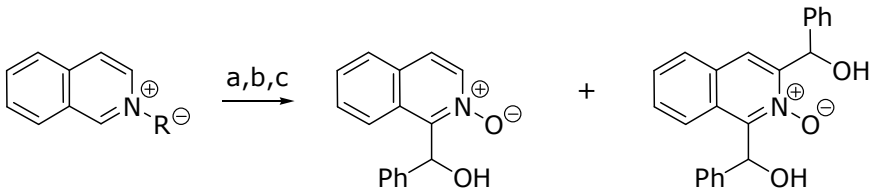
Similar results are observed starting from isoquinoline *N*-oxide (**124**) and its BF_3 complex **125**. In this case, mono- and difunctionalized compounds **126–127** are obtained because the oxide activates two positions of the ring (Scheme 41).[44] Attempts to deprotonate BF_3 complexes of quinoline and isoquinoline were unsuccessful.[44]

7. Functionalization of other substituted quinolines and isoquinolines

7.1. Triazoloquinolines

Owing to their accessibility and possible conversion into useful derivatives, triazoloquinolines have been submitted to deprotonation studies. Lithiation of 1,2,3-triazolo[1,5-*a*]quinoline (**128**) with LDA at

–40 °C followed by reaction with aldehydes and ketones allows to graft an alcohol function at the 3-position of the triazoloquinoline (compounds **129**). When carbon dioxide is used instead, the 3-carboxylic acid is obtained, and next converted into the corresponding *N*,*N*-diethylcarboxamide **130** by a standard procedure. The lithiation of the latter using LDA then occurs at the 4-position of the triazoloquinoline, as evidenced by interception with carbonyl electrophiles (compounds **131**) (Scheme 42).[45]

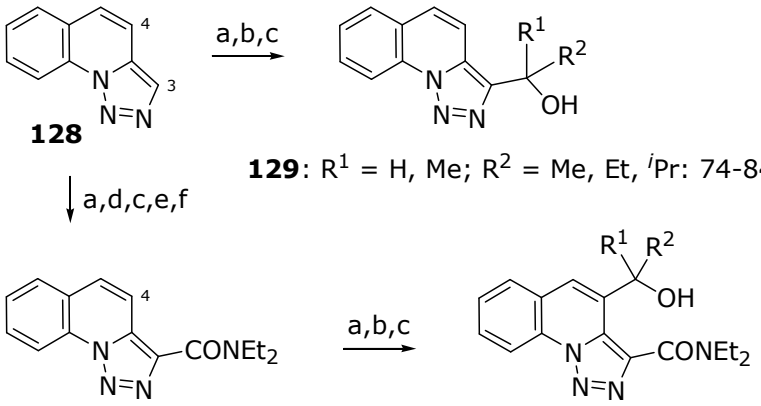


124
125

126: R = O, 28 and 17%
127: R = OBF_3, 19 and 17%

a. LTMP, TMEDA, DEE, −75 °C, 1.5 h; b. PhCHO; c. hydrolysis.

Scheme 41



128

129: R^1 = H, Me; R^2 = Me, Et, ^{i}Pr: 74-84%

130: 66%

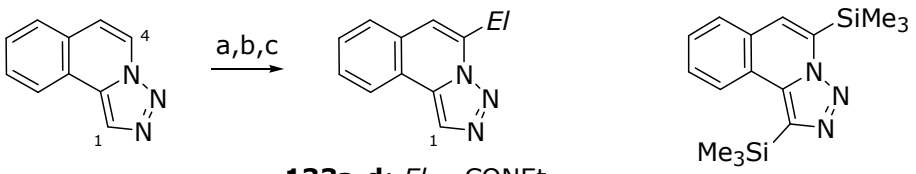
131: R^1 = H, Me; R^2 = Me, CH(OH)(4-(OMe)Ph): 54-65%

a. LDA, −40 °C; b. $R^1R^2C=O$; c. hydrolysis; d. CO_2; e. $SOCl_2$; f. Et_2NH.

Scheme 42

7.2. Triazoloisoquinolines

Unlike 1,2,3-triazolo[1,5-*a*]quinoline, 1,2,3-triazolo[5,1-*a*]isoquinoline (**132**) is directly lithiated at the 4-position of the triazoloisoquinoline when treated with LDA in DEE at –40 °C, as evidenced by trapping with electrophiles (compounds **133**). Using chlorotrimethylsilane, the expected 4-silylated compound **133b** (60% yield) is formed together with the 1,4-disilylated derivative **134** (23% yield) (Scheme 43).[46] Subsequent hydrolytic ring opening provides a synthesis of 1,3-disubstituted isoquinolines.



132

133a-**d**: *El* = $CONEt_2$, $SiMe_3$, CH(OH)Me, CH(OH)(4-(OMe)Ph): 45-70%

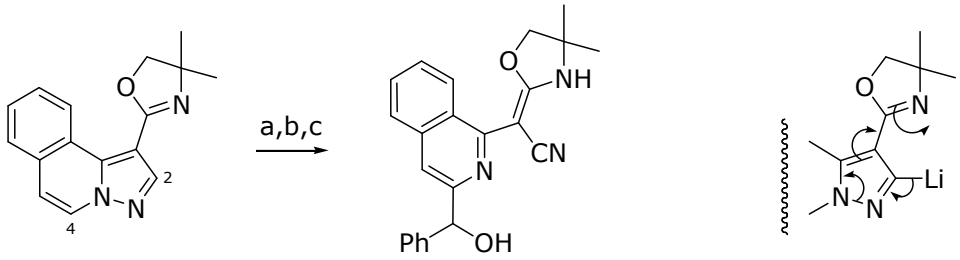
134: 23%

a. LDA, DEE, −40 °C; b. *Electrophile*; c. hydrolysis.

Scheme 43

7.3. Pyrazoloisoquinolines

Treatment of 1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)pyrazolo[5,1-*a*]isoquinoline (**135**) with 2 equiv of butyllithium in THF at –75 °C enables the deprotonation at both the 2- and 4-position to give after trapping with benzaldehyde the 3-substituted isoquinoline-2-acetonitriles **136** (cleavage of the pyrazole ring) (Scheme 44).[47]



135 **136**: 90%

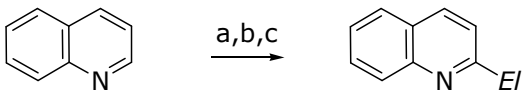
a. 2 equiv BuLi, THF, –75 °C, 30 min; b. PhCHO; c. hydrolysis.

Scheme 44

8. Functionalization of unsubstituted quinoline and isoquinoline

Unlike alkyllithiums, hindered lithium dialkylamides such as LDA and LTMP hardly add to π-deficient heterocycles in the absence of good leaving groups at the 2- and 4- position. When submitted to LDA in DEE at very low temperatures (around –70 °C), quinoline and isoquinoline undergo complex reactions of formation of 2,2'- and 1,1'-dimer, respectively.[48] Addition of hexamethylphosphoramide (HMPA) proves to increase the yields of dimers. Attempts to trap the lithiated species fail. A single electron transfer (SET) route between LDA and the substrate, giving a radical anion, which can add to a neutral molecule, was suggested on the basis of electron spin resonance (ESR) studies to rationalize these coupling reactions.[49] A 1,2-migration of lithium ate complexes ($[(2\text{-quinolyl})_2\text{Li}]^-,\text{Li}^+\cdot$HMPA or $[(1\text{-isoquinolyl})_2\text{Li}]^-,\text{Li}^+\cdot$HMPA) was also advanced as an alternative mechanism to explain the dimers formation.[50]

The use of unimetallic superbases for the deprotonation of π-deficient aza-aromatics has been studied. Using an excess of butyllithium in the presence of lithium 2-(dimethylamino)ethoxide, quinoline (**137**) is deprotonated at the 2-position, and the lithio intermediates formed trapped by various electrophiles (compounds **138**, Scheme 45). Nevertheless, large amounts of unchanged quinoline are recovered after the reaction, this is attributed to a lower reactivity of the deprotonated quinoline.[51]

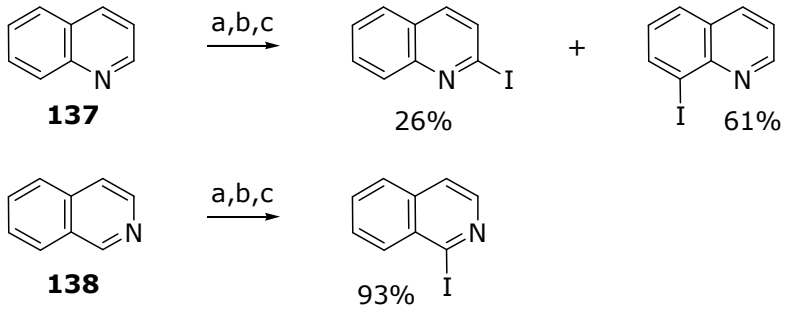


137 **138**: *El* = $SiMe_3$, D, Et, SMe, $CH(OH)^tBu$, CH(OH)Ph, CH(OH)MeEt, $C(OH)Ph_2$: 25-70%

a. 4 equiv BuLi-LDMAE, hexane, –75 °C, 30 min; b. *Electrophile*; c. hydrolysis.

Scheme 45

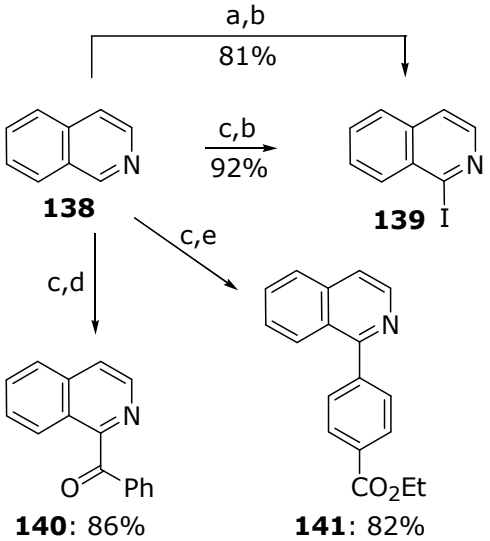
The chemoselective deprotonation of quinoline (**137**) and isoquinoline (**138**) through the formation of an arylzincate has been studied. Using lithium di-*tert*-butyl(2,2,6,6-tetramethylpiperidino)zincate as a base and conducting the reactions at room temperature, quinoline is deprotonated at both the 2- and 8-position whereas isoquinoline is deprotonated regioselectively at the 1-position (Scheme 46).[52]



a. TMPZn(^{t}Bu)$_2$Li, THF, rt, 3 h; b. I_2; c. hydrolysis.

Scheme 46

The chemoselective magnesiation of isoquinoline (**138**) has been examined using DAMgCl·LiCl (DA = diisopropylamino) and TMPMgCl·LiCl. Whereas reaction with 2 equiv of DAMgCl·LiCl provides only the magnesiated isoquinoline after 12 h at room temperature (compound **139** in 81% yield after trapping with iodine), more hindered and less aggregated TMPMgCl·LiCl (1 equiv) leads to complete magnesiation within 2 h at room temperature (compound **139** in 92% yield after trapping with iodine). Quenching the deprotonated quinoline with benzoyl chloride under copper catalysis or transmetalation to the corresponding zinc derivative to allow a palladium-catalyzed Negishi cross-coupling reaction with ethyl 4-iodobenzoate affords the expected ketone **140** and arylated quinoline **141** in 86 and 82% yield, respectively (Scheme 47).[21]



a. DAMgCl·LiCl, THF, 25 °C, 12 h; b. I_2; c. TMPMgCl·LiCl, THF, 25 °C, 2 h;
d. CuCN·2 LiCl then PhCOCl; e. $ZnCl_2$ then ethyl 4-iodobenzoate, cat. $Pd(dba)_2$ and P(2-furyl)$_3$.

Scheme 47

The potential of methods avoiding the use of highly reactive lithium bases is far from being explored and exploited.

9. Conclusions

The numerous examples of quinoline metalation highlighted in this review demonstrate the synthetic utility of this methodology. The main problem encountered is nucleophilic addition of the base to the substrate. With appropriate experimental conditions, lithium bases may therefore be used to deprotonate

quinolines containing various heterosubstituents. In particular, lithium amides, although less basic (pK_a 35.7 for LDA or 37.3 for LTMP) than alkyllithiums (pK_a ~ 40–50), can help to bias the reactions in favor of deprotonation and an even larger set of heterosubstituents are then compatible.

For quinolines with little or no activation, the use of an additive such as TMEDA, which is known to enhance the basicity of alkyllithiums, can often promote metalation. Unimetallic and mixed metal complex bases that are less nucleophilic or/and more basic than alkyllithium reagents are increasingly finding application in the metalation of azines. Importantly, such bases can often facilitate the metalation of bare quinolines.

Attention has largely focussed to date on the generation and application of lithiated quinolines. Increasingly other organometallic derivatives are finding favor. Advances in this field will further widen the scope and application of quinoline metalation chemistry.

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TETRAFLUOROACRIDINES: SYNTHESIS, PROPERTIES AND APPLICATIONS IN MATERIALS SCIENCE

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Abstract. *1,2,3,4-Tetrafluoro-acridines are an interesting example of fluorescent semiconducting molecules with applications in materials science. The syntheses developed so far allow the preparation of a wide class of fluorinated acridines, starting from pentafluoro-benzaldehyde and substituted anilines. The reactivity of tetrafluoro-acridines has been explored, in order to obtain polyfluoro-acridines which are not accessible by one-pot synthesis. Chemico-physical characterization and some examples of applications of these systems in materials science are also reported.*

Contents

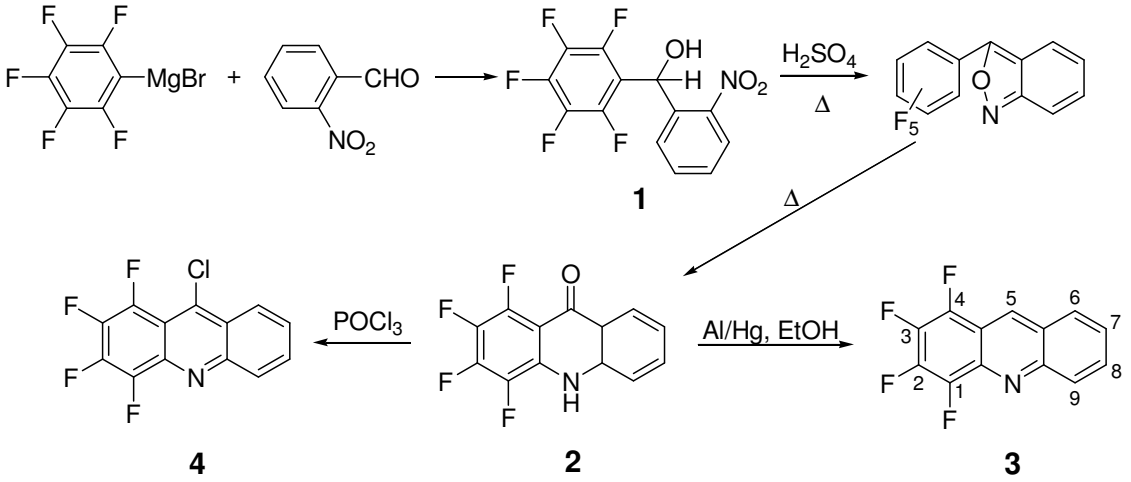
1. Introduction

During the last decades, organo-fluorine compounds have attracted a huge and growing interest for their peculiar physical properties and for their promising applications in materials science. In addition, starting from the 1990's, fluorinated aromatic and heteroaromatic systems have been proposed as good candidates for electron transport molecules (n-type semiconductors) in the research field of organic semiconductors.[1–4] The availability of both p-type and n-type organic semiconductors is necessary for the full development of organic electronics. Polyfluoro-acridines are potentially superior systems, since they

combine the interesting properties of acridine, which is a fluorescent, electron-poor aromatic heterocycle, with those of fluoro-arenes, giving rise to new promising fluorescent and n-type semiconductors. In addition, the acridine nucleus has important applications in medicine; indeed, the antibacterial activity of acridines is known since 1913,[5] and 5-amino- and 2,8-diamino-acridines (this latter known as proflavine) have been used as antibacterial drugs while quinacrine (*i.e.* 2-chloro-5-(1-methyl-4-diethylamino)-butylamino-7-methoxy-acridine) has been proposed as antiprotozoal drug. More recently, 1,2,3,4-tetrafluoro-acridines, synthesized for the first time in the 1960's, have been deeply investigated in order to ascertain the effect of fluorination on pharmacological properties.[6] Finally, studies on fluorinated acridines as potential antimalarial drugs are currently in progress.[7]

1.1. Multi-step syntheses of 1,2,3,4-tetrafluoro-acridines

The earlier attempts to synthesize 1,2,3,4-tetrafluoro-acridines **3** (Scheme 1) are based on multi-step ring-closure reactions.[6] The synthesis was undertaken starting from 2,3,4,5,6-pentafluoro-2'-nitrophenyl-methanol **1**, which was prepared by reacting pentafluorophenyl-magnesium bromide with *o*-nitro-benzaldehyde. Pyrolysis of nitrophenyl-methanol gave 1,2,3,4-tetrafluoro-acridone **2** by a mechanism, proposed by the authors, which involves the formation of a 3-pentafluorophenyl-anthranyl derivative. Reduction of the acridone derivative with aluminum/mercury amalgam gave the desired 1,2,3,4-tetrafluoro-acridine while its treatment with phosphorous oxychloride gave 1,2,3,4-tetrafluoro-5-chloro-acridine **4**.

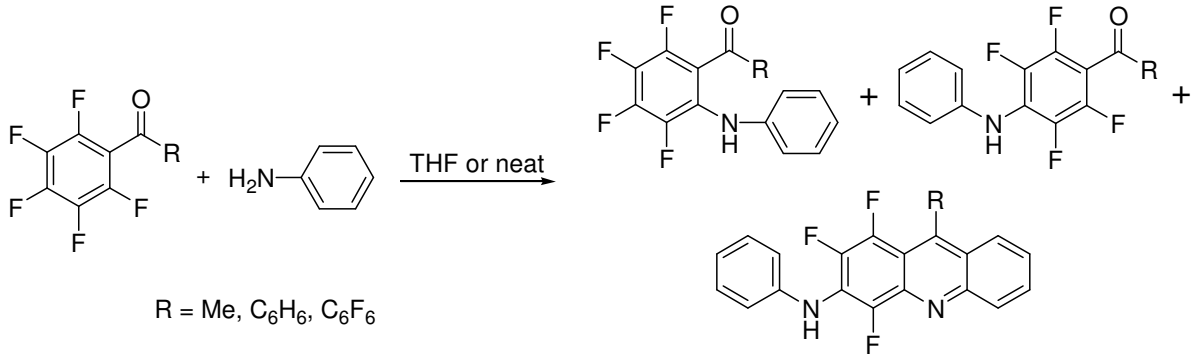


Scheme 1. First synthesis of 1,2,3,4-tetrafluoro-acridine.

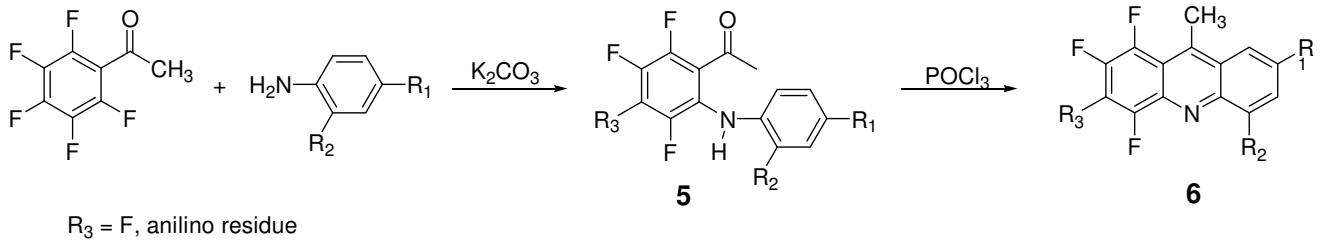
A wide and detailed study about the synthesis of polyfluoro-acridines was presented in the 1970's by Russian researchers. They reported on the synthesis of trifluoro-anilino-acridines, which was obtained by treatment of pentafluorophenyl-ketones with aniline (Scheme 2).[8]

This represents the first example of a one-pot synthesis of polyfluoro-acridines. However this method is not of general application since only the 5-Me, 5-C_6H_5 and 5-C_6F_5 substituted-tetrafluoro-acridines are directly accessible by this route. In general the 5-substituted-tetrafluoro-acridines can be prepared *via* electrocyclic reaction of 2-anilino-tetrafluoro-ketones in hot H_2SO_4 by a two step protocol which involves the reaction of the pentafluoro-acetophenone with aniline (eventually in presence of a base) to give, by nucleophilic substitution of fluorine, a mixture of *ortho* and *para* anilino-tetrafluorophenyl-acetophenone **5**

(Scheme 3). The *ortho*-substituted derivative by treatment with $POCl_3$ or H_2SO_4 undergoes the electrocyclic ring closure reaction to the desired polyfluoro-acridine **6**.[9]



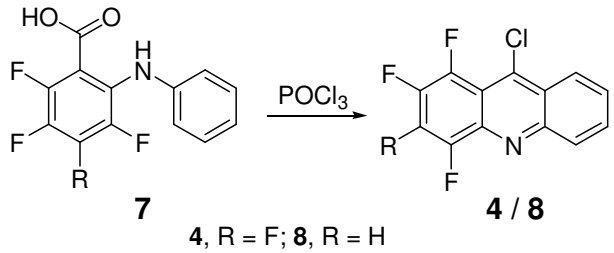
Scheme 2. Synthesis of 1,3,4-trifluoro-acridine from pentafluorophenyl-ketones and aniline.



Scheme 3. Synthesis of 1,2,3,4-tetrafluoro-5-methyl-acridines.

This protocol displays some useful features: 1) it is a multi-step synthesis, so that the reaction can be carried out under controlled conditions, permitting the introduction of substituents in the position 5. 2) It is compatible with the presence of electron-donating groups on the aniline both on the *ortho*- (R_2 = CH_3, OCH_3; R_1=H) and *para*-position (R_1 = CH_3, OCH_3, Br, $N(CH_3)_2$; R_2=H). However, when an EWG group (-NO_2 for instance) is present on the starting aniline, the reaction does not proceed beyond the *ortho*-substituted tetrafluoro-acetophenone intermediate.

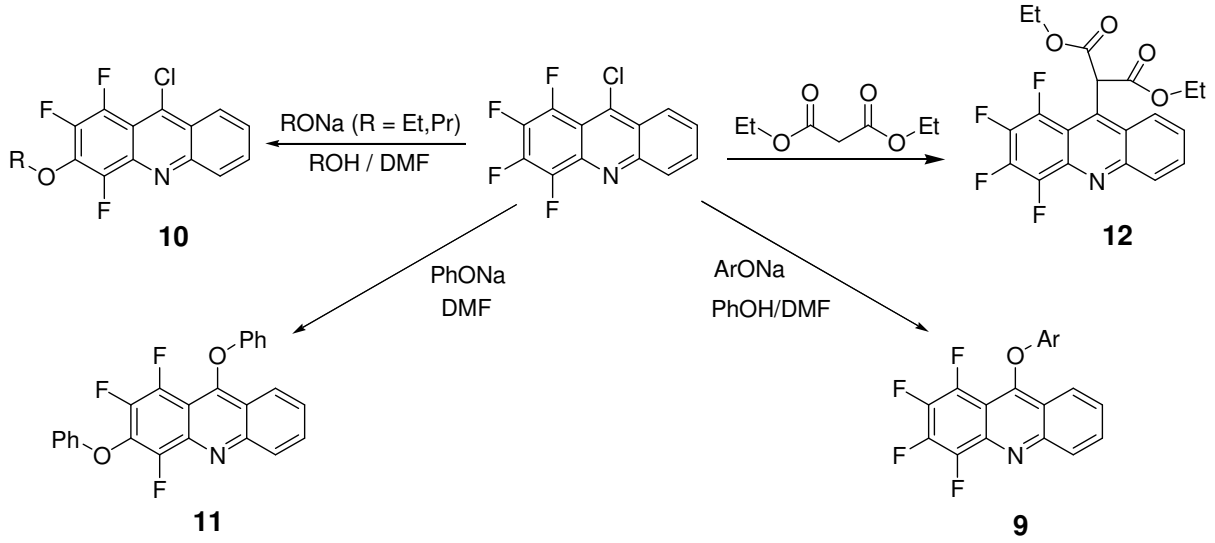
Other interesting derivatives prepared by a similar protocol are trifluoro- and tetrafluoro-5-chloro-acridines **8**, obtained by treatment of 2-anilino-polyfluoro-benzoic acids 7 with $POCl_3$ (Scheme 4).[10]



Scheme 4. Synthesis of polyfluoro-5-choro-acridines.

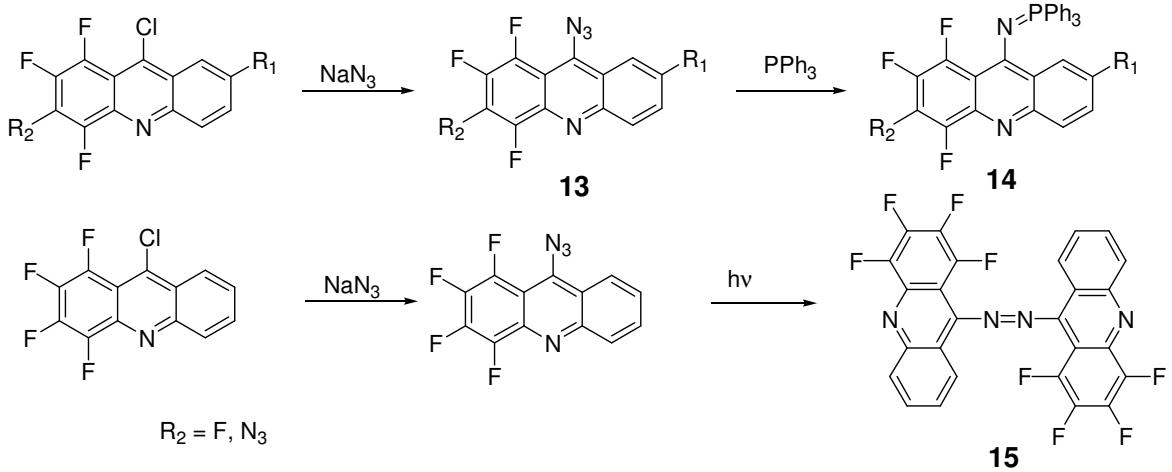
Polyfluoro-5-chloro-acridines represent a versatile intermediate for the preparation of other new acridines by nucleophilic aromatic substitution with amines,[10] alcohols[11] or other nucleophiles. By modifying the experimental conditions it is possible to substitute selectively the chlorine in 5 or the fluorine atom in 2 or both of them (Scheme 5). Indeed, treatment of 1,2,3,4-tetrafluoro-5-chloro-acridine with PhOH

or ArONa (Ar = *p*-$NO_2C_6H_4$, C_6F_5) in DMF afforded tetrafluoro-5-aryloxy-acridines **9**, while the reaction with RONa (R = Et, Pr) in ROH and DMF gave products **10** resulting from substitution of 2-F. When PhONa is used as nucleophile, products **11** resulting from the substitution of both 5-Cl and 2-F were obtained. Finally, the reaction of 5-chloro-tetrafluoro-acridine with the conjugated base of diethyl-malonate or malono-nitrile gave 2-(1,2,3,4-tetrafluoro-5-acridinyl)-diethyl-malonates **12**.[12] From these results we can conclude that the substitution of the fluorine atom in position 2 requires drastic conditions or the presence of hard nucleophiles, while by using soft nucleophiles the substitution goes preferentially on soft atoms (chlorine in this case). The treatment of 5-methyl-tetrafluoro-acridine with nitrogen nucleophiles (NH_3, $MeNH_2$, Me_2NH) gave the corresponding 2-amino-1,3,4-trifluoro-5-methyl-acridine derivatives.[13]



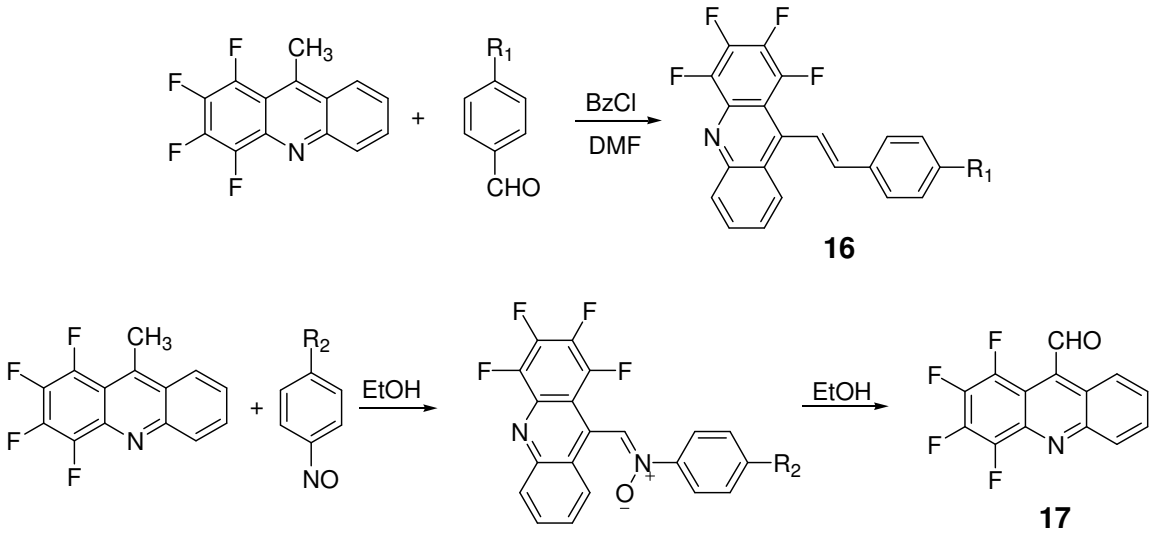
Scheme 5. Nucleophilic substitution of fluorine on 1,2,3,4-tetrafluoro-5-chloro-acridine.

Staudinger reaction of tetrafluoro-5-azido-acridine **13** (prepared by reacting 1,2,3,4-tetrafluoro-5-chloro-acridine with NaN_3)[14] with Ph_3P gave in moderate yield the corresponding imino-phosphoranes **14** from which 5-amino-acridines can be obtained by hydrolysis. Furthermore, photochemical decomposition of the azido-group to nitrene affords the corresponding 5,5'-azo-bis-tetrafluoro-acridine **15** in good yield (Scheme 6).[14]



Scheme 6. Synthesis and reactions of 5-azido-acridines.

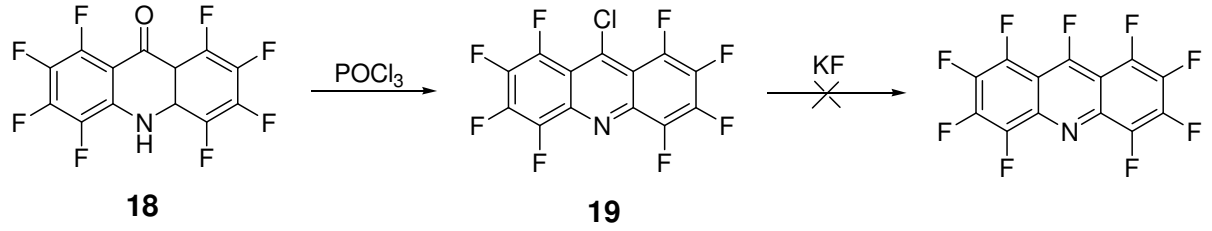
The reactivity of the methyl group in the 1,2,3,4-tetrafluoro-5-methyl-acridine has been also tested in some condensation reactions (Scheme 7). The corresponding styryl derivatives **16** have been synthesized by Knoevenagel condensation with benzaldehydes[12] (in presence of benzoyl chloride as drying agent). In addition the methyl group can be oxidized to the formyl one by reaction with nitroso-aromatic compounds (4-RC_6H_4NO, R = H, Me_2N, OH). The corresponding nitrones are intermediates of this reaction which were not isolated, but directly hydrolyzed to the 5-acridine-carboxaldehyde **17** (Scheme 7).[15]



R_1 = Ph, C_6F_5, 2-FC_6H_4, *p*-$C_6H_4NO_2$, *p*-$NMe_2C_6H_4$; R_2 = H, Me_2N, OH

Scheme 7. Nitrosation of methyl-acridine and hydrolysis of the nitrone.

1,2,3,4,6,7,8,9-Octafluoro-5-chloro-acridine **19** is accessible from the reaction of octafluoro-acridone **18** with $POCl_3$,[16] and this latter can be prepared by cyclization of 2-amino-nonafluoro-benzophenone in DMF. Attempts to prepare the completely fluorinated acridine by chloro-fluoro exchange with KF in sulpholane (a procedure used for the synthesis of decafluoro-anthracene) failed, so, at the moment, no procedures are described to access this derivative (Scheme 8).



Scheme 8. Synthesis of octafluoro-5-chloro-acridine. Perfluoro-acridine is not known.

1.2. One-pot synthesis of 1,2,3,4-tetrafluoro-acridines

A new way to synthesize tetrafluoro-acridines was reported in the 1990's.[17,18] During a study on Schiff bases of the type C_6F_5CH=NHAr (Ar= *p*-MeO-C_6H_4-), a new fluorescent product was isolated when this base was refluxed in butylacetate in presence of *p*-anisidine. On the basis of mass spectral data, elemental analyses and NMR, to this new product was assigned the structure of 7,8,9,10-tetrafluoro-2-methoxy-phenanthridine. Only X-ray diffraction analysis performed on a single crystal revealed its real

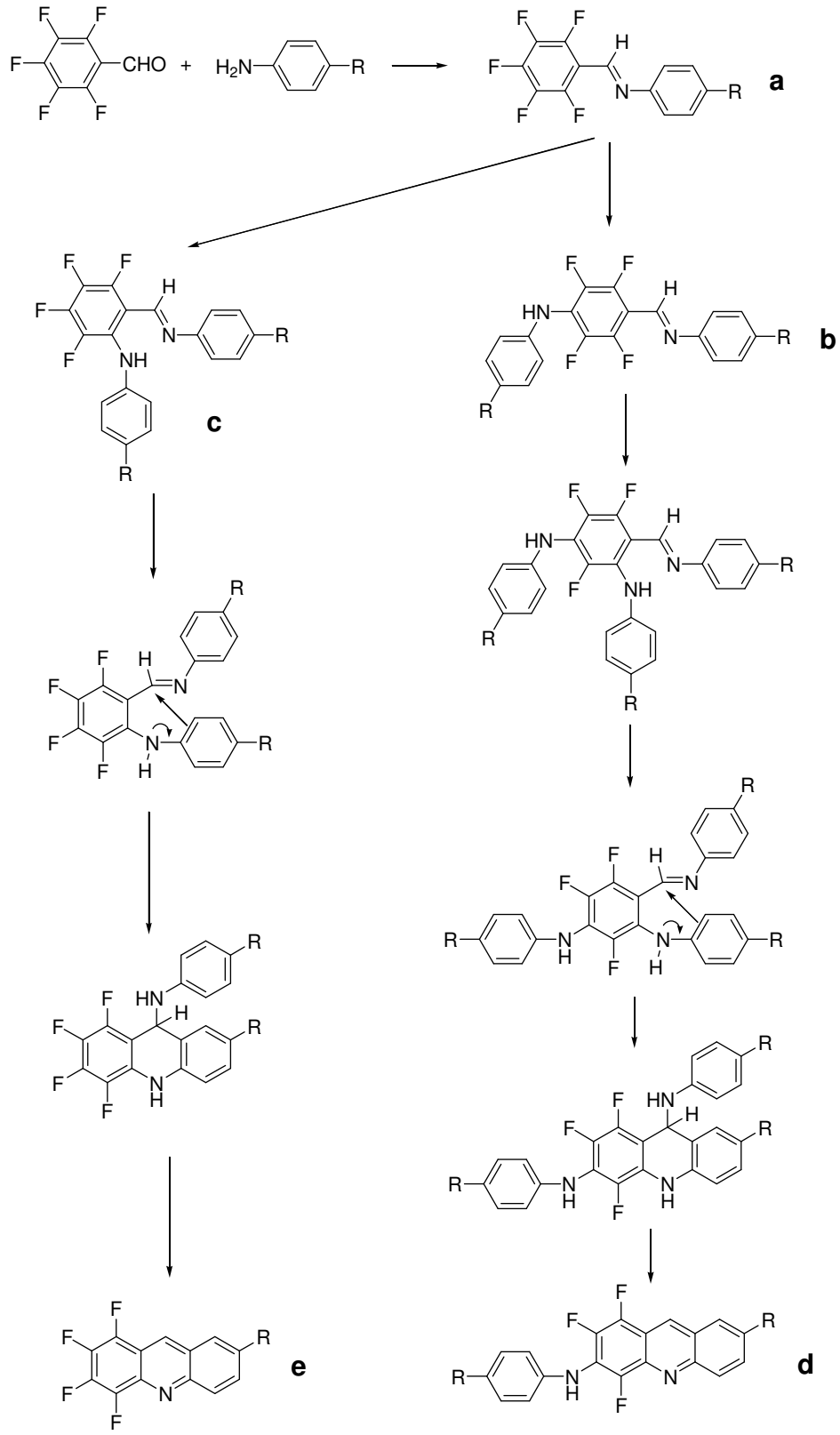
nature: 1,2,3,4-tetrafluoro-7-methoxy-acridine. Later, the same authors prepared a series of 7-substituted tetrafluoro-acridines starting from *para*-substituted anilines, by heating the preformed Schiff base (*E*-isomers according to X-ray diffraction analysis)[19] with the corresponding aniline (1:1 molar ratio) or by heating a mixture of pentafluoro-benzaldehyde and anilines (1:2 molar ratio) in boiling inert solvents such as toluene (b.p. 110 °C) or 1,2-dichloro-benzene (b.p. 179 °C). They also analyzed in deep details all by-products present in the crude reaction mixture and found polyfluorinated Schiff bases (pentafluoro- and 4-anilino-tetrafluoro derivatives, **a**, **b** and **c** in Scheme 9) and polyfluoro-acridines (tetrafluoro- and 2-anilino-trifluoro-acridine, **d** and **e** in Scheme 9). Appreciable amounts of the *ortho*-substituted Schiff base **c** were formed and isolated when R = Cl, Br. While pentafluoro-benzaldehyde and anilines readily react to form the corresponding Schiff bases, the subsequent ring closure reaction to acridine nucleus required prolonged (up to 70 hours) reflux in high boiling point solvents. The ratios between **b** and **c** and between **d** and **e** strongly depend on the boiling point of the solvent used to carry out the reaction and on the nucleophilic character of the aniline.

The rationalization of the experimental data allowed the authors to propose a reaction mechanism accounting for the observed products (Scheme 9). The first step of the reaction is the condensation of one molecule of pentafluoro-benzaldehyde with one molecule of aniline, producing the Schiff base **a**. When a molecule of aniline substitutes the fluorine atom in the *para* position, compound **b** is obtained, while when the same substitution occurs on the *ortho* position the product quickly evolves to compound **e**, with elimination of one molecule of aniline. When a second substitution by a molecule of aniline occurs on compound **b**, the same mechanism produces **d**. The substitution of a fluorine atom is a thermally activated reaction and for this reason a prolonged reflux in high boiling solvents is required for the synthesis of compounds **b** and **c**. The main features of this reaction and some useful observations are:

- 1,2,3,4-tetrafluoro-acridines are formed by nucleophilic attack of one molecule of aniline on the Schiff base, followed by an intramolecular nucleophilic ring closure reaction leading to the elimination of one molecule of aniline and HF. HF reacts with aniline producing the corresponding hydrofluoride salt, which tends to sublimate out of the reaction mixture and to collect in the reflux condenser as white solid.
- At least 2 equivalents of aniline are necessary for each equivalent of pentafluoro-benzaldehyde. If the Schiff base is heated under reflux the formation of tetrafluoro-acridine is not observed. The two-step procedure (synthesis and isolation of Schiff base followed by the synthesis of tetrafluoro-acridine) and the one-pot method (heating under reflux of pentafluoro-benzaldehyde with an excess of aniline) gave similar yields.
- The insertion of a molecule of aniline leading to products **b** and **d** occurs on the Schiff base; indeed, when heating a preformed tetrafluoro-acridine with aniline, the formation of trifluoro-anilino-acridine was not observed.
- When the reaction is carried out in dichlorobenzene, products **b** and **d** are predominant. The formation of trifluoro-anilino-acridines is observed only when using electron-rich anilines, such as *p*-toluidine (R = CH_3) or *p*-anisidine (R = OCH_3). In fact, by using electron-poor anilines (R = Cl, Br) tetrafluoro-acridines are predominant over trifluoro-anilino-acridines.

More recently,[20] we further explored the mechanism of formation; we confirmed that the fluorine nucleophilic substitution at the tetrafluoro-acridine level by a molecule of aniline is not possible and we found that the presence of anilinium salts is, to some extent, responsible for the formation of the intermediate

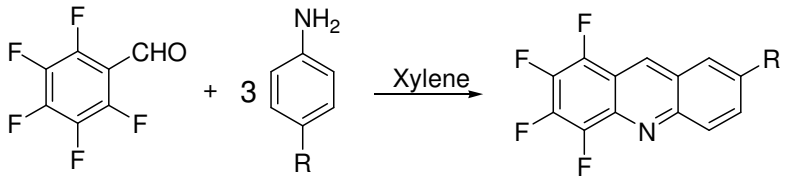
b. The anilinium salt behaves as source of H^+ in nitrogen protonation of imine **a** and consequently makes this intermediate more prone to *para*-substitution (Scheme 9).



Scheme 9. Synthesis of 1,2,3,4-tetrafluoro-acridines from pentafluoro-benzaldehyde and *para*-substituted anilines.

1.3. Synthesis of new 1,2,3,4-tetrafluoro-acridines

The flexibility and feasibility of the synthesis presented in the previous paragraph, together with the availability of a large number of different anilines, open the possibility of preparing a large pool of these molecules. Simply by modifying the starting aniline, it is possible to introduce different substituents on the tetrafluoro-acridine nucleus, allowing to finely tune the electronic properties (and therefore the optical and electrochemical properties) of these substrates. Although the synthesis of tetrafluoro-acridines has already been studied, the fundamental properties of tetrafluoro-acridines remained largely unexplored. The flexible synthesis presented above, allowing to prepare new compounds, to investigate their properties and finally to apply these substrates in materials science aroused our interest for this class of compounds.[21] First, we have repeated some of the synthesis of tetrafluoro-acridine in refluxing toluene, as described in the literature, obtaining similar results. However, the increase of the aniline amount to 3 equivalents together with the use of refluxing xylene as the reaction medium, allowed us to improve the yields. By using these new experimental conditions we prepared not only some of the acridines already synthesized, but also new terms, such as tetrafluoro-acridines bearing in position 7 a phenyl, a phenoxy, a dimethyl-amino, a phenyl-amino, a carbazolyl, a thiomethyl group and the pinacolic ester of boronic acid (Scheme 10). Boronic and bromo substituted acridines are useful intermediates for cross coupling reactions and open the possibility of a wider structural diversity. Some of these possibilities are presented later on.



R = H, Ph, tolyl, OMe, OPh, NMe_2, NHPh, SCH_3, carbazyl, and boronic ester

Scheme 10. One-pot synthesis of tetrafluoro-acridines with optimized conditions.

The nucleophilic character of the amino group of aniline is crucial for the substitution of the *ortho* fluorine atom at the imine level. Indeed, when using an electron-rich aniline (R = OCH_3, $N(CH_3)_2$) the ring closure to acridine occurs in fair to good yields (70–80%), whereas with electron-poor anilines such as 3,5-bis(trifluoro)-methyl- or 2,4-difluoro-aniline, the reaction stops at the stage of Schiff base without formation of the corresponding tetrafluoro-acridine, even when the reaction was performed using the aniline as solvent and heating to 200 °C. Steric effects are also of critical importance: when using electron-rich and bulky anilines such as *p*-carbazolyl or *p*-diphenyl-amino group, the reaction does not proceed beyond the imine level. In the case of *p*-carbazolyl-aniline, after heating the reaction mixture without solvent at 200 °C for several hours, we were able to isolate the corresponding tetrafluoro-acridine in moderate yield (26%). On the other hand, in the case of *p*-(biphenyl-amino)-aniline, even when using these forcing conditions, we were not able to observe the formation of the tetrafluoro-acridine. The results obtained in this preliminary part are fully consistent with the mechanism proposed by Banks *et al.*; the "bottlenecks" in this reaction are the nucleophilic displacement of the fluorine atom in the *ortho* position on the pentafluoro-phenyl moiety and the following intramolecular, nucleophilic, ring-closure reaction. Both these reactions are promoted by the presence of electron-donating groups (such as $N(CH_3)_2$) on the aniline ring and by heating the reagents at

high temperatures; indeed, using xylene (mixture of isomers, b.p 138–140 °C) instead of toluene (b.p. 110 °C), we observed a sharp increase of the yields. The use of solvents with boiling points higher than xylene should be avoided, because they could enhance the formation of trifluoro-2-anilino-acridines. The choice of xylene was proved to be a good compromise between higher yields in tetrafluoro-acridine and the absence or a limited formation of trifluoro-anilino-acridines. We must highlight that, under these new reaction conditions, we were not able to obtain 1,2,3,4-tetrafluoro-acridine from pentafluoro-phenyl-ketones. The reaction of decafluoro-benzophenone or octafluoro-acetophenone with anilines (*p*-anisidine or (N,N)-phenylen-diamine) were unsuccessful, affording the product of substitution of one fluorine atom (we obtained both 2- and 4-anilino-pentafluoro-phenyl-ketones). The only way to produce 5-substituted-tetrafluoro-acridines seems to be the cyclization (in presence of $POCl_3$ of H_2SO_4) of a 2-anilino-tetrafluoro-ketone.

As already observed,[18] the presence of a substituent in the *ortho* position of the aniline can hinder the ring closure reaction of tetrafluoro-acridine. We observed a similar behavior when we reacted pentafluoro-benzaldehyde with some *ortho*-substituted anilines: when a rather small substituent is present in position 2 (such as OCH_3), the overall yield of the synthesis is halved, but when a bulky substituent (Br or SCH_3) is present on the aniline ring, the ring closure reaction is totally hindered (See Table 1). We highlight that in the case of 2,4-difluoro-aniline probably this steric effect is absent (vdW radius of Fluorine: 1.47 Å) and the lack of reactivity can be attributed reasonably to the poor nucleophilic character of the amino group.

Table 1. Tetrafluoro-acridines synthesized from *o*-substituted anilines.

R	vdW radius[a] (Å)	Time (h)	Yield (%)
Br	1.85	71	0[b]
SCH_3	1.80 (S)	60	0[c]
OCH_3	1.52 (O)	86	45

[a]Values from different sources may differ. Those quoted here are taken from A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441. [b]A small amount of a fluorescent product was detected in the crude reaction mixture by Thin Layer Chromatography (TLC), but we were not able to isolate it. [c]Even when using forcing conditions (*i.e.* heating without solvent up to the b.p. of the amine) we were not able to detect the desired product.

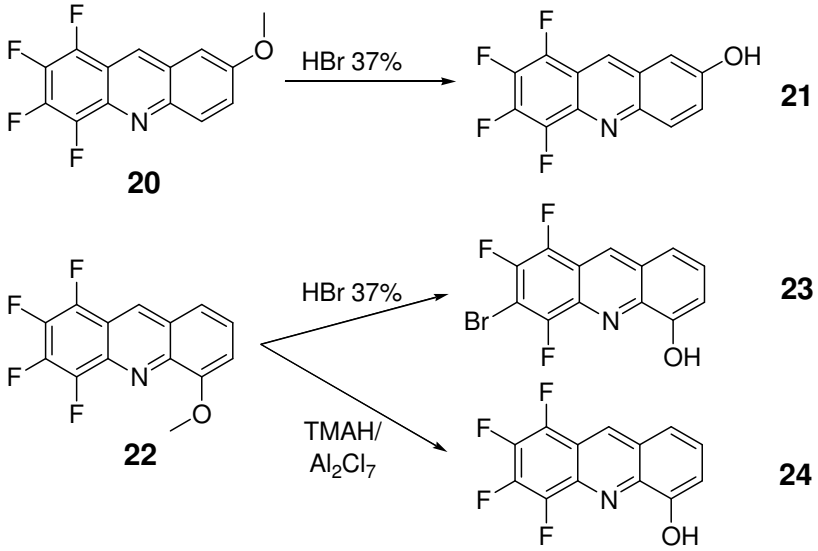
1.4. Synthesis of polyfluoro-hydroxy-acridines

1-Hydroxy-acridines, prepared for the first time by Matsumura in 1927, were so far synthesized by different ways involving, in almost all cases, the preparation of alkyloxy-acridones, their reduction to acridines and the hydrolytic cleavage of the ether function. 1-Hydroxy-acridine has been initially studied for its pharmacological properties[22] and, more recently, has been extensively studied and employed in analytical chemistry, exploiting the fluorescence properties of its complexes for the detection of metal cations by spectrofluorimetry. In materials science the fluorescence properties of its complexes with divalent cations have also found applications as the emitting component in developing new Organic Light Emitting Devices (OLEDs).[23–25] From this point of view 1,2,3,4-tetrafluoro-9-hydroxy-acridine should be an interesting substrate, since the fluorination can modify both optical and electrochemical properties of acridine nucleus.

1,2,3,4-Tetrafluoro-5-methyl-9-hydroxy-acridine has been already prepared by hydrolysis of the corresponding 1,2,3,4-tetrafluoro-5-methyl-9-methoxy-acridine but we were not able to find any report concerning its use as chelating agent.[26]

The synthesis of tetrafluoro-acridines previously described fails when 2-hydroxy-aniline is employed, thus the corresponding 1,2,3,4-tetrafluoro-9-hydroxy-acridine is not accessible by this route. Indeed, with this amine the reaction does not stop at imine level and the substitution of the *ortho* fluorine atoms occurs, leading to benzoxazepine derivatives.[27] Moreover, in this reaction the imine is in equilibrium with the hemi-aminal form of the aldehyde function or the substitution of more fluorine atoms can occur, as already reported in the literature.[28–30] The alternative synthesis of 7- and 9-hydroxy-1,2,3,4-tetrafluoro-acridines, based on the hydrolysis of the ether function in the corresponding methoxy-tetrafluoro-acridine derivatives was undertaken.[31] The methyl-ether cleavage of both 7-methoxy- and 9-methoxy-1,2,3,4-tetrafluoro-acridines **20** and **22** (Scheme11) has been performed with 47% HBr in water, following the classical aromatic ethers hydrolysis. The hydrolysis requires prolonged refluxing in 47% HBr water and proceeds on the corresponding acridinium hydrobromide salt. From the 1,2,3,4-tetrafluoro-7-methoxy-acridine we prepared the corresponding 1,2,3,4-tetrafluoro-7-hydroxy-acridine **21**, while from 1,2,3,4-tetrafluoro-9-methoxy-acridine an hydroxy acridine derivative was recovered in good yield. On the basis of spectroscopic (^{19}F NMR) and mass analyses, this latter resulted to be a trifluoro-bromo-hydroxy-acridine. The structure of 2-bromo-1,3,4-trifluoro-9-hydroxy-acridine **23** has been assigned by single crystal X-ray diffraction analysis. The incorporation of a bromine atom was unexpected and occurred with high regioselectivity *via* fluorine atom nucleophilic substitution by the bromine anion present in the hydrolytic reaction medium. Fluorine substitution has been already observed on similar substrates but with harder nucleophiles; we highlight that also in this case the substitution occurred on the same position. Since the nucleophilic attacks on 2 and 3 positions are sterically equivalent, the reasons of this high regioselectivity can be addressed to differences in the electrophilic character between carbon atoms 2 and 3 at the acridinium salt level.

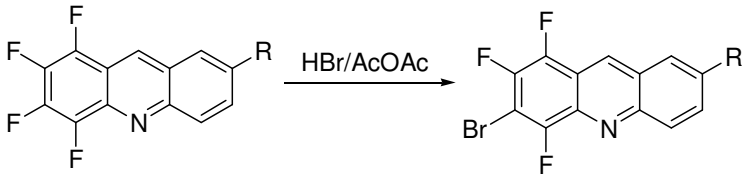
Looking for milder hydrolysis conditions avoiding the presence of nucleophilic species, we have tried the ionic liquid trimethyl-ammonium-heptachloro-dialuminate (TMAH-Al_2Cl_7), recently proposed as highly efficient ether cleavage reagent for a wide range of methoxy aromatic and heteroaromatic derivatives under very mild conditions.[32] The use of this reagent effectively affords the expected 1,2,3,4-tetrafluoro-9-hydroxy-acridine **24** in excellent yield (Scheme 11). Both tetrafluoro- and bromo-trifluoro-hydroxy-acridines have been used as ligands for metal cations.[31]



Scheme 11. Synthesis of polyfluoro-hydroxy-acridines.

1.5. Nucleophilic substitutions on 1,2,3,4-tetrafluoro-acridines

The unexpected reactivity of tetrafluoro-acridine towards a soft nucleophiles, such as bromide, suggested us a further analysis on the reactivity of tetrafluoro-acridines towards HBr. The introduction of bromine atom into the fluorinated moiety of tetrafluoro-acridine, is not easy when using the previously described one-pot synthesis since the corresponding bromo-tetrafluoro-benzaldehydes are not commercially available and their synthesis difficult to perform. In addition, the interest for these bromo-acridines arises essentially from their synthetic potential in metal-mediated cross-coupling reactions. After many trials, the best experimental condition has been individuated by performing the reaction using HBr 47% water solution in acetic anhydride as solvent at room temperature. Under these conditions, some tetrafluoro-acridines have been transformed into the corresponding 1,3,4-trifluoro-2-bromo-acridines **25** in good to excellent yields (Scheme 12).



25

R = H, OMe, NMe_2

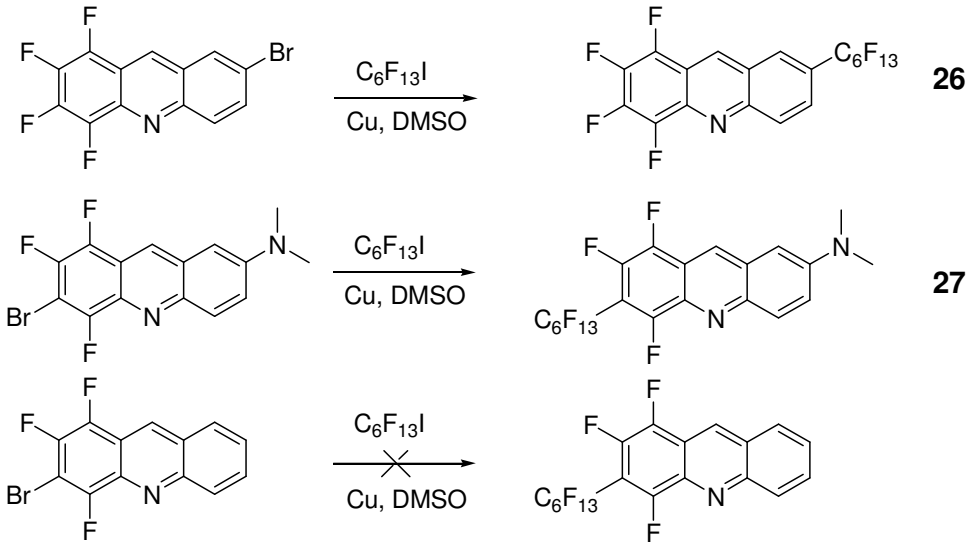
Scheme 12. Synthesis of 1,3,4-trifluoro-2-bromo-acridines.
When R = OMe the hydrolysis of methyl ether occurs at the same time.

The reaction proceeds on the corresponding acridinium hydrobromide salt and, probably, under this condition (HBr/Ac_2O) the bromine anion shows a higher nucleophilic character than in water. When R = $N(CH_3)_2$, the reaction is very fast; this is probably due to the fact that both annular and dimethylamino nitrogen atoms are protonated in the HBr/Ac_2O solution and the acridine nucleus is more prone to nucleophilic substitution.

1.6. Introduction of electron-poor, fluorinated substituents on 1,2,3,4-tetrafluoro-acridines

The introduction of EWGs on tetrafluoro-acridines represents an interesting modification of these nuclei for their application as n-type semiconductors and electron-transporters. As already explained, the direct introduction of EWGs is not possible, because of the lack of reactivity of the corresponding anilines. Thus, the only way to introduce an EWG is to functionalize a preformed tetrafluoro-acridine. Among the various substituents we decided to investigate the introduction of perfluorinated alkyl substituents, since the insertion of perfluoro-alkyl chains has important effects on the properties and on the performances of organic semiconductors.[33] We decided to insert the perfluoro-alkyl chain by a coupling reaction of bromo-polyfluoro-acridines and 1-iodo-perfluoro-hexane or 1-iodo-perfluoro-decane in the presence of copper bronze (Scheme 13).

Although in previous reports aryl iodides were preferred in the coupling reactions,[34-36] our reactions worked equally well with the readily available brominated derivatives. After activation of the suspension of Cu bronze in DMSO, the organometallic reagent is formed by adding 1-iodo-perfluoro-alkane to the suspension, then the bromo-acridine is added and the mixture is heated for several hours at T<135 °C.



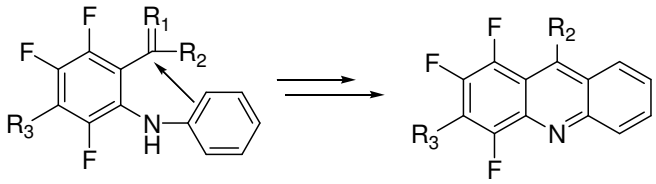
Scheme 13. Synthesis of trifluoro- and tetrafluoro-acridines bearing perfluoro-alkyl chains.

Coupling reaction of 1,2,3,4-tetrafluoro-7-bromo-acridine with iodo-perfluoro-alkane proceeded as expected, with good yield; besides the desired product **26**, we isolated the unreacted reagent and the 1,2,3,4-tetrafluoro-acridine, produced by the reduction of 1,2,3,4-tetrafluoro-7-bromo-acridine is the presence of copper bronze. On the other side, when 1,3,4-tetrafluoro-2-bromo-acridine was reacted under the same conditions, the reaction was much less straightforward and we were not able to obtain the desired product. Also when reacting compound 1,3,4-trifluoro-2-bromo-7-(N,N)dimethylamino-acridine a complex mixture of fluorescent products was obtained, but in this case the desired product **27** was predominant and isolated in 26% yield. The different outcomes in the two reactions can be explained assuming that in the case of 1,3,4-trifluoro-2-bromo-acridine the carbon-bromine bond is very reactive. Furthermore, after perfluoroalkyl chain insertion, the reactivity of fluorine atoms on acridine could be enhanced by the presence of a strong EWG and they could react with the copper bronze or the organo-metallic reagent present in solution. On the contrary, when an electron donor such as a dimethyl-amino moiety is present, the same phenomenon is less pronounced. The strategic feature of these reactions is based on the possibility of comparing the effect of the perfluoro-alkyl chain at different positions on the structural and electronic properties. Indeed the insertion of a perfluoro-alkyl can induce the appearance of liquid-crystalline phases, or introduce peculiar and interesting phenomenon such as superficial segregation of fluorinated chain when these compounds are dispersed in a polymeric matrix. This latter possibility could be used not only for modifying the surface properties of the matrix but also to induce a non-centrosymmetric arrangement of these molecules at the surface of the polymeric matrix.

The effects of these substituents on the optical and electrochemical properties of these compounds will be discussed in the next section.

1.7. Final remarks

In all the synthetic procedures of tetrafluoro-acridines developed after the 1970's, we can recognize a common root: formation of the acridine nucleus is due to an electrocyclic reaction occurring on a 2-anilino-polyfluorophenyl-ketone (Scheme 14).



Scheme 14. Electrocyclic reaction leading to polyfluoro-acridine.

In Scheme 14, R_1 can be oxygen atom (ketone or benzoic acid) or a nitrogen atom (of a Schiff base). The nature of this substituent has a deep impact on the ring closure reaction: while for a Schiff base only the thermal activation is required to achieve the cyclization, with ketones or benzoic acids the presence of $POCl_3$ or H_2SO_4 is necessary. Nevertheless, the behaviour of this group in both cases is the same: R_1 is the leaving group during the ring closure reaction. The Schiff base has the advantage to give the acridine without the use of a secondary reagent (such as $POCl_3$ or H_2SO_4), but one could insert a leaving group other than phenyl-imino to obtain the same effect. In all the syntheses of polyfluoro-acridines presented so far, the nature of R_2 is closely related to R_1. Indeed Schiff bases are readily available only with pentafluoro-benzaldehyde, while Schiff bases of pentafluoro-phenyl-ketones are not accessible from the reaction with anilines, because this reaction produces only the corresponding tetrafluoro-anilino-phenyl-ketones through aromatic nucleophilic substitution of a fluorine atom. Finally, R_3 can be a fluorine atom or an aniline residue, but this has only minor effects on the ring closure reactions.

2. Electronic properties: photophysics and electrochemistry

The introduction of four fluorine atoms on acridine lowers the molecular symmetry of acridine (from C_{2v} to C_s); however, since electronic states of acridine, up to 6 ev (about 200 nm), have already the lowest symmetry, a further splitting of the electronic levels due to symmetry lowering is not possible, while as a principle it could be possible for vibrational states.[37] The main effect due to introduction of fluorine atoms is on the electronic density of the aromatic ring. Fluorine atoms have two different effects when directly bonded to aromatic rings: they have donor mesomeric effect, similarly to other halogen atoms, and they also have an inductive electron-withdrawing effect, because of their large electronegativity. As already observed for other fluorinated organic semiconductors such as α,ω-diperfluorohexyl-oligothiophenes and perfluoro-oligothiophenes, the fluorination can increase the optical gap and then can cause a blue shift of the absorption bands; in the case of perfluoro-pentacene the opposite effect is observed.[38]

Nevertheless, there is only a small difference between the absorption spectra of acridine and 1,2,3,4-tetrafluoro-acridine (Figure 1). For the low energy band system, we observe a small red shift of the main peak but the introduction of four fluorine atoms does not change significantly the main features of the absorption spectrum.[17]

The situation for 1,2,3,4-tetrafluoro-acridines bearing a substituent is slightly more complicated. Tetrafluoro-acridine is a moderate EWG and when an electron donor group (EDG) is present, electronic transfer configurations can have an important role in the description of the electronic states of the molecule. The interaction between EWG and EDG causes a red shift of the absorption bands, different transitions showing red-shifts of different magnitudes due to different interactions of the electronic states of the parent compound with those of the substituent. When these effects are more pronounced, the interaction between

EWG and EDG, mediated by the conjugated system, leads to the appearance of a new transition related to the electron transfer between the two aforementioned groups. Usually, this new charge-transfer transition is observed at lower energies than those of the unperturbed conjugated molecule. Absorption spectra of 1,2,3,4-tetrafluoro-7-(N,N)dimethylamino-acridine is a typical example of this effect: the lower absorption band of this molecule is strongly red shifted and a similar effect is present also in the phenyl-amino derivative.[20]

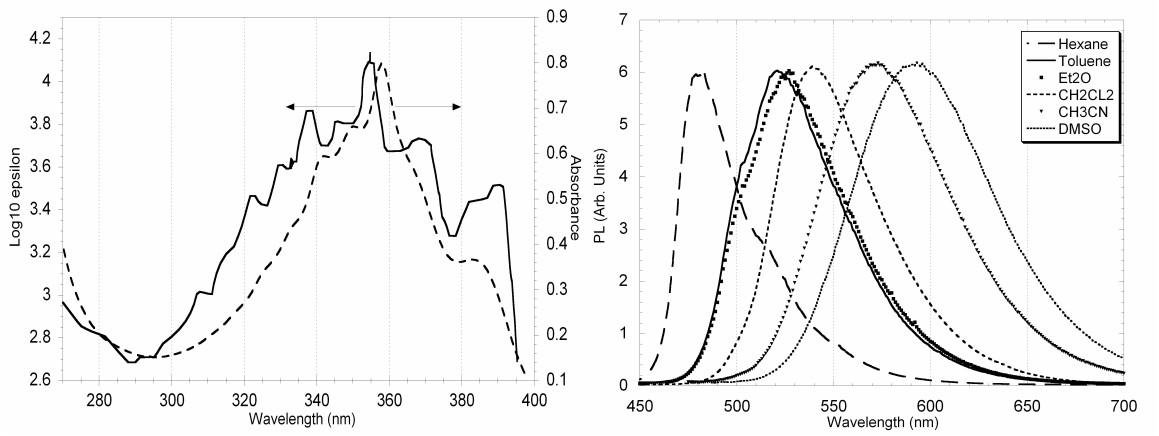


Figure 1. On the left, comparison between the absorption spectra of acridine (bold line) and 1,2,3,4-tetrafluoro-acridine (dashed line). On the right, fluorescence spectra of 1,2,3,4-tetrafluoro-7-(N,N)dimethylamino-acridine in solvents of increasing polarity.

The effect of fluorination is more evident in the fluorescence spectra. Non-fluorinated acridine is fluorescent only in polar solvents, while is almost non fluorescent in apolar solvent.[33] This effect is ascribed to the presence of a dark state associated to the $\pi^* \rightarrow n$ transition, due to the lone pair of the annular nitrogen; this transition is symmetry forbidden both in absorption and in emission for the isolated molecule. In apolar solvents this dark state is the lowest excited state, thus fluorescence has a very low intensity, but in polar solvents this state is shifted to higher energy and thus fluorescence becomes allowed.[33] On the other side, tetrafluoro-acridines are always fluorescent, even in apolar solvents: this behavior can be explained assuming the hypothesis that the presence of fluorine atoms shifts to higher energies the $\pi^* \rightarrow n$ transition. The chemical counterpart of this effect is the lower basicity of tetrafluoro-acridine with respect to non fluorinated acridine. Tetrafluoro-acridines bearing an EDG (NMe_2, NHPh) show a large Stokes shift, *i.e.* the fluorescence maximum is very far from the absorption band with the lowest energy. We can interpret this result formulating the following hypothesis: in the excited state the aforementioned molecules have a large dipole moment, which can be stabilized in moderate to polar solvents. We measured for molecule 1,2,3,4-tetrafluoro-7-(N,N)dimethylamino-acridine fluorescence spectra in solvents of different polarities and we found that in apolar solvents the Stokes shift is very small, while in polar solvent this effect is very strong (Figure 1). The same phenomenon is not present with moderate EDGs (like OCH_3).

The presence of EDG and EWG on the same conjugated molecule can increase the second order hyperpolarizability, opening the possibility of applications in non-linear optics for second harmonic generation (SHG). The most part of molecules proposed for SHG belongs to the class of push-pull molecules, *i.e.* a conjugated π-electron system terminated by an EDG and an EWG (Figure 2).

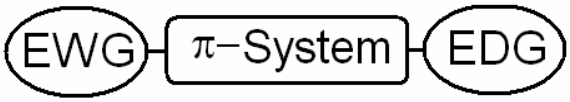


Figure 2. General structure of a push-pull molecule.

Preliminary measurements of SHG show that tetrafluoro-acridine is a promising EWG for push-pull molecules, featured by μβ values comparable with those of pentafluoro-stilbenes.[39]

The replacement of hydrogen atoms with more electronegative fluorine atoms has, as expected, an appreciable influence on oxidation and reduction potential of the acridine nucleus. Indeed, as reported by Russian researchers for 1,2,3,4-tetrafluoro-5-methyl-substituted-acridines,[40] 1,2,3,4-tetrafluoro-5-methyl-acridine shows a increased reduction potential increased of 0.2 V with respect to acridine; in the case of 1,2,3,4-tetrafluoro-acridine both the reduction potential (less negative by 0.3 V) and the oxidation potential are increased (See Table 2). In all cases a prepeak has been observed, ascribed to the formation of a complex between acridine and oxygen, already observed in previous reports for similar substrates.[40] This prepeak strongly decreases by bubbling argon through the solution for 20-30 minutes before performing Cyclic Voltammetry (CV). As expected, the oxidation and reduction potentials of acridines reflect the nature and the position of the substituents. The introduction of a perfluoro alkyl chain shifts to higher potentials the oxidation peak and to less negative potential the reduction peak; this effect was observed in compounds **26** and **27** (See Table 2); compound **26** could be a n-type semiconductor, thanks to its favorable reduction potential and to the positive effect of perfluoro-alkyl chain, shielding the effects of moisture, as observed for other compounds bearing perfluoroalkyl substituents.[1–3]

Table 2. Cyclic voltammetry results for some 1,2,3,4-tetrafluoro-acridine[a].

Compound	E_p^{Red}	E_p^{Ox}	Energy gap [b]
1,2,3,4-tetrafluoro-acridine (**3**)	–1.34	1.91	3.25
1,2,3,4-tetrafluoro-7-methoxy-acridine (**20**)	–1.45	1.61	3.06
1,2,3,4-tetrafluoro-7-hydroxy-acridine (**21**)	–1.20	1.60	2.80
1,2,3,4-tetrafluoro-9-methoxy-acridine (**22**)	–1.65	1.51	3.16
1,3,4-trifluoro-2-bromo-9-hydroxy-acridine (**23**)	–1.25	1.91	3.16
1,2,3,4-tetrafluoro-9-hydroxy-acridine (**24**)	–1.35	2.00	3.35
1,2,3,4-tetrafluoro-7-perfluorohexyl-acridine (**26**)	–1.12	2.15	3.27
1,3,4-trifluoro-2-perfluorohexyl-7-(N,N)dimethylamino-acridine (**27**)	–1.43	1.01	2.44
1,2,3,4-tetrafluoro-7-phenyl-acridine (**28**)	–1.45	1.78	3.23
1,2,3,4-tetrafluoro-7-(N,N)-dimethylamino-acridine (**29**)	–1.50	0.83	2.33

[a]Oxidation (E_p^{Ox}) and reduction (E_p^{Red}) potentials in V vs. SCE from the oxidation and reduction peak of the CVs. On Platinum, scan rate: 0.1 Vs^{-1} in AN + TBAP (0.1M). [b]Electrochemical HOMO-LUMO-gap estimated by the voltammetric measurements (peak-to-peak difference for one-electron processes) (eV).

The shift of the oxidation and reduction potentials after introduction of a perfluoro-alkyl chain in the case of compound **27** is smaller; in fact, while the observed shifts of the oxidation potentials of **26** and **27** are

comparable, the shift of the reduction potential of compound **27** is about one third than that observed in compound **26**. This effect is probably due to the presence of a strong electro-releasing group such as dimethyl-amino, which partially lowers the effect of the perfluoroalkyl chain. The observed trend agrees with the results found with α,ω-disubstituted oligothiophenes; the shifts observed in their reduction potentials spans from 0.55 V for terthiophene (from –2.14 V for α,ω-dihexyl-terthiophene to –1.59 V for α,ω-diperfluorohexyl-terthiophene) to 0.36 V for hexathiophene (from –1.78 V for α,ω-dihexyl-hexathiophene to –1.42 V for α,ω-diperfluorohexyl-hexathiophene).[30] In this latter case, the introduction of a perfluoroalkyl chain has a larger impact because oligothiophenes are electron-rich systems. In the case of tetrafluoro-acridines a sort of saturation effect is observed; tetrafluoro-acridines are already electron-poor systems and the introduction of a further EWG has a minor impact, if compared with the case of oligothiophenes.

The reversibility of electrochemical processes has been evaluated, by defining the i_p *ratio* as the ratio of the area of the reverse oxidation peak to the area of the reduction peak. A high value of i_p *ratio* indicate a good reversibility; and it was observed when the tetrafluoro-acridine nucleus bears EDGs (*i.e.* NMe_2, compound **29**, i_p *ratio* = 0.70 or OMe, compound **20**, i_p *ratio* = 0.65) while 1,2,3,4-tetrafluoro-acridine (compound **3**) or tetrafluoro-acridines bearing EWGs present i_p *ratios* close to zero[21]. A good reversibility is obtained when the acridine nucleus is attached to groups able to delocalize the net charge introduced by reduction or oxidation; nevertheless a low i_p *ratio* is not directly related to the efficiency of a solid state device, in fact, preliminary results suggest that a good Thin Film Transistor can be obtained with compound **26**, which show a very low value of i_p *ratio*.[20]

Concluding, the introduction of four fluorine atoms does not affect significantly the molecular gap, except when also an electron-releasing group is present; in this case the fluorinated moiety is the EWG in a dipolar, "push-pull" molecule. On the other side, it was observed that tetrafluoro-acridines are fluorescent in almost all solvents, then n→π* transition is no more the lowest excited state in non polar solvents as in the case of acridine. Moreover, introduction of four fluorine atoms and later of a perfluoroalkyl chain shifts the electronic states, as observed from the electrochemical analyses. These effects open the possibility to apply tetrafluoro-acridines as fluorescent systems and the interesting results obtained from electrochemical analyses suggest their use as electron-poor, n-type semiconductors in the solid state. The application of a tetrafluoro-acridine as fluorescent dopant of an electrically active polymer is presented in the next paragraph.

3. OLEDs based on tetrafluoro-acridines

In the research field of Organic LEDs (OLEDs), the availability of a big pool of organic molecules, showing a fluorescence covering a wide spectrum of visible region and with high quantum yield, is extremely important for optimizing the efficiency or tuning the emitted wavelength of the electroluminescent device (Figure 3).

Chemical doping of organic semiconductors is a useful strategy to improve performance of OLEDs. The controlled introduction of a dopant can improve the efficiency of the device and minimize the effects of accidental doping due to chemical impurities or structural defects. Following this approach it is possible to separate the function of light or electrical excitation harvesting (host) and light emission (luminescent guest)[41] and these two functions can be optimized separately through the choice of materials with suitable optical and electrical properties. The advantages of obtaining emission from a doped electrically active

matrix after a process of energy transfer are due to the fact that the usually low concentration of the dopant prevents concentration quenching due to the migration of the excitation toward non-radiative traps.[42]

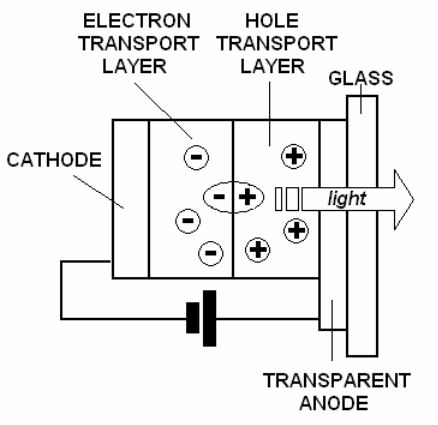


Figure 3. Schematic representation of the working principle of an OLED: charge injection from the electrodes introduces both positive and negative charges. The union of a charges of different sign generates excitons, which decay producing visible light.

Moreover, excitation transfer usually results in a large Stokes shift between absorption and emission spectrum, thus eliminating unwanted re-absorption losses of the emitted light. Better stability and material processability have also been achieved in the polymeric blends with respect to those of the pure chromophore. We have chosen poly-vinyl-carbazole (PVK) as electrically active, luminescent, host polymer; PVK is a semiconducting polymer which was studied since the 1960's because of its photoconducting properties and it is already used in electrophotography applications. These properties stimulated a great interest in its electrical and optical properties, which have been thoroughly studied. Nowadays it is still used as a photoconductor when blended with an electron acceptor (trinitro-fluorenone, for instance) and it is studied for photorefractive application when blended with electro-acceptors and chromophores active in non-linear optics.

Among all the synthesized tetrafluoro-acridines, compound **29** has been selected because of its good spectral overlap with the PVK emission band and the high fluorescence quantum yields in solution (η = 46%). These are essential conditions to observe an efficient energy transfer from PVK to the acceptor. We carried out a photophysical study of the sensitized green emission of the PVK doped with 1,2,3,4-tetrafluoro-7-(N,N)dimethylamino-acridine, followed by the preparation of a OLED prototype.[43,44]

The efficiency of the energy transfer is evaluated by the Foerster's radius (R_0, equation 1):

$$R_0^6 = k\int \frac{F_D(\nu)\varepsilon_A(\nu)}{\nu^4} d\nu \qquad \text{eq. 1}$$

where F_D is the normalized emission spectrum of the donor (PVK) and ε_A is the molar extinction coefficient of the acceptor (compound **29**). A high value of R_0 indicates that the transfer is efficient; typical values range from few Å to 100 Å.

Theoretical and experimental data gave a high value for the Foerster's radius (about 40 Å), indicating that an efficient energy transfer can take place between PVK and the tetrafluoro-acridine. In fact PVK is

strongly quenched for dopant concentration above 0.6%/w with appearance of the emission spectrum of the dopant. The position of this emission is very similar to that observed in CH_2Cl_2 solution, thus indicating that the dispersion of the chromophore in the blend is at the molecular level. Several devices have been prepared and characterized using the blend PVK/tetrafluoro-acridine as light-emitter. Electroluminescence spectrum is very similar to PL spectrum of the blend of PVK with 1% of tetrafluoro-acridine for position and shape; the device produces green light (CIE[1931] coordinates are 0.26;0.61). The energy transfer in the PL spectrum is almost complete for a concentration of acceptor in PVK of 1% and also in the EL spectrum the contribution of PVK is absent; indeed, while (electro-) excitation can occur also directly on the acceptor (*i.e.* tetrafluoro-acridine), in the case of PL, the photo-excitation occurs mainly on the donor (*i.e.* PVK) and then the resonant energy transfer to the acceptor takes place. The maximum efficiency of electroluminescence is about 0.1% and it is quite stable.

4. Vinyl-tetrafluoro-acridine: a monomer for semiconducting polymer?

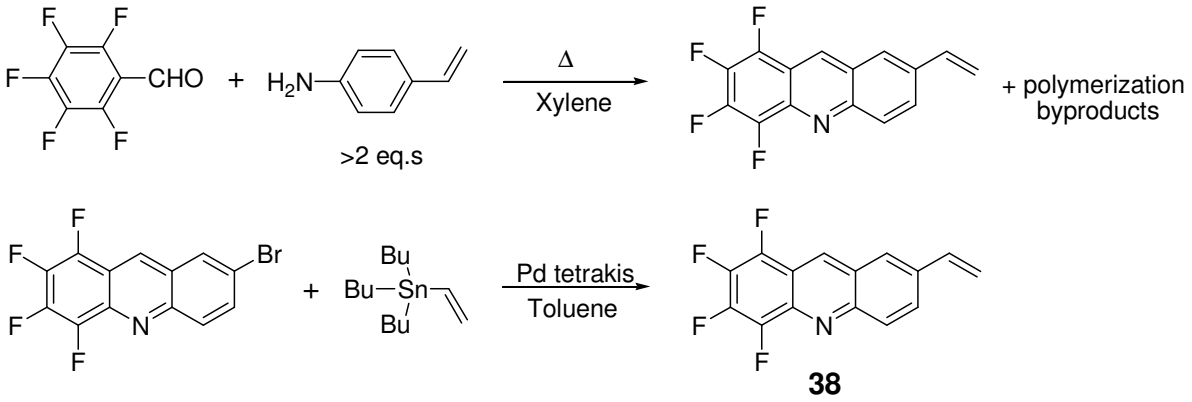
Vinyl polymers with large pendant conjugated systems, like (PVK) or poly(vinyl-anthracene), are a peculiar class of semiconducting polymers, where the main chain is saturated and a hopping process is responsible for the charge transport. Their first application was as photo-conducting systems; more recently they have found new applications as electroluminescent polymers and in holographic systems. Of course, the nature of the conjugated systems linked to the saturated main chain determines structure and properties of the polymer. To the best of our knowledge, all the polymers belonging to this class prepared so far are p-type semiconductors, *i.e.* charge carriers are holes (positive carriers). The transport of the electric charges is thermally activated and occurs by hopping. Poly-vinyl-naphthalene, poly-vinyl-quinoline and poly-vinyl-anthracene were prepared by polymerization of the corresponding vinyl-monomers and their properties are similar to those of PVK, the most studied and used polymer belonging to this class.

When acridine was introduced in such polymers instead of anthracene,[45,46] a worsening of photo-conducting properties was observed; this effect was partially attributed to the poor electron-donating character of acridine. Starting from these results, it is clear that introduction of fluorine atoms into the acridine moiety should definitively convert a vinyl-acridine polymer into an n-type semiconductor. A semiconducting vinyl polymer, bearing a tetrafluoro-acridine as substituent, could be a promising candidate to obtain n-type organic semiconductors and, moreover, due to the peculiar sensitivity to oxygen which leads to the formation of reversible complex with acridine, another potential application could be as a sensor for molecular oxygen.

Anyway, 1,2,3,4-tetrafluoro-7-vinyl-acridine (**38**) can be produced by a one-step synthesis instead of multi-step procedures. As already described, 1,2,3,4-tetrafluoro-acridines substituted in position 7 can be easily obtained by reacting pentafluoro-benzaldehyde with the correct *para*-substituted aniline in boiling xylene; tetrafluoro-acridines can be obtained with good yields only if an electron-donating groups is present on the parent aniline. From this point-of-view, such a synthetic approach is fully compatible with the presence on aniline of the moderate electron releasing vinyl group. Thus, following this procedure, 1,2,3,4-tetrafluoro-7-vinyl-acridine showed be accessible by reacting pentafluoro-benzaldehyde with 4-amino-styrene (Scheme 15). Unfortunately the stability of 4-amino-styrene is not compatible with the reaction conditions. As a matter of fact, while the Schiff base of pentafluoro-benzaldehyde with 4-amino-styrene and 4-amino styrene itself are sufficiently stable at room temperature, they polymerize quickly under heating in

refluxing xylene, prior to give the ring closure reaction leading to the tetrafluoro-acridine. Under these reaction conditions we were able to isolate only traces of the desired product from the insoluble matter produced at the end of the reaction. Only by adding to the reaction mixture a little amount of a radical inhibitor (hydroquinone, 5%w), we were able to improve the yield of the reaction (up to 10%). The reason of the failure of this approach comes from the high reactivity of the vinyl group under the reaction conditions, causing a spontaneous polymerization of the reagent (*p*-vinyl-aniline) and the other vinyl-derivatives present in the reaction mixture as soon as they are formed.

A very appealing alternative to this way, based on standard organic modifications of reactive groups, is represented by the organometallic approach. Following this approach, we can introduce the vinyl group into a pre-formed tetrafluoro-acridine by a cross coupling reaction, catalyzed by a transition metal. Starting from 1,2,3,4-tetrafluoro-7-bromo-acridine, following a Stille cross coupling protocol, tributyl-vinyl-stannane was introduced, with catalysis by $Pd(PPh_3)_4$ in refluxing toluene (Scheme 15). To avoid the spontaneous polymerization of the reagent (tributyl-vinyl-stannane) and of the product, a small amount of a radical inhibitor (hydroquinone) was added to the reaction mixture. After 4 hours the reaction goes to completeness and the desired product was obtained with a good yield (69%).

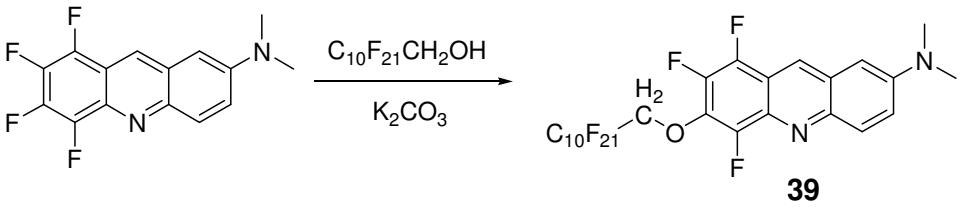


Scheme 15. Syntheses of 1,2,3,4-tetrafluoro-7-vinyl-acridine.

Explorative experiments were done to test the reactivity of 1,2,3,4-tetrafluoro-7-vinyl-acridine in polymerization reactions. Preliminary results show that the fluoro-acridine nucleus lowers significantly the reactivity of the vinyl moiety in radical polymerizations.

5. Modification of the surface of polyamide nanofibers doped with a fluorinated acridine

Perfluorinated alkyl chains show the tendency to spontaneously segregate at the surface when dispersed in a polymeric matrix.[47–49] This phenomenon can be applied to obtain a fluorinated surface; this route is an interesting alternative to conventional methods, such as plasma treatments. We tried to modify the wettability of nanofibres of Nylon 6 produced by electrospinning, doping them with a tetrafluoro-acridine.[50] We focused our attention on 1,2,3,4-tetrafluoro-7-(N,N)dimethylamino-acridine, due to its fluorescence properties, already exploited for the preparation of OLEDs. We decided to insert a fluorinated chain exploiting the reactivity of fluorine atoms towards nucleophilic reagents, by reacting 1,2,3,4-tetrafluoro-7-dimethylaminoacridine with a fluorinated alcohol (perfluorodecyl-methanol) in the presence of K_2CO_3 (Scheme 16).[51]



Scheme 16. Synthesis of the trifluoro-acridine used for doping Nylon 6 nanofibres.

As the tendency of perfluorinated molecules to segregate on the surface is well known, small amounts of acridine **39** were used. The contact angles of water onto the surface showed an increase, on increasing the concentration of acridine; with a load of 6%/w a contact angle of 123° was measured. This indicates that small amounts of acridine strongly decrease the wettability of the polymer. It is noteworthy that the contact angle at 6% of doping is higher than that typical of PTFE,[52] which is usually taken as reference material among not-wettable polymers. Surface segregation of perfluorinated alkyl chains is a thermally stimulated process, thus the possibility to increase the contact angle by thermal annealing has been investigated. Measurements of the contact angle were carried out on sample kept at the Tg of the polymer. After few minutes a sharp increase of the contact angle is observed, reaching the impressive value of 131° (sample with 4%w of acridine), without any loss of acridine for sublimation. This result is a clear evidence of superficial segregation of acridine in the polymer fibers induced by thermal annealing.

Modifications of the wettability of polyamide (and also of other polymers) may have many applications in textiles. Furthermore, the incorporation of the acridine described here, can conjugate the hydrophobic properties of fluorinated chains with the antibacterial properties of acridine, opening the way to new applications.

6. Conclusions and outlook

Tetrafluoro-acridines are an interesting class of heteroaromatic compounds, with many applications in materials science; electronic properties can be easily tuned by acting on the substituents, giving the opportunity to do molecular tailoring. The synthesis of polyfluoro-acridines has been explored in depth, highlighting possibilities and limits. Several derivatives of polyfluoro-acridines are already known, but the flexibility of this substrate allows to the preparation of many other compounds, with applications spanning from materials science to biology.

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THE HYPERVALENT IODINE MEDIATED INTRAMOLECULAR NITROGEN–HETEROATOM BOND FORMATION IN THE SYNTHESIS OF PYRAZOLE AND ISOTHIAZOLE TYPE HETEROCYCLES

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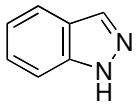
Abstract. *We describe here a selection of the most important procedures for the formation of nitrogen–heteroatom bonds leading to the formation of different systems such as indazoles (N–N) or isothiazoles (N–S), through a diverse array of synthetic approaches. We will also disclose our own strategy based on the use of the hypervalent iodine reagent PIFA, [phenyliodine(III)bis-(trifluoroacetate)], to promote the heterocyclization steps to these systems.*

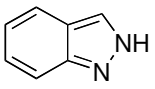
Contents

1. Introduction

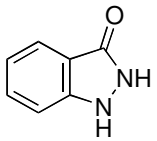
Although there is a plethora of tools available for carbon–carbon and carbon–heteroatom bond formation, the field of heteroatom–heteroatom bond formation remains comparatively less developed. In this review we intend to give an overall inspection of the methods available for N–N and N–S bond formation, as well as our most recent observations in this research area. Considering space limitations, we plan to limit the given information to those strategies developed for the preparation of indazoles, indazolones and benzisothiazoles. These general terms will be used for simplicity along this paper when referred to 1*H*- or 2*H*-indazoles, 1,2-dihydro-3*H*-indazol-3-ones, and benzo[*d*]isothiazol-3-ones, respectively.



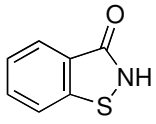
1*H*-indazole



2*H*-Indazole



1,2-Dihydro-3*H*-indazol-3-one



Benzo[*d*]isothiazol-3-one

Figure 1

In fact, this group of heterocycles is probably one of the most required targets to explore new nitrogen–heteroatom bond forming processes. Notwithstanding, in order to attain a general view, other synthetic approaches that employ reagents such as hydrazines (N–N) or hydroxylamines (N–O), in which the selected bond is already preformed, will be also partially considered for this literature survey.

1.1. Indazoles, indazolones and benzisothiazolones. Biological activity and synthetic approaches

Nature does not offer many examples of heterocyclic compounds structurally based on the indazole system. In fact, these examples are limited to *nigellicine*[1] and *nigellidine*[2] isolated from the seeds of *Nigela sativa* (Figure 2).

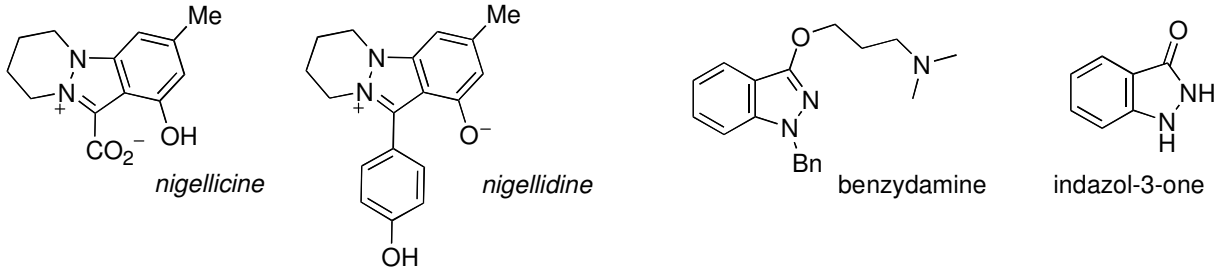
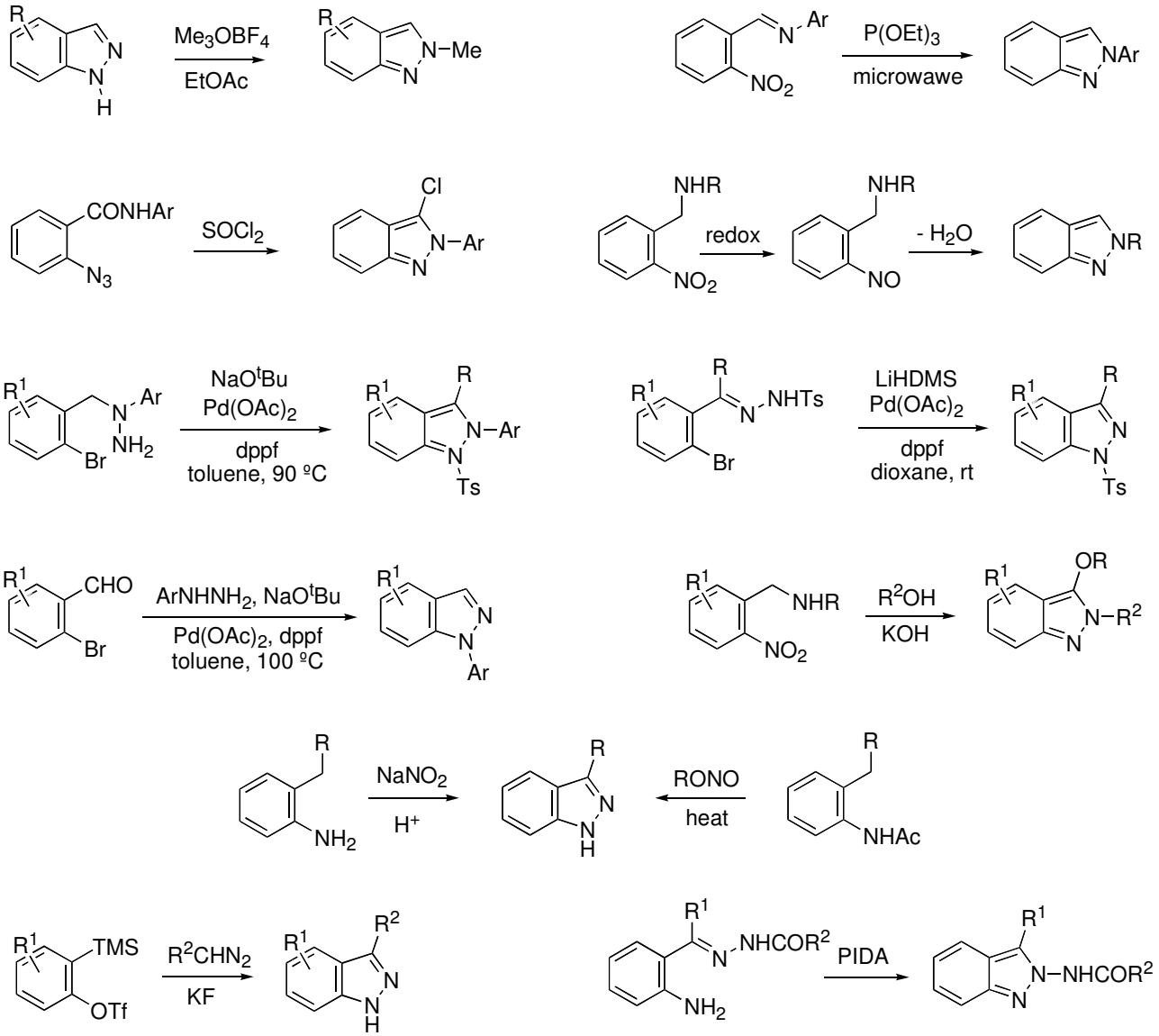


Figure 2

On the contrary, the indazole nucleus is a pharmaceutically important structure and constitutes the key skeleton in many drug substances with a broad range of pharmacological activities.[3] In fact, since benzydamine, the first non-steroidal anti-inflammatory drug (NSAID) bearing an indazole subunit, was commercialized in 1960,[4] many reports on the anti-inflammatory,[5] antitumor,[6] anti-HIV,[7] antidepressant,[8] antipyretic,[9] analgesic,[10] antihyperlipidemic[11] and contraceptive activities[12] of this kind of compounds, particularly of indazol-3-one derivatives, have appeared in the literature. Additionally, other simplified related structures, such as pyrazolones, have recently caught the attention of the medicinal community because of their bioactivity as inhibitors of tumor necrosis factor–α (TNF–α) production.[13]

Different approaches to the synthesis of substituted indazoles have been proposed.[14] Among them (Scheme 1), it can be outlined the reduction of secondary *ortho*-nitrobenzylamines with Sn, Zn or Fe in acidic medium;[15] the direct *N*-alkylation[16] and *N*-arylation[17] of indazole (although normally yielding mixtures of 1- and 2-substituted indazoles without selectivity);[18] the reaction of *ortho*-nitrobenzylidenamines with trivalent organophosphorous reagents as deoxygenating agents,[19] recently improved by a microwave enhanced synthesis of indazoles *via* nitrenes;[20] the palladium complex-catalysed reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines to afford *2H*-indazole derivatives;[21] the treatment of *ortho*-azidoamides under the conditions of Smalley *et al.* with thionyl chloride at reflux;[10a] the electrochemical cyclization of 2-nitrobenzylamines that affords 2-substituted indazoles through the generation of *ortho*-nitrosobenzylamines;[22] the palladium-catalyzed intramolecular amination reaction of *N*-aryl-*N*-(*ortho*-bromobenzyl)hydrazines[23] or hydrazones,[24] a method that applies to a wide range of substrates containing electron-donating and electron-withdrawing substituents; a one-pot synthesis from 2-bromobenzaldehydes and arylhydrazines,[25] sometimes in the presence of a catalytic amount of a palladium catalyst and a phosphorus chelating ligand along with NaO^tBu;[26] the basic treatment of *ortho*-nitrobenzylamines to yield 3-alkoxyindazoles;[27] the diazotization of the corresponding 2-alkyl anilines;[28] the

nitrosation of the *N*-acetyl derivatives of 2-alkyl anilines (Jacobson modification);[29] the rearrangement of azobenzenes that occurs in cases where the azo group is placed in the *ortho* position to carbonyl electrophiles;[30] the 1,3-dipolar cycloaddition of arynes with diazomethane derivatives;[31a] or, finally, the phenyliodine(III)diacetate (PIDA)-mediated synthesis from acylhydrazones.[31b]

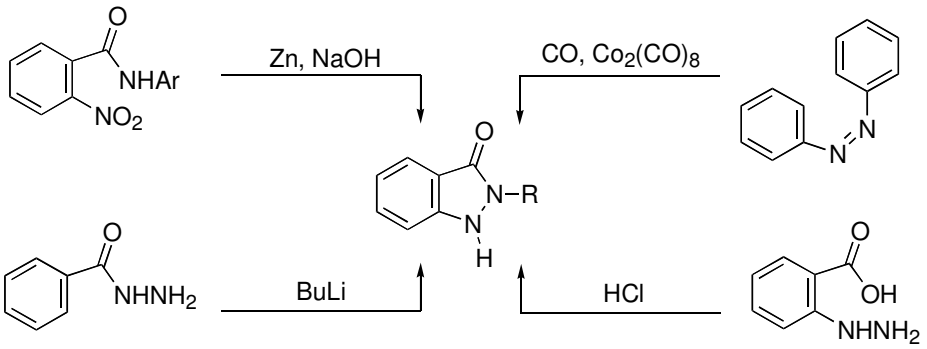


Scheme 1. Selected examples of indazole oriented strategies.

Compared to indazoles and despite the promising pharmacological properties shown by several of their members, indazolones have received less attention according to the specific literature. The high-pressure transition metal catalyzed carbonylation of azobenzenes,[32] the acid-promoted cyclization of *ortho*-arylhydrazinobenzoic acids,[33] the isomerization of 3-aryl-2-hydroxyindazoles, the base catalyzed cyclization of arylhydrazides[34] and the reductive cyclization of *ortho*-nitrobenzanilides with zinc and sodium hydroxide in aqueous methanol[35] can be cited among the most widely used protocols to access indazolone derivatives (Scheme 2).

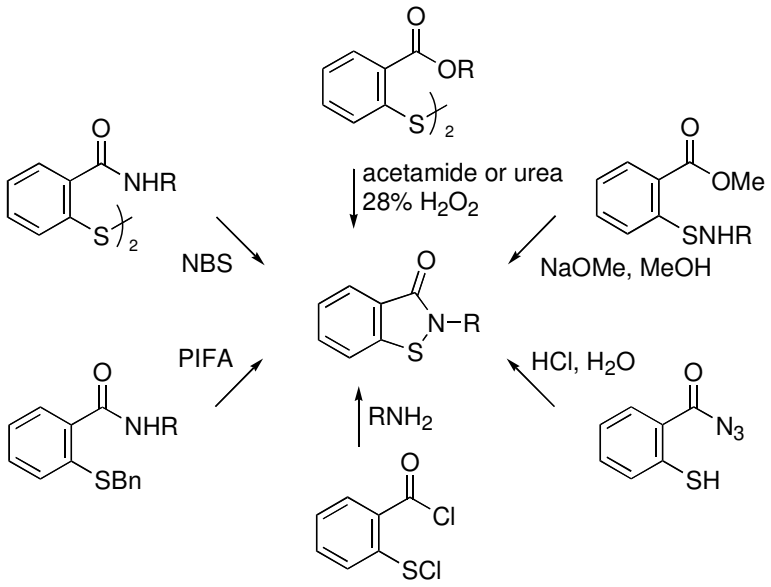
The inspection of this literature survey leads to conclude that many of the reported methods classically used for indazole synthesis lack of generality, they involve harsh reaction conditions and thus limiting their

usefulness in obtaining variously functionalized indazoles and require careful manipulation of toxic or sensitive reagents. Additionally, in many cases, the connection between N(1) and N(2) is preformed in the substrates as hydrazine, hydrazone or azide functionalities.



Scheme 2. Selected examples of indazolone oriented strategies.

Probably due to their well-recognized biomedical action[36] that includes effective antifungal, antibacterial and antipsychotic properties,[37] as well as anti–HIV activity for some of their members,[38] benzisothiazolone derivatives have been the targets for extended synthetic studies. Therefore, among the most established strategies for their preparation, it has to be mentioned the bromine or NBS[39] promoted cyclization of dithiobenzamides, the cyclization of dithiobenzoic acids or esters,[40] the intramolecular transamination of 2-sulfenamoylbenzoates,[41] the ring closure reaction on mercaptobenzoyl azides,[42] the cyclization of acyl chlorides promoted by amines[43] and the PIFA-mediated [phenyliodine(III)*bis*-(trifluoroacetate)] cyclization of 2-(benzylthio)benzamides,[44] as shown in Scheme 3.



Scheme 3. General approaches to the construction of benzisothiazoles.

2. Hypervalent iodine assisted heteroatom–heteroatom bond formation

2.1. Oxidative processes mediated by hypervalent iodine reagents

In the last decades, the chemistry of hypervalent iodine reagents has witnessed a profound progress in the field of synthetic organic chemistry. Their low toxicity, readily availability and easy handling have

allowed their application to a number of important transformations[45] and, besides, their environmentally friendly nature also suggests future applications in "green chemistry". Indeed, hypervalent iodine reagents are now extensively used in organic synthesis as a mild, safe and economical alternative to heavy metal reagents such as lead (IV), thallium (III) and mercury (II).[46] In particular, PIFA [phenyliodine(III)-*bis*(trifluoroacetate)], PIDA [phenyliodine(III)diacetate)] and HITB [hydroxy(tosyloxy)iodobenzene, Koser´s reagent] have found a wide application in the synthesis of heterocyclic compounds,[47] as three of the most active members of this family of compounds.

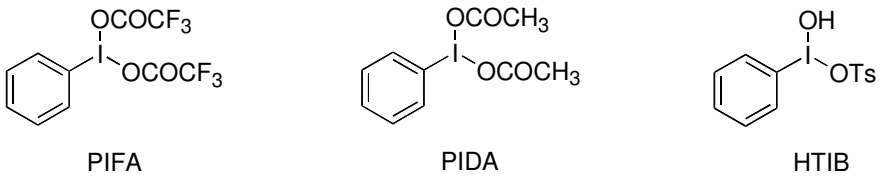
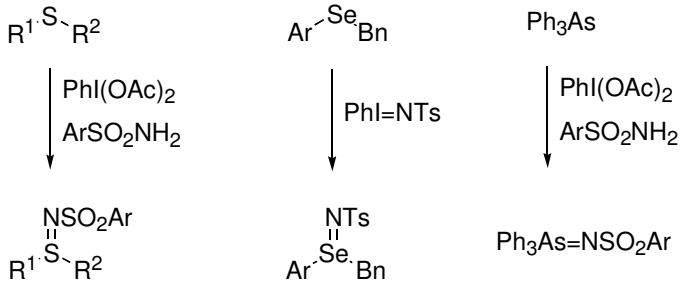


Figure 3. Structures of I(III) reagents commonly used in organic synthesis.

In addition, the use of this family of reagents for heteroatom–heteroatom bond construction is well documented in the context of classical oxidation chemistry and, for instance, the oxidation of anilines to azobenzenes, thiols to disulfides, and sulfides to sulfoxides are well known processes assisted by hypervalent iodine reagents.[48] Particularly, the use of sulfonyliminoiodanes, ArI=NSO$_2$R, has contributed enormously to the development of new strategies towards that end.[49] Thus, since the pioneering work by Evans[50] on the copper-catalyzed tosylaziridination of olefins using PhI=NTs, the use of such reagents has become an effective tool for the formation of N–S,[51] N–Se,[52] N–P[53] and N–As[54] bonds (Scheme 4).



Scheme 4. Selected reactions of sulfonyliminoiodanes with heteroatom-containing substrates.

2.2. The acylnitrenium approach

In addition to the above-mentioned procedures, a methodology based on the generation of heteroatom-centered intermediates and their subsequent intramolecular connection with heteroatom containing fragments of the substrate would represent an evident access to the preparation of the systems under study. In connection with this idea, nitrenium ions can be selected as good candidates to perform the designed synthetic strategy. These highly reactive intermediates continue to receive attention not only because of their suspected role in the carcinogenesis initiated by nitro and aminoaromatic compounds[55] but, particularly, because of their utility in organic synthesis.[56] However, synthetic applications of these electrophilic intermediates remain limited, except when such nitrenium ions are stabilized by the electron-donating effect of a proper neighboring group (aryl, alkoxy or nitrogen, *inter alia*).[57] In these cases, the so-stabilized *N*-acylnitrenium ions (**I**, **II**, **III**, Figure 4) exist for a long enough time to be useful as synthetic intermediates.

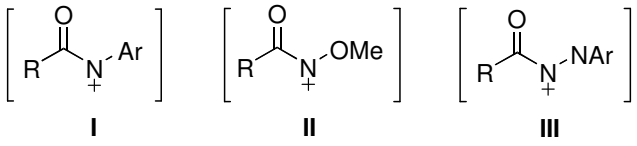
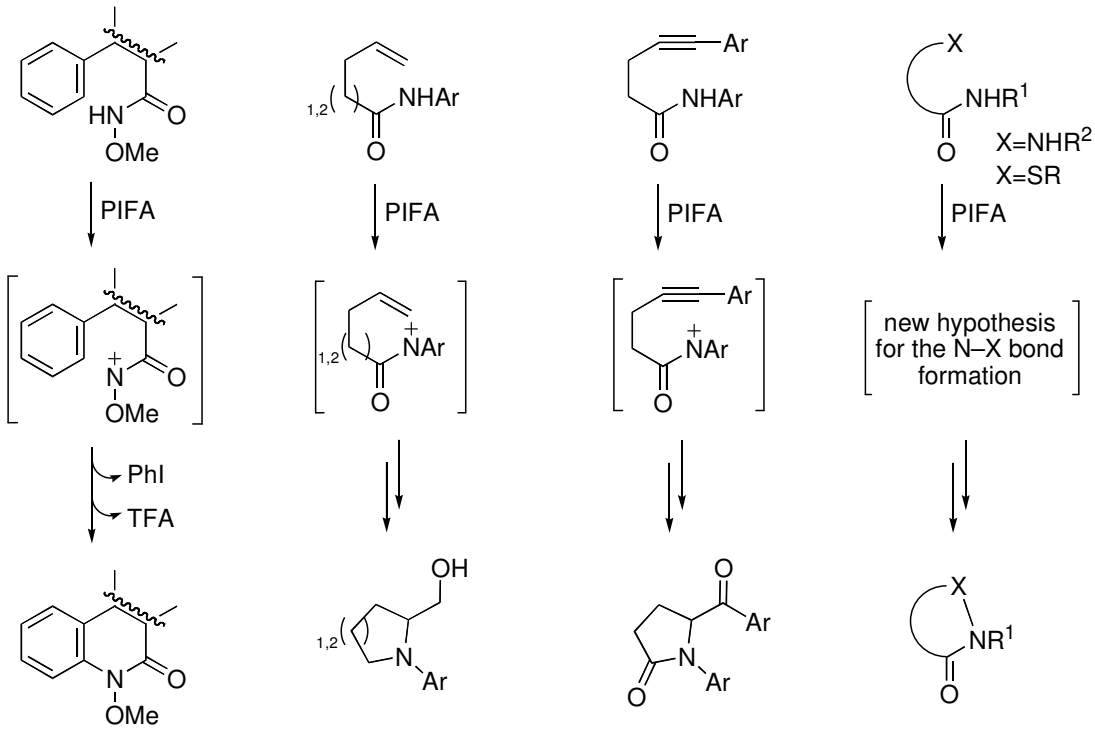


Figure 4. Some stabilized acylnitreniun ions.

Despite the fact that *N*-acylnitrenium ions can be generated by a variety of methods, for example, by the treatment of *N*-alkoxy-*N*-chloroamides with a variety of Lewis acids, such as silver[57a] or zinc salts,[58] the use of the hypervalent iodine reagent PIFA for this purpose overcomes the limitations associated with those protocols[59] and, therefore, its use has been widely applied to the synthesis of a number of different heterocyclic compounds.[60] Nevertheless, as far as we are aware, only the use of carbon nucleophiles as the nucleophilic counterparts of the reaction has been described. Particularly, we had previously designed (Scheme 5) the synthesis of different quinoline and benzodiazepine heterocycles based on the intramolecular trapping of I(III)-generated nitrenium intermediates by (hetero)arene rings in an electrophilic amidation reaction,[61] and by C–C double and triple bonds in a novel amidohydroxylation protocol rendering 2-hydroxymethylpyrrolidinones and piperidines, and 5-aroyl-substituted pyrrolidinones, respectively.[62]



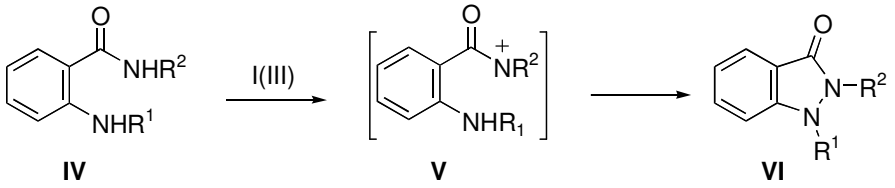
Scheme 5. Selected examples and new proposal, of the use of PIFA in the synthesis of some *N*-containing heterocycles.

Therefore, in our particular context, an effective intramolecular connection of these powerful electrophiles with heteroatom-centered nucleophiles would represent a general strategy for the construction of a number of heterocyclic systems through *N*–heteroatom bond forming processes.

2.3. Iodine (III) mediated synthesis of indazolones and pyrazolones

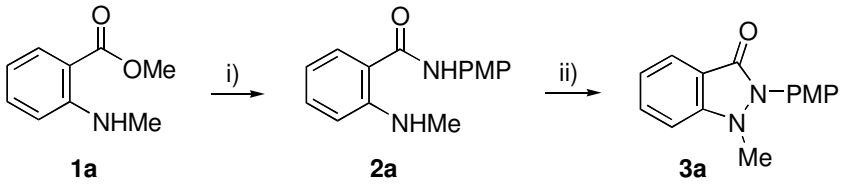
As mentioned in the introduction section, we were interested in designing a complementary route to the synthesis of pyrazole-type heterocycles that features the formation of a nitrogen–nitrogen bond as the

key step. Therefore, since the indazole system had been selected as our target to explore the N–N bond forming process promoted by PIFA, the nature of R^1 and R^2 substituents had to be determined (Scheme 6).



Scheme 6. Proposed strategy for the synthesis of indazolones of type **VI**.

On the basis of our previous experience, we selected the *para*-methoxyphenyl substituted benzamide **2a**, as a model system to optimize the experimental conditions for the proposed cyclization step. This substrate was easily prepared by treatment of the commercially available methyl *N*-methylanthranilate (**1a**) with $AlMe_3$ and *para*-anisidine in the conditions depicted below (Scheme 7).[63] Next, as shown in Table 1, we briefly examined the effect of different solvents, sources of hypervalent iodine, temperature and additives on the success of the oxidative cyclization step.



i) $AlMe_3$, *p*-anisidine, CH_2Cl_2, reflux (69%); ii) See Table 1.

Scheme 7. Synthesis of indazolone **3a**.

Table 1. Selected assays performed on amide **2a**.

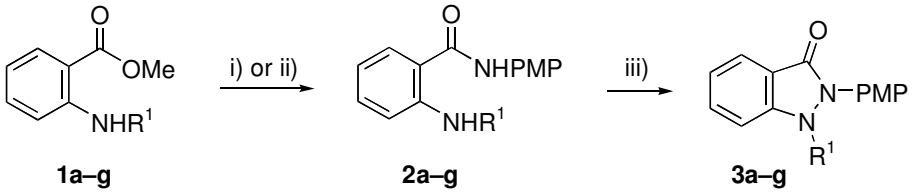
entry	Conditions	3a[a]
1	PIFA (0.05 M), CH_2Cl_2[b]	51%
2	PIDA (0.05 M), CH_2Cl_2[b]	21%
3	HTIB (0.05 M), CH_2Cl_2[b]	10%
4	PIFA (0.05 M), TFEA[b]	51%
5	PIFA (0.05 M), CH_3CN[b]	33%
6	PIFA (0.05 M), Toluene[b]	36%
7	PIFA (0.05 M), DMF[b]	15%
8	PIFA (0.05 M), CH_2Cl_2[c]	51%
9	PIFA (0.05 M), CH_2Cl_2, TFA[b]	54%
10	PIFA (0.01 M), CH_2Cl_2, TFA[b]	68%
11	PIFA (0.01 M), CH_2Cl_2, $BF_3{\cdot}OEt_2$[b]	7%

[a] Isolated yield after purification by flash chromatography.
[b] Reaction carried out at 0 ºC. [c] Reaction carried out at –78 ºC.

The results obtained from these experiments indicated that PIFA was the most efficient oxidant. Indeed, the use of other related I(III) reagents, such as PIDA (entry 2) and HTIB (entry 3), was also tested

but, unlike PIFA, they afforded the indazolone **3a** in very low yields. On the other hand, the nature of the solvent had a significant influence on the success of the reaction. Thus, whereas the employment of polar aprotic solvents such as CH_3CN (entry 5) or DMF (entry 7) afforded the desired product in low yields, the use of either CH_2Cl_2 (entries 1, 8–10) or trifluoroethanol (TFEA in entry 4) proved to be a better solution since the desired heterocycle **3a** was obtained in slightly higher yields. Since both solvents behaved similarly, the selection of CH_2Cl_2 over TFEA was made on the basis of economical costs. Furthermore, although yields did not improve at all when carrying out the reaction at low temperatures (entry 8), the use of two equivalents of TFA as an additive (entry 9) made the reaction take place much more cleanly, although the yields were not highly affected. In contrast, the use of other additives, such as the Lewis acid $BF_3{\cdot}OEt_2$ (entry 11), which had been extensively reported to increase the reactivity of this kind of reagents,[64] provided in this case only traces of the desired product. Interestingly, the use of more dilute solutions of PIFA (entry 10) turned out to be the key for the best conditions leading to indazolone **3a** in 68% yield. Therefore, these preliminary results suggest that *N*-acylnitrenium ions generated by PIFA, as we presumed before, can be also trapped intramolecularly by amine moieties, featuring consequently an interesting approach to the construction of new N–N linkages.

Having established an optimal protocol for the projected process, a more detailed examination of the electronic requirements of the structure of the substrates was performed. Thus, the behavior of a variety of substrates, which include different amine functionalities as well as different amide moieties, under the action of PIFA was examined. First of all, we analyzed the influence of the nature of the amine moiety on the efficiency of the cyclization step. Thus, a series of the required *para*-methoxyphenylbenzamide derivatives **2a–g** were effectively prepared starting from easily accessible or commercially available anthranilates **1a–g** either by treatment with $AlMe_3$ and *p*-anisidine or through basic hydrolysis followed by a known amidation protocol (Scheme 8).[65] As shown in Table 2, the proposed PIFA-mediated cyclization process proved to be suitable for substrates in which the amine functionality was substituted by either alkyl (entries 1–3) or aryl groups (entry 4). Once again, the positive effect of the presence of TFA as an additive was confirmed in all cases. On the other hand, neither aminobenzamide **2e** (entry 5) nor the ones substituted by an electron withdrawing group **2f–g** (entries 6–7) rendered the desired indazolones **3e–g**. Thus, it can be concluded that the scope of this PIFA promoted oxidative cyclization requires highly nucleophilic amines.



1a–g **2a–g** **3a–g**

i) $AlMe_3$, *p*-anisidine, CH_2Cl_2, reflux; ii) (a) $LiOH{\cdot}H_2O$, THF/H_2O, rt. (b) *p*-anisidine, Et_3N, EDC·HCl, HOBt, CH_2Cl_2, 0 ºC → rt; iii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 ºC.

Scheme 8. Synthesis of indazolone **3a–g**.

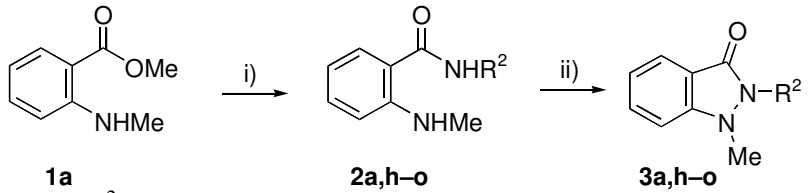
A different part of the research was designed to determine the scope of the cyclization process with respect to the amide functionality. Thus, a series of amides were successfully prepared in a single step by an $AlMe_3$ mediated aminolysis of methylanthranilate **1a** in the presence of different amines (Scheme 9). When the amides **2a,h–o** were treated with PIFA under the optimized conditions (Table 3) the effectiveness of this

cyclization reaction proved to be restricted to *N*-arylamides (entries 1–5). Although a wide range of experimental conditions was tested on either alkyl (entries 7–8) or alkoxyamides (entry 9), they all failed to afford the desired indazolone and a complex mixture of products was obtained in all cases. Similar results were observed with amide **2l**. Consequently, it must be pointed out that an aromatic ring seems to be necessary to stabilize the corresponding *N*-acylnitrenium intermediate.

Table 2. Scope of the cyclization with respect to amides **2a–g**.

entry	R^1	2 (%)[a]	3 (%)[b]
1	Me	**2a** (69)[c]	**3a** (68)
2	allyl	**2b** (77)[c]	**3b** (62)
3	$PhCH_2$	**2c** (67)[c]	**3c** (67)
4	Ph	**2d** (68)[c]	**3d** (61)
5	H	**2e** (71)[c]	**3e** (0)[e]
6	CO_2Et	**2f** (85)[d]	**3f** (0)[e]
7	$TolSO_2$	**2g** (86)[d]	**3g** (0)[e]

[a] Isolated yield after purification by crystallization. [b] Isolated yield after purification by flash chromatography. [c] Synthesis through conditions i. [d] Synthesis through conditions ii. [e] Indazolone **3** was not detected in the complex mixture of compounds that was obtained.



1a **2a,h–o** **3a,h–o**

i) $AlMe_3$, R^2NH_2, CH_2Cl_2, reflux; ii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 ºC.

Scheme 9. Synthesis of indazolones **3a,h–o**.

Table 3. Scope of the cyclization with respect to amides **2a,h–o**.

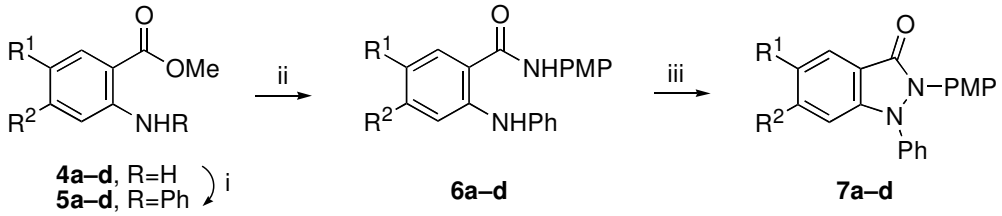
entry	R^2	2 (%)[a]	3 (%)[b]
1	*p*-OMePh	**2a** (69)	**3a** (68)
2	Ph	**2h** (88)	**3h** (60)
3	1-Naph	**2i** (91)	**3i** (61)
4	*p*-EtPh	**2j** (89)	**3j** (60)
5	*p*-BrPh	**2k** (22)	**3k** (45)
6	H	**2l** (90)	**3l** (0)
7	$PhCH_2$	**2m** (88)	**3m** (0)
8	allyl	**2n** (65)	**3n** (0)
9	OMe	**2o** (18)	**3o** (0)

[a] Isolated yield after purification by crystallization.
[b] Isolated yield after purification by flash chromatography.

To the view of the obtained results, and taking into account that a radical mechanism can be excluded, supported by the fact that either oxygen atmosphere or an addition of a radical trap such as TEMPO or

DPPH[66] did not affect the projected reaction at all, it can be proposed that this novel N–N bond formation takes place through an *N*-acylnitrenium ion generated by the action of the mild oxidant PIFA on aromatic amides. These intermediates react intramolecularly with the amine moiety, as the nucleophilic partner of the reaction, giving rise to the highly valued heterocyclic systems **3**.

Once the application of the PIFA–mediated N–N bond forming process to the synthesis of a series of indazolone derivatives had been achieved, we decided to investigate the success of this transformation in related systems with aromatic and heteroaromatic rings and, therefore, a series of substrates **6a–d** was chosen to construct the target indazolone derivatives. These precursors were obtained in a two–step synthesis from commercially available methyl anthranilates **4a–d** by a palladium–catalyzed *N*-arylation, reaction using bromobenzene as the arylating agent,[67] followed by the direct transformation of the resulting aminoesters **5a–d** into the desired amides **6a–d** by a $AlMe_3$–mediated aminolysis reaction (Scheme 10). Next, we studied the reaction of these aromatic amides with PIFA under the cyclization conditions previously optimized.



a, R^1=R^2=H; **b**, R^1=R^2=OMe; **c**, R^1=H, R^2=Cl; **d**, R^1=F, R^2=H

i) PhBr, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 100 ºC, sealed tube; ii) $AlMe_3$, *p*-anisidine, CH_2Cl_2, reflux; iii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 ºC.

Scheme 10. Preparation of indazolones **7a–d**.

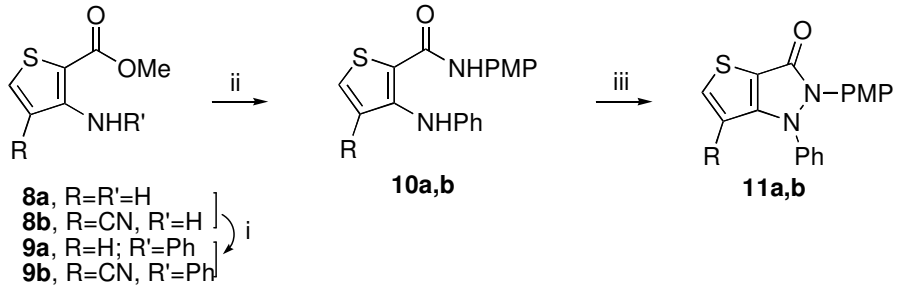
Table 4. Yields of the transformation of **5a–d** into **7a–d**.

entry	**5a–d** (%)[a]	**6a–d** (%)[b]	**7a–d** (%)[a]
1	**5a** (93)	**6a** (69)	**7a** (61)
2	**5b** (85)	**6b** (68)	**7b** (0)
3	**5c** (71)	**6c** (70)	**7c** (81)
4	**5d** (85)	**6d** (70)	**7d** (77)

[a] Isolated yields after purification by flash-chromatography.
[b] Isolated yields after purification by crystallization from Et_2O.

As shown in Table 4, the success of the proposed PIFA–mediated cyclization process revealed a strong dependence on the nature of the substituents in the aryl ring. Thus, it proved to be suitable for unsubstituted substrates (entry 1) and for substrates bearing electron–withdrawing groups such as chlorine (entry 3) and fluorine (entry 4) affording the desired indazolones **7a**, **7c** and **7d** in 61%, 81% and 77% yields, respectively. In contrast, the cyclization process failed when it was tested on the dimethoxy–substituted amide **6b** (entry 2). In this case the desired indazolone **7b** was not even detected and a complex mixture of products was obtained instead. The existence of a competitive oxidation process on the electronically enriched aromatic ring in substrate **6b** can be argued to explain this particular result.

As mentioned above, in order to investigate the extension of the presented methodology to other fused heterocyclic systems, we also faced the synthesis of the related thieno-fused pyrazolone derivatives **11a,b** by a common sequence as shown in Scheme 11. Thus, methyl 3-amino-2-thiophenecarboxylates **8a,b** were submitted to a palladium–catalyzed *N*-arylation process affording satisfactorily the corresponding *N*-phenyl derivatives **9a,b**, which were next efficiently transformed into the desired aromatic amides **10a,b**. On treatment with PIFA, it was observed that, even after application of a complete array of experimental conditions (by modifying solvents, temperature, and additives), amide **10a** could never furnish the corresponding bicycle **11a** and complete degradation of the starting material was observed. Although synthetically discouraging, this result could be anticipated considering the similar electronic nature of the 3,4-dimethoxyphenyl and thienyl systems. For that reason, we also examined the behavior of amide **10b** under our PIFA–promoted cyclization conditions. In this particular case, the desired thieno–fused pyrazolone **11b** was obtained in a nice 61% yield. Apparently, the decrease of the oxidation potential of the thiophene ring due to the presence of the electron–withdrawing cyano group allows nitrogen oxidation and, therefore, the cyclization reaction to take place.[68]

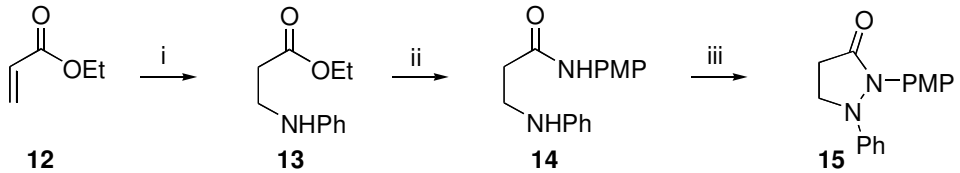


i) PhBr, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 100 ºC, sealed tube (69% for **8a**, 57% for **8b**);
ii) $AlMe_3$, *p*-anisidine, CH_2Cl_2, reflux (82% for **10a**, 68% for **10b**);
iii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 ºC (0% for **11a**, 61% for **11b**).

Scheme 11. Preparation of thieno–fused pyrazolone **11b**.

Additionally, and taking into account the already described favorable results, we decided to test the presented oxidative process on a linear amide to determine its suitability for the construction of the simple pyrazolone skeleton. In this case (Scheme 12), the synthesis of the required *para*-methoxyphenylamide **14** was accomplished by following a known[69] aza–Michael reaction on ethyl acrylate **12**, followed by a $AlMe_3$–promoted amidation protocol on the so–obtained derivative **13**.

Next, when amide **14** was submitted to the action of PIFA, the desired pyrazolone derivative **15** was obtained in a moderate 35% yield using trifluoroethanol as solvent, instead of CH_2Cl_2/TFA as for the previous examples, to attain complete conversion of the starting material.



i) $PhNH_2$, $FeCl_3 \cdot 7H_2O$, H_2O, room temperature (72%); ii) $AlMe_3$, *p*-anisidine, CH_2Cl_2, reflux (72%);
iii) PIFA (0.01 M), TFEA, 0 ºC (35%).

Scheme 12. Preparation of pyrazolone **15**.

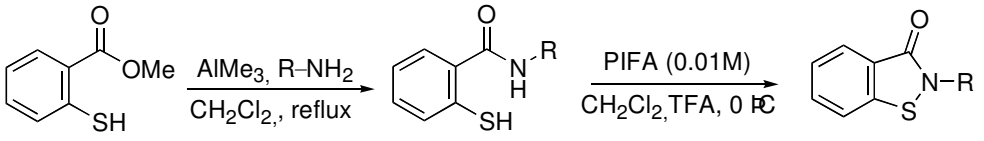
2.4. Iodine (III) mediated synthesis of isothiazolones

In connection with the previous work and following with our research on the synthesis of highly valuable heterocycles through oxidative processes mediated by the environmentally friendly reagent PIFA, we investigated the extension of the former strategy to the synthesis of benzisothiazol-3-one derivatives of type **16**. This novel approach (Scheme 13) features, once again, the PIFA–mediated oxidation of properly substituted amides **17** and the subsequent trapping of the so-obtained *N*-centered electrophilic species by the thiole moiety to form a new N–S bond.

Scheme 13. Proposed strategy for the synthesis of benzisothiazolones **16**.

A number of routes leading to the target compounds have been described in the literature but, although they have been proven to be useful protocols, some of them are of limited use because they require the use of highly toxic and corrosive agents such as chlorine gas.[70] Therefore, the development of a chlorine–free synthetic protocol would be rather desirable and, in this context, we envisaged that the employment of PIFA would be of high practical value.

Our synthetic study started by an effective preparation of the required 2-mercaptoamide derivatives **17a–j** following a $AlMe_3$–promoted aminolysis protocol[71] on commercially available methyl thiosalicylate (**18**), as outlined in Scheme 14. Next, on the basis of our previous experience and in order to optimize the experimental conditions for the proposed cyclization step, we selected *para*-methoxyphenylamide **17a** as a model system that could guarantee the stability of the corresponding *N*-acylnitrenium intermediate.[72] Thus, we briefly examined its behavior under the action of PIFA using different solvents (trifluoroethanol, CH_2Cl_2, acetonitrile and toluene), temperatures (from 0 ºC to 60 ºC), and additives (TFA and $BF_3{\cdot}OEt_2$) to conclude that the optimal results were obtained when amide **17a** was treated with PIFA (0.01 M) in CH_2Cl_2 at 0 ºC in the presence of TFA (3.0 eq.) leading to benzisothiazolone **16a** in 78% yield.

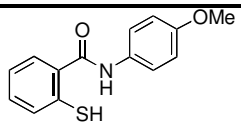
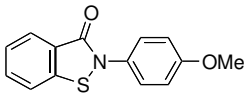
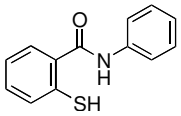
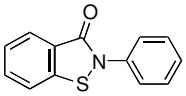
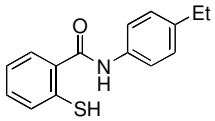
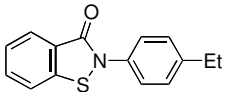
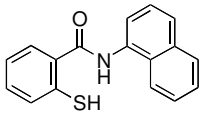
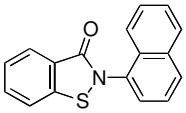
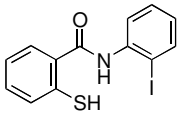
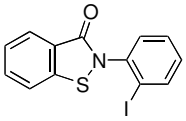
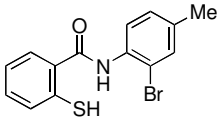
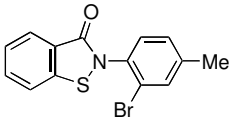
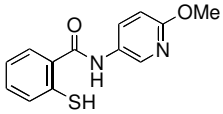
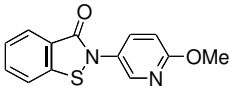
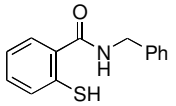
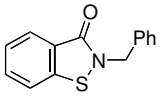
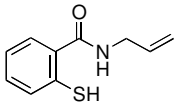
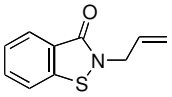
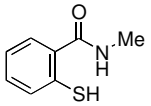
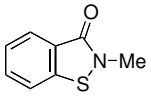


Scheme 14. Synthesis of benzisothiazolones **16a–j** from amides **17a–j**.

Having established an optimal protocol for the key cyclization step, and with the aim to determine its scope with respect to the amide motif, we analyzed the influence of the nature of this functionality on the efficiency of the cyclization step. Thus, when treated with the easy-to-handle reagent PIFA under the optimized reaction conditions, amides **17a–j** afforded the corresponding benzisothiazolones **16a–j** in good yields (Table 5). Consequently, these results suggest that activated (**17a,c**), non-activated (**17b,d**), and

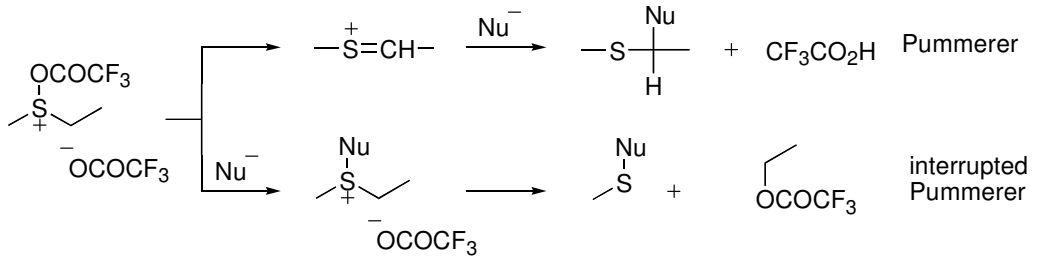
moderately deactivated (**17e,f**) aryl rings, as well as the methoxypyridyl system (**17g**), are able to stabilize the *N*-acylnitrenium intermediate and, therefore, to accomplish successfully the scheduled cyclization. To our delight, alkylamides **17h** and **17j** also rendered successfully the corresponding benzisothiazolones **16h** and **16j**, respectively.[73] Thus, while the previously reported oxidative process for the construction of N–N linkages by employing amine moieties as the nucleophilic counterpart of the reaction proved to be restricted to aromatic amides, the presented process can be efficiently extended to a number alkyl amides.[74]

Table 5. Synthetic details for the transformation of amides **17** into benzisothiazolones **16a–j**.

entry	Amide	17 (%)[a]	Benzisothiazolone	16 (%)[b]
1		**17a** (92)		**16a** (78)
2		**17b** (95)		**16b** (71)
3		**17c** (95)		**16c** (66)
4		**17d** (95)		**16d** (62)
5		**17e** (95)		**16e** (64)
6		**17f** (91)		**16f** (67)
7		**17g** (61)		**16g** (70)
8		**17h** (60)		**16h** (60)
9		**17i** (63)[b]		**16i** (0)
10		**17j** (76)		**16j** (60)

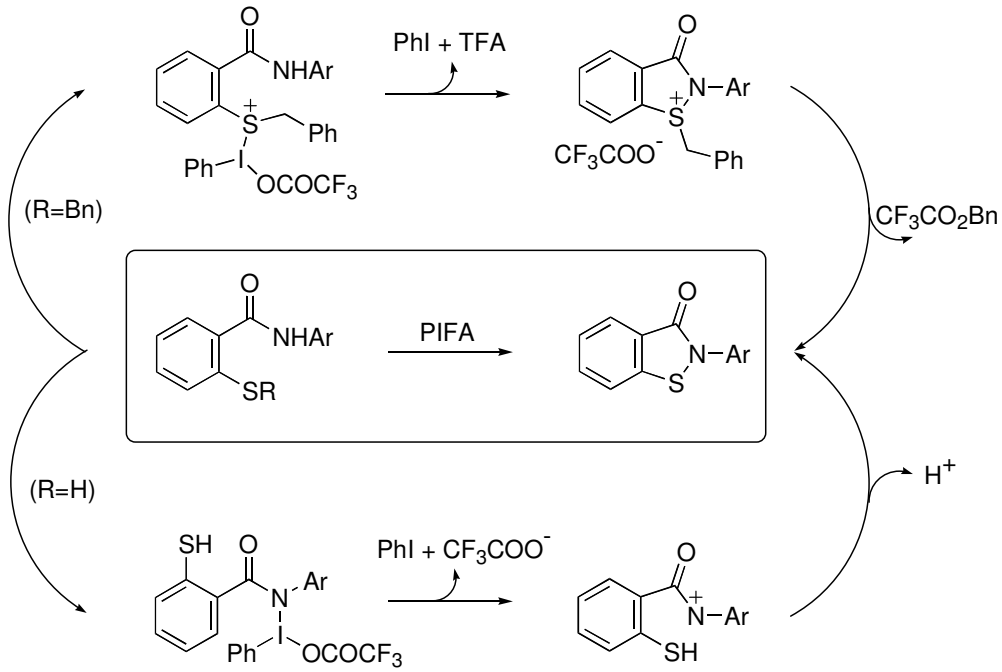
[a] Isolated yields after purification by crystallization from Et_2O.
[b] Isolated yields after purification by column chromatography.

Previously, it has been shown in Scheme 3 (section 1.1.) a poorly developed, but closely related, synthetic approach to the construction the benzisothiazolone system based on the action of PIFA on *S*-benzylated mercaptobenzamides, that takes place through an interrupted Pummerer type reaction.



Scheme 15. Schematic representation of a Pummerer and an interrupted Pummerer reactions.

Although formally very similar, both strategies differ both in the operating mechanism and also in the required substrates. Thus, as shown in Scheme 16, while our reaction takes place directly on mercaptobenzamides through the generation of a nitrenium intermediate, Chen´s approach involves an additional step to benzylate the thiol group. The action of PIFA on such substrate leads to the formation of thionium intermediate that, after cyclization, expels benzyl trifluoroacetate to render the final benzisothiazolone derivative.



Scheme 16. Alternatives to the PIFA-mediated synthesis of benzisothiazolones from mercaptobenzamides.

Acknowledgments

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4. This drug is commercially known under a number of trade names, including Andolex®, for example.
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72. When nitrenium ions are stabilized by the electron-donating effect of a proper neighbor group (such as aryl, alkoxy or nitrogen groups), they exhibit sufficient long-life to undergo further transformations. See reference 57.
73. Alkyl substituents at the 2-position bearing a basic group are sometimes necessary for *ex vivo* biological activity of the 1,2-benzisothiazol-3-ones. See reference 43.
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range of experimental conditions was tested on amide **17i**, they all failed to afford the desired heterocycle leading, in all cases, to a complex mixture of products. Apparently double bond reacts faster than the amide functionality with PIFA. See, for example: Çelik, M.; Alp, C.; Coskun, B.; Gültekin, M. S.; Balci, M. *Tetrahedron Lett.* **2006**, 3659–3663.

1,2,4,5,10b,10c-HEXAHYDROPYRROLO[1',2',3':1,9a,9]IMIDAZO[1,2-*a*]INDOLE, A NOVEL TETRAHETEROCYCLIC SYSTEM: STUDIES TOWARD INDOLE ALKALOID ANALOGUES

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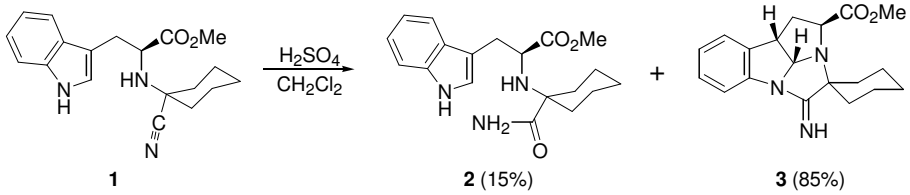
Abstract. *This review covers our studies on the highly stereoselective synthesis of indole alkaloid analogues containing the novel tetraheterocyclic ring system 1,2,4,5,10b,10c-hexahydropyrrolo[1',2',3':1,9a,9]-imidazo[1,2-a]indole by acid-mediated domino cyclative electrophile additions upon tryptophan-derived α-amino nitriles. When the electrophile is a proton, a tautomerization takes place to give 10b-unsubstituted-hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-a]indoles, while, the acid-mediated reaction with other electrophiles, such as halosuccinidides, prenyl bromide, the Corey-Kim reagent, or oxidants, leads to 10b-substituted analogues. This reaction requires the acid-mediated activation of the cyano group, which is transformed in an endocyclic amidine. Further manipulation of the 10b-halo- or 10b-methylthiomethyl groups allows to extend the diversity of substituents at this position. The endocyclic amidine can be N-acetylated and N-benzyloxycarbonyl-protected, but not N-tert-butoxycarbonyl-protected. Finally, the alkylative hydrolysis of the amidine leads to the corresponding lactam analogues.*

Contents

1. Introduction

1.1. 1,2,4,5,10b,10c-Hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles from tryptophan-derived α-amino nitriles. An unexpected synthesis

As part of a wide program to develop methodologies for generating peptidomimetics, we focused our attention on the potential of amino acid derived α-amino nitriles as a source of diversity of privileged scaffolds,[1] such as piperazine,[2] 1,4-benzodiazepine,[3] and pyrazino[1,2-*c*]pyrimidine derivatives.[4] In the course of this research, we were interested in the tryptophan-derived α-amino carboxamide **2** (Scheme 1) as a starting material for the synthesis of spirocyclic piperazines. The access to this carboxamide was planned *via* acid-mediated hydration of the tryptophan-derived amino nitrile **1**. However, under the usual conditions developed for acid-mediated hydration of amino acid-derived α-amino nitriles[2b] [treatment with (1:1) H_2SO_4/CH_2Cl_2], amino nitrile **1** yielded the carboxamide **2** as a minor product (15%), along with the unexpected product **3** (85%), tautomer of amino nitrile **1**, which includes the novel ring system 1,2,4,5,10b,10c-hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indole (**A**) in its structure.[5]



Scheme 1

The ring system **A** (Figure 1) could be considered as a hybrid of 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**B**) and 2,3,9,9a-tetrahydroimidazo[1,2-*a*]indole (**C**), both present in a growing class of indole alkaloids as shown in sections 1.2. and 1.3. However, we did not find any precedents of this novel ring system in the literature, except for compound **4** (Scheme 2) which had been unexpectedly obtained from the pyrrolo[2,3-*b*]indole derivative **5**, in a synthetic scheme which had been initially planned for the preparation of the indole alkaloid roquefortine C (**6**).[6]

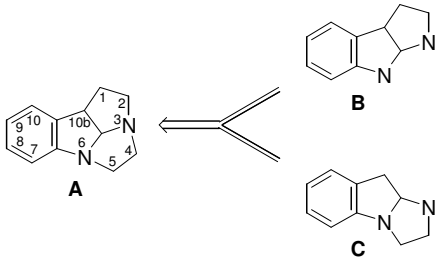
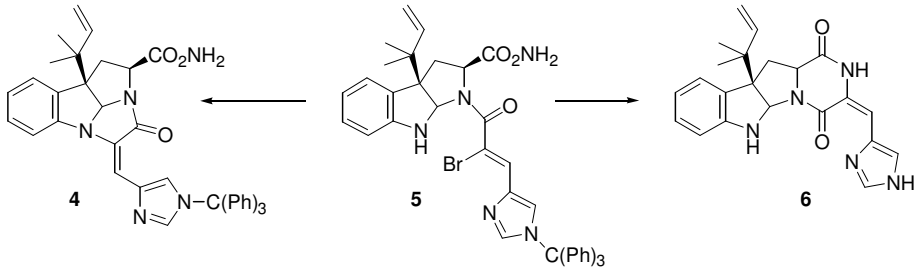


Figure 1

The recurrent presence of indole-based heterocycles in natural products and in diverse compounds of therapeutic interest, along with the novelty of the tetraheterocyclic ring system **A**, pushed us to further study the potential of tryptophan-derived α-amino nitriles for the synthesis of hexahydropyrrolo[1',2',3':1,9a,9]-imidazo[1,2-*a*]indole derivatives as well as the reactivity of this novel ring system. This review covers the main results of these studies.



Scheme 2

1.2. Hexahydropyrrolo[2,3-*b*]indole alkaloids

The hexahydropyrrolo[2,3-*b*]indole-based alkaloids constitute one of the most numerous families of indole alkaloids. For example, the scaffold **B** is present in the acetylcholinesterase inhibitor physostigmine (**7**, Figure 2) and its analogue phenserine (**8**),[7] currently in clinical phase II for the Alzheimer's disease treatment, in the antibacterials flustramines (**9** and **10**)[8] and mollenines (**11**)[9] and in the urochordamines.[10]

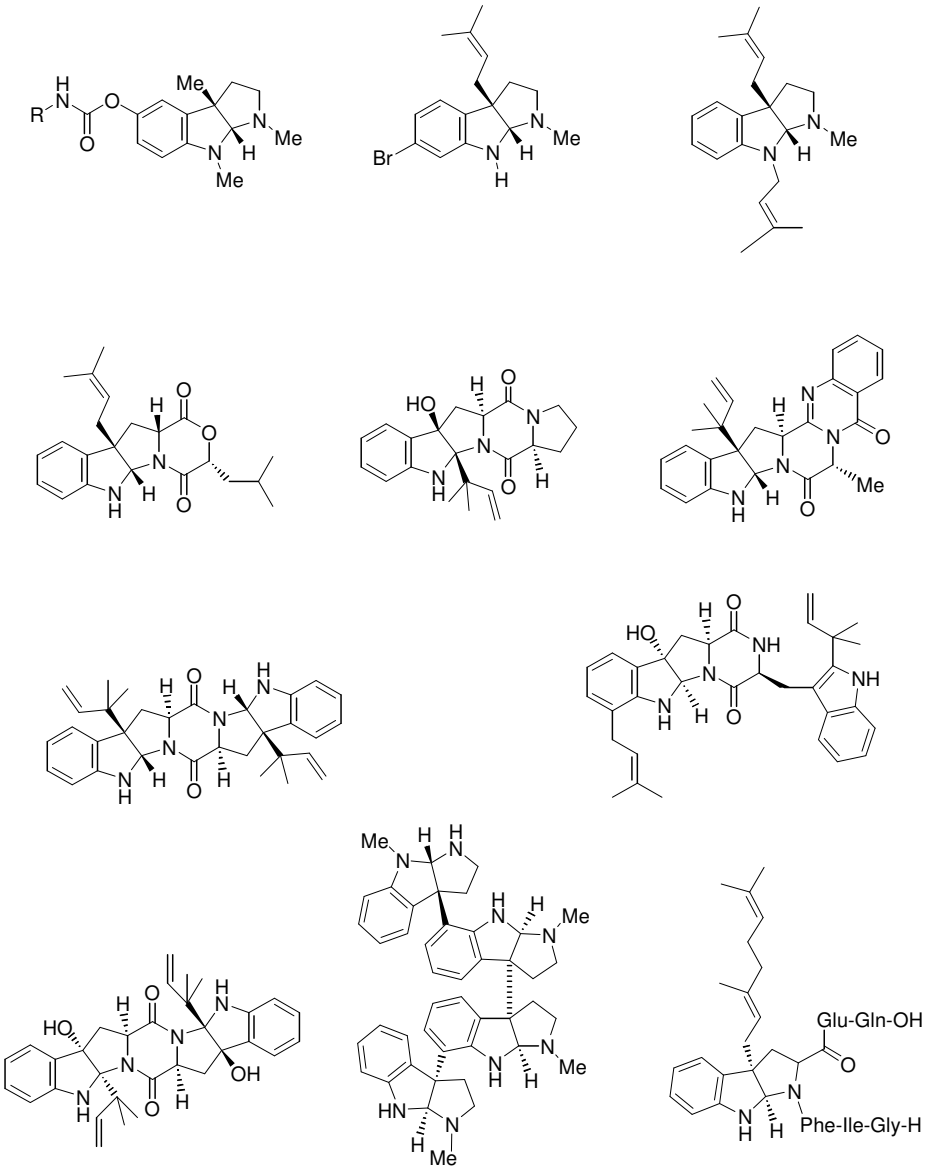


Figure 2. Examples of hexahydropyrrolo[2,3-*b*]indole-containing alkaloids.

Furthermore, this scaffold is present in a numerous group of alkaloids which contain also a fused piperazine ring, such as, among others, the mycotoxin brevianamide E (**12**),[11] the multidrug resistance reversal agents ardeemins (**13**),[12] the vasodilator amauromine (**14**),[13] roquefortines,[14] leptosins,[15] frugtigenines,[16] okaramines (**15**),[17] the cholesterol acyltransferase inhibitor gypsetin (**16**)[18] or the inmunomodulators sporidesmins.[19] The 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole is also present in dimeric and polymeric indole alkaloids, for instance in the somatostatin antagonists psycholeine and quadrigemine C (**17**).[20] It is also frequent to find the skeleton **B** as a modified tryptophan residue in peptides, such as himastatin,[21] chloptosin[22] and the *Bacillus subtilis* pheromone ComX (**18**).[23]

1.3. Tetrahydroimidazo[1,2-*a*]indole alkaloids

The 2,3,9,9a-tetrahydroimidazo[1,2-*a*]indole skeleton is present in the cholecystokinin CCK_1 receptor antagonist asperlicin (**19**, Figure 3),[24] the substance P antagonist fiscalin A (**20**),[25] the antifungic fumiquinazolines (**21**),[26] tryptoquivalines (**22**),[27] and in chaetominine (**23**)[28] and kapakahines (**24**),[29] which contain an additional *peri*-fused piperidone ring.

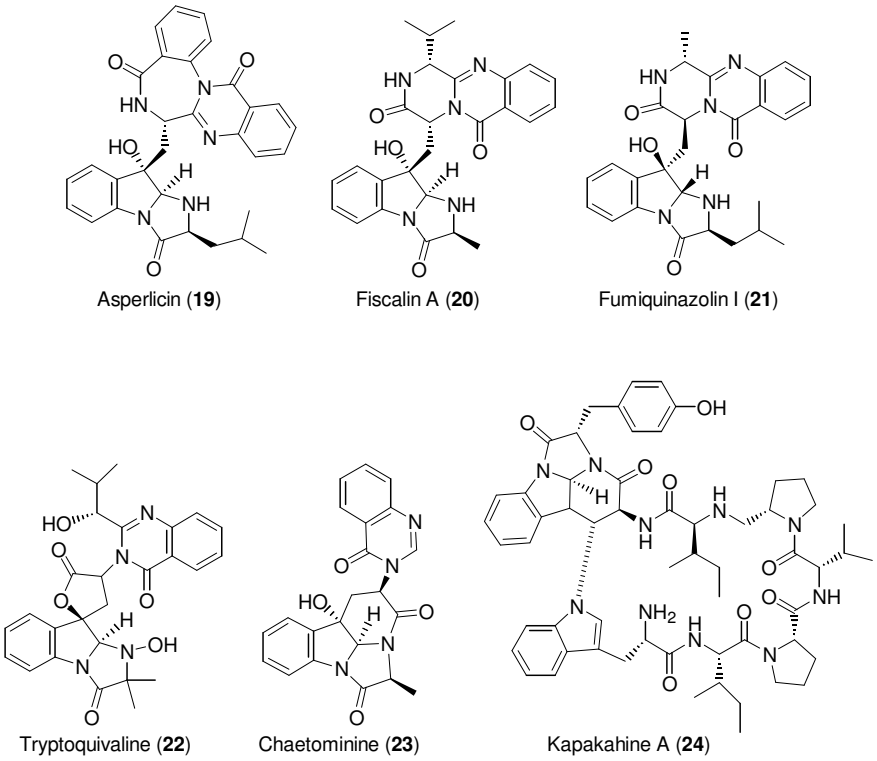


Figure 3. Examples of tetrahydroimidazo[1,2-*a*]indole-containing alkaloids.

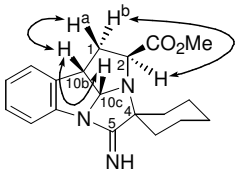
2. 10b-Unsubstituted hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles

2.1. Characterization

The FAB-HRMS mass spectra of compound **3**, unexpectedly resulting from the treatment of α-amino nitrile **1** with H_2SO_4, showed a [M+1] ion at a *m/z* value of 326.1884 corresponding to an identical molecular formula as that of the starting amino nitrile **1**. This fact indicated that both compounds were isomers. On the other hand, the ^{1}H NMR spectrum of the tetracycle **3** in $CDCl_3$ showed the disappearance of the signals corresponding to the indole NH and 2-H protons of the starting amino nitrile **1**, and the appearance of a doublet at 5.82 ppm and a triplet at 3.76 ppm for 10c-H and 10b-H protons, respectively. Accordingly, the

^{13}C NMR spectrum of **3** showed the disappearance of the indole C_2 and C_3 signals and the appearance of the corresponding fusion carbons C_{10c} and C_{10b} at 87.3 and 43.0 ppm, as well as the disappearance of the nitrile carbon (at 121.6 ppm) of **1**, and the presence of the amidine carbon at 173.9 ppm. The amidine NH did not appear either in the ^{1}H NMR or in the ^{15}N NMR spectra, probably due to a very fast exchange with the solvent. However, the IR spectrum showed a narrow band at 3311 cm^{-1} corresponding to the stretching vibration of the amidine NH.[30] The changes at the α and β positions of the starting amino nitrile **1** and the lost of aromaticity at positions 2 and 3 of the indole ring pointed out to the formation of a hexahydropyrroloindole ring, while the transformation of the nitrile carbon into a carbonilic or enaminic carbon pointed out to the pyrroloimidazoindole skeleton. This structure was confirmed by the HMBC ^{1}H,^{13}C-correlation spectrum. Although, in this spectrum we did not observed correlation between the C_5 and the 10c-H, probably because these nuclei form an angle near to 90º, as it could be deduced from a 3D model built with the Chem3D® program.

The stereochemistry at the fusion positions C_{10b} and C_{10c} in the pyrroloimidazoindole **3** was established on the basis of the NOE correlations observed in the 1D NOESY spectra. Thus, as shown in Figure 4, 10c-H showed NOE effect with 10b-H, and this proton gave NOE with the 1-H proton which did not show NOE with 2-H. These data indicated a relative disposition *sin-cis* for 10b-H and 10c-H protons, with respect to the carboxylate group at C_2, which orients itself towards the less hindered face in a 2-*exo* disposition.[5] Attempts to obtain good crystals of **3** for X-ray analysis were unsuccessful. Therefore, its unequivocal structural assignment, including the *E*/*Z* configuration at the amidino group, was indirectly attempted by chemical derivatization as it is commented in section 2.3.



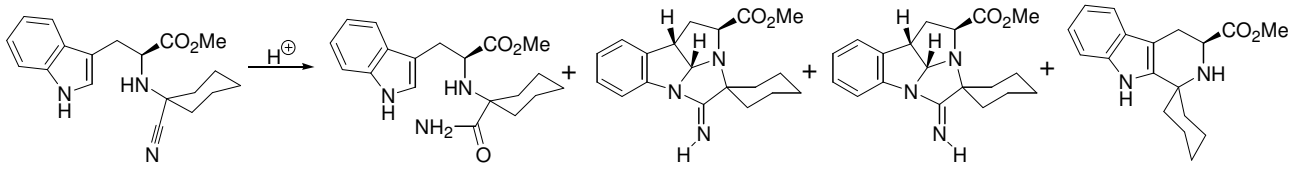
3

Figure 4. NOE effects observed in the ^{1}H NOESY 1D spectra of **3**.

2.2. Synthesis optimization

As above indicated, we did not find precedents for the synthesis of hexahydropyrrolo-[1',2',3':1,9a,9]imidazo[1,2-*a*]indole derivatives, however, the precedents on the synthesis of hexahydro-pyrrolo[2,3-*b*]indole derivatives were numerous. Firstly, in 1978 Taniguchi and Hino reported on the formation of tryptophan and tryptamine cyclic tautomers by treatment with acids.[31] Later, several groups have reported on the building of a hexahydropyrrolo[2,3-*b*]indole ring system on tryptophan and tryptamine derivatives by reaction with electrophiles.[32] In these cases, mixtures of diastereoisomers at the pyrroloindole fusion stereogenic centers are usually obtained for tryptophan derivatives, in which the product with the 2-*endo* carboxylate group is the thermodynamically more stable, while the isomer with the 2-*exo* carboxylate group (like in **3**) is the kinetically controlled product. In our case, as compound **3** had been initially obtained as one single diastereoisomer, we studied the possibility of controlling the stereochemistry modifying the reaction conditions (acid, temperature and time). As summarized in Table 1, the pyrroloimidazoindole **3a** (Scheme 3) was quantitatively obtained by decreasing the amount of conc. H_2SO_4 (entry 3), or replacing it

by 85% H_3PO_4 or neat trifluoroacetic acid (TFA) (entries 5 or 6). When we decreased the TFA concentration or increased the reaction temperature (entries 7, 8 or 10), the formation of a minor isomer **3b** (less than 7%) was also observed, along with the tetrahydro-β-carboline derivative **25**.[33] The resulting mixture was chromatographically resolved and the NOE correlations observed for **3b** showed the same relative disposition for 2-H, 10b-H, and 10c-H protons as in the major isomer **3a**. Therefore, we assumed that **3a** and **3b** should be isomers at the amidine group. Neither the formation of the *endo* isomer of **3a**, nor the formation of intermediates of partial reaction (pyrroloindole-cycled nitrile or carboxamide or indole-amidine derivatives), were detected in any case.



Scheme 3. Reactivity of Trp-derived amino nitrile **1** in acid media. Yield of products shown in Table 1.

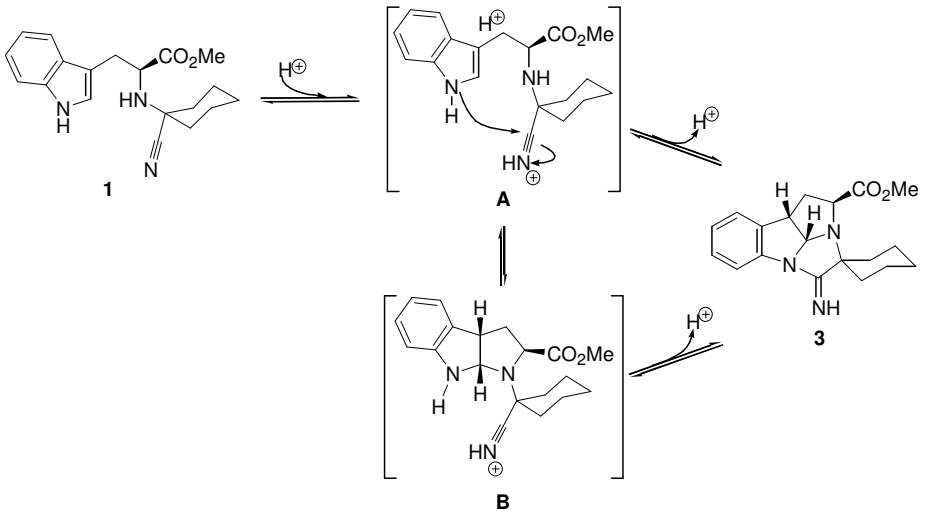
Table 1. Influence of reaction conditions on the results of the treatment of amino nitrile **1** with acids.

Entry	Acid	% of acid in CH_2Cl_2	T ºC	t	Yield (%)[a]				
					1	**2**	**3a**	**3b**	**25**
1	conc.H_2SO_4	50	25	2 h	0	15	85	0	0
2	conc.H_2SO_4	33	25	2 h	0	15	85	0	0
3	conc.H_2SO_4	25	25	2 h	0	0	100	0	0
4	conc.H_2SO_4	10	25	3 h	34	0	66	0	0
5	85% H_3PO_4	33	25	2 h	0	0	100	0	0
6	TFA	100	25	48 h	0	0	100	0	0
7	TFA	50	25	4 d	0	0	75	7	18
8	TFA	25	25	4 d	11	0	60	5	24
9	TFA	10	25	8 d	13	0	23	0	64
10	TFA	100	50	24 h	40	0	44	6	10
11	TFA	10[b]	50	8 d	9	0	7	0	85

[a]Yields were determined by integration of characteristic signals in the ^{1}H NMR spectra of the crude reaction mixture. [b]10% of TFA in $CHCl_3$.

As shown in Scheme 4, the formation of the pyrroloimidazoindole skeleton could be explained by two possible mechanisms. The first one (**A**) would involved a concerted domino reaction[34] initiated by nitrile protonation, followed by the electrophilic attack of a proton to the C_3 position of the indole, with a simultaneous prototropic shift and the formation of two new C-N bonds. Alternatively, the tautomerization could take place *via* a two steps process, which would involve a first cyclization to a pyrroloindole intermediate (**B**), followed by the nucleophilic attack of the indole NH upon the activated cyano group to give the endocyclic amidine. The fact that intermediates of partial cyclization could not be detected in the

reaction media supports our first proposed mechanism.[5] Interestingly, the reaction was stereospecific, as the enantiomer of amino nitrile **1** (**1c**, derived from D-Trp) led to the enantiomer of **3a** (**3c**).



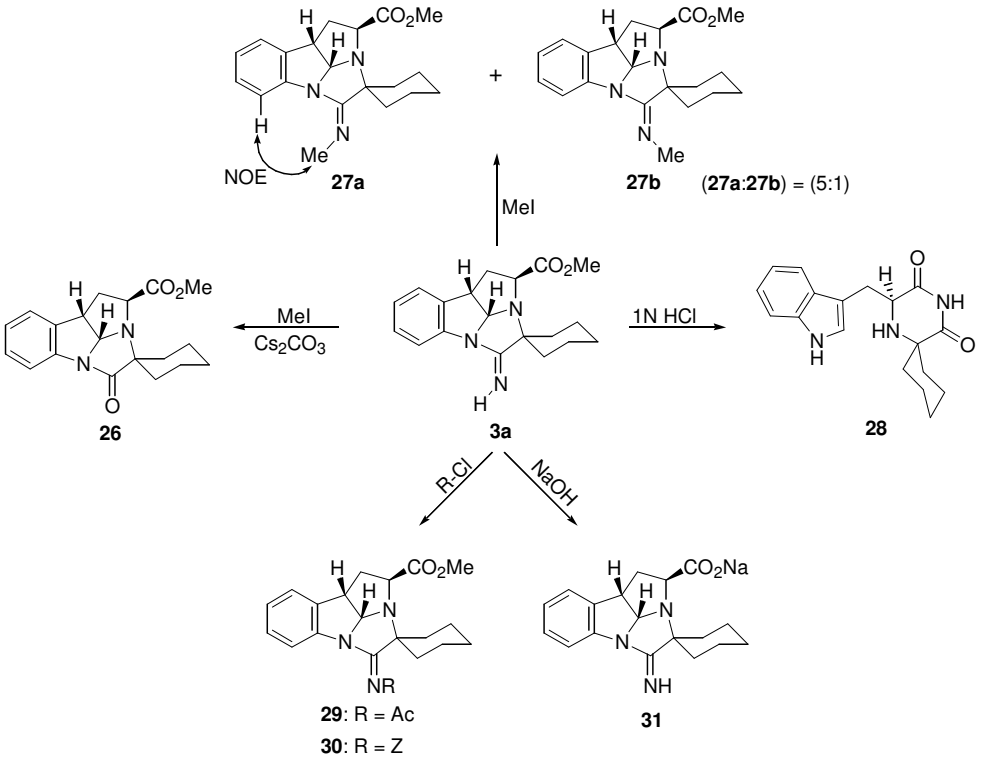
Scheme 4. Proposed mechanisms for the construction of the hexahydropyrrolo[1',2',3':1,9a,9]-imidazo[1,2-*a*]indole system of **3**.

2.3. Reactivity

In view of the impossibility of obtaining good crystals of compound **3a** for X-ray analysis, we undertook the assignment of the E/Z configuration at the amidine group indirectly by means of its methylation. This was initially attempted by the treatment of **3a** with MeI at 80 ºC in the presence of Cs_2CO_2. Under these conditions, the reaction was very slow (3 days) and it led only to the hydrolysis of the amidine group, providing the lactam analogue **26** (Scheme 5). When the methylation was attempted by treatment with Me_2SO_4 at room temperature (10 days), using K_2CO_3 as base, a 54% yield of **26** was obtained, along with a (5:1) mixture of the methyl derivatives **27a/27b** (37%). Finally, to avoid the hydrolysis of the amidine group, the methylation was performed without base, by treatment with MeI (6 equiv.) at 80 ºC for 24 h, obtaining the (5:1) **27a,b** mixture (89%), which could not be resolved. The NOE correlation observed in 1D NOESY spectra of this mixture between the methyl group and the 7-H proton of the major isomer **27a** allowed the assignment of a *Z*-configuration to this isomer. Interestingly, the amidine derivative **3a** was stable after 6 days of treatment with Cs_2CO_3 at 80 ºC. This unreactivity indicated that the hydrolysis of the amidine should take place after its methylation. The comparison of the pattern of ^1H and ^{13}C NMR signals corresponding to **27a** and **27b** with those of **3a** and **3b** showed a higher similarity of **3a** with **27a** than with **27b**. Although this result did not allow an unequivocal assignment, it suggests that **27a** and **3a** have the same configuration (*Z*) at the amidino group. When we tried to obtain the lactam analogue **26** by acid hydrolysis with 1N HCl, **3a** was stable at room temperature, but after 2 days refluxing at 100 ºC, the 2,6-dioxopiperazine derivative **28** was isolated (74%), without detecting the formation of **26**.

To facilitate the further chemical manipulation of the tetracyclic ring system, the protection of the amidine group and the saponification of the carboxylate group were also studied. As shown in Scheme 5, the reaction of **3a** with acetyl chloride or benzyl chloroformate, in the presence of propylene oxide, yielded the corresponding *N*-acetyl and *N*-benzyloxycarbonyl derivatives **29** (65%) and **30** (100%), respectively.

However, **3a** was recovered unaltered after treatment with di(*tert*-butyl)dicarbonate, in the presence of TEA and a catalytic amount of 4-(dimethyl)aminopyridine. With regard to the saponification, it required the treatment with an excess of NaOH [in (1:2) H_2O/MeOH] for 10 h, and the resulting acid was unstable, being isolated as the sodium salt **31**, with ~10% of the sodium salt of L-Trp. When this salt was treated with acid resin Dowex 50×4, to liberate the free acid, it decomposed into a complex mixture.



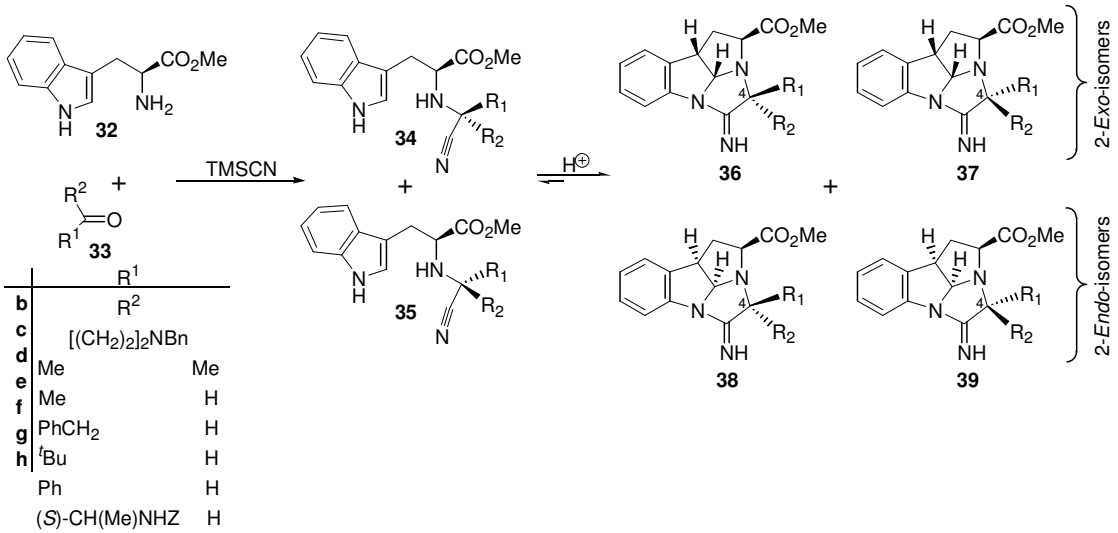
Scheme 5. Reactivity of the amidine group of the pyrroloimidazoindole **3a**.

2.4. Scope and stereoselectivity of the domino tautomerization of Trp-derived α-amino nitriles

After having optimized the reaction conditions for the tautomerization of amino nitrile **1** to the pyrroloimidazoindole derivative **3a**, we studied the scope and stereoselectivity of that tautomerization in other Trp-based α-amino nitriles derived from other ketones, different from cyclohexanone, and aldehydes.[35] Among the ketones, we selected *N*-benzyl-4-piperidone and acetone (Scheme 6, **33b** and **33c**, respectively), while, among the aldehydes, aliphatic ones of variable steric volume [acetaldehyde (**33d**), phenylacetaldehyde (**33e**) and pivalaldehyde (**33f**)] and benzaldehyde (**33g**) were selected. Furthermore, *N*-Z-L-alaninal (**33h**) was also included, as a model, to explore the synthesis of amino acid-derived hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles as intermediates for the preparation of fused piperazine derivatives, which could be analogues of the pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-containing natural products aforementioned (as **12–16** in Figure 2).

The starting α-amino nitriles **34** and **35** were obtained *via* our modified Strecker synthesis,[2b] which involved the coupling of tryptophan methyl ester (**32**) with the corresponding carbonylic compound **33**, followed by *in situ* $Yb(OTf)_3$-promoted addition of TMSCN. Since the starting ketones **33b** and **33c** are symmetric, only one amino nitrile was obtained from their coupling with **32** (**34b,c = 35b,c**). However, in the case of the aldehyde-derived amino nitriles **d–h**, a new stereogenic center was generated, to give the corresponding epimeric mixture of **34** and **35** in an ~2:1 ratio, except for the phenylacetaldehyde and

pivalaldehyde derivatives **34**,**35e** and **34**,**35f**, which were obtained in an ~3:2 ratio. These epimeric mixtures were resolved by radial chromatography, except for the pivalaldehyde derivatives **34f** and **35f**, which could not be chromatographically separated, but were kinetically resolved in the subsequent reaction of cyclization (within 24 h of reaction, **35f** cyclized completely, while 70% of **34f** was recovered unchanged). The cyclization was carried out by treating a CH_2Cl_2 solution of the corresponding amino nitrile with a 50% sample of 85% H_3PO_4, except for the alanine derivatives **34h** and **35h**, which were treated with neat TFA, due to the instability of the Z-protecting group in H_3PO_4. In the major and less reactive epimer **34h**, the TFA treatment produced, besides the cyclization to its tautomer **39h** (48%), partial simultaneous replacement of the Z group by a trifluoroacetyl group (38%).



	R^1	R^2
b	$[(CH_2)_2]_2NBn$	
c	Me	Me
d	Me	H
e	$PhCH_2$	H
f	^{t}Bu	H
g	Ph	H
h	(*S*)-CH(Me)NHZ	H

Scheme 6. Synthesis and tautomerization of Trp-derived α-amino nitriles.

The mentioned literature precedents on the synthesis of hexahydropyrrolo[2,3-*b*]indoles had demonstrated the high preference for *cis* versus *trans* fusion in the pyrroloindole junction, and that the 2-*endo*-carboxylate isomers are thermodynamically more stable, while the 2-*exo*-isomers are the kinetically controlled products.[31,32] Bearing in mind these precedents, two stereoisomers might be expected from the cyclization of the amino nitriles derived from symmetrical ketones (**34b** and **34c**), while in the case of the amino nitriles derived from aldehydes (**34** and **35d–h**) the four stereosisomers **36–39**, shown in Scheme 6, might be formed. As shown in Table 2, the results depended mostly upon the steric volume of the starting amino nitrile R^1 and R^2 substituents, and upon the reaction time. Thus, similarly to the amino nitrile **1**, in the acetone derivative **34c** (entries 5 and 6), the cyclization was stereospecific toward the 2-*exo*-isomer **36c**, independently on the reaction time. However, in the *N*-benzyl-4-piperidone derivative **34b**, the results depended on the reaction time. Thus, within 3 h of reaction (entry 3), the 2-*exo*-isomer **36b** was the major reaction product in a 3:1 ratio, while after 8 days (entry 4) the thermodynamic controlled product **39b** was major in a **36b**:**39b** ratio of 1:4.

Respecting the aldehyde derivatives, the cyclization of each isolated acetaldehyde-derived epimer **34d** and **35d** was completely stereoselective toward the corresponding 2-*exo*-isomer **36d** and **37d**, respectively, with retention of the stereochemistry at the α-amino nitrile chiral center. This result allowed the assignment of the absolute configuration at that chiral center of **34d** and **35d** by correlation. In the other amino nitriles **34e–h** and **35e–h**, that configuration was tentatively assigned by comparison of their respective ^{1}H NMR

and HPLC data with those of **34d** and **35d**. Thus, in the major isomer **34** (*S*), the Trp 2-H, 3-H, and indole protons 1-H and 2-H appeared at a higher field than in the corresponding (*R*)-epimer **35**. Furthermore, the major isomer **34** showed higher t_R (Novapak C_{18}) than the respective minor one **35**.

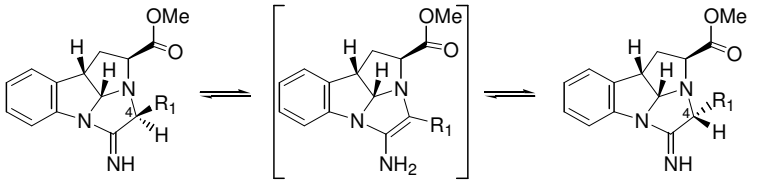
Table 2. Stereoselectivity of the cyclization of Trp-derived α-amino nitriles.

	Starting α-amino nitrile[a]				Pyrroloimidazoindole (%)[b]		
Entry	nº	R^1	R^2	Time (h)	**36**	**37**	**39**
1	**1**[c]	$(CH_2)_5$		1	100[c]		0
2	**1**[c]	$(CH_2)_5$		192	100[c]		0
3	**34b**[c]	$[(CH_2)_2]_2NBn$		3	74[c]		26
4	**34b**[c]	$[(CH_2)_2]_2NBn$		192	19[c]		81
5	**34c**[c]	Me	Me	1	95[c]		0
6	**34c**[c]	Me	Me	192	95[c]		0
7	**34d**	Me	H	2	71	0	0
8	**35d**	Me	H	2	0	72	0
9	**35d**	Me	H	24	100	0	0
10	**34e**	$PhCH_2$	H	24	72	0	21
11	**34e**	$PhCH_2$	H	96	64	0	34
12	**34e**	$PhCH_2$	H	360	25	0	72
13	**35e**	$PhCH_2$	H	10	96	0	0
14	**35e**	$PhCH_2$	H	24	90	0	7
15	**35e**	$PhCH_2$	H	360	26	0	74
16	**34f**	^{t}Bu	H	24	7	0	6
17	**34f**	^{t}Bu	H	48	7	0	13
18	**34f**	^{t}Bu	H	192	25	0	72
19	**34f**	^{t}Bu	H	360	13	0	84
20	**34f+35f**	^{t}Bu	H	24	41[d]	0	7[d]
21	**34g**	Ph	H	2	100	0	0
22	**34g**	Ph	H	24	100	0	0
23	**34g**	Ph	H	192	80	0	0
24	**35g**	Ph	H	2	100	0	0
25	**34h**	(*S*)-CH(Me)-NHZ	H	3	18	0	12
26	**34h**	(*S*)-CH(Me)-NHZ	H	144	0	0	48[e]
27	**35h**	(*S*)-CH(Me)-NHZ	H	3	70	0	0

[a]The **34**:**35** ratio was determined as ~2:1 by ^{1}H NMR or HPLC analysis of the crude amino nitrile mixture, except for **34,35e** and **34,35f**, where it was determined as ~3:2. [b]Isolated yields (%), except for entries 9–11, 14, 16–18, and 25, where the ratio was determined in the HPLC analysis of the reaction mixture. [c]As $R^1 = R^2$, **34** = **35**, **36** = **37**, and **38** = **39**. [d]70% of **34f** was recovered. [e]This low yield was due to the partial simultaneous replacement (38%) of the Z protecting group of **39h** by a trifluoroacetyl group.

Interestingly, both isolated acetaldehyde-derived epimers **36d** and **37d** exchanged slowly, and, at room temperature in $CDCl_3$ solution, the equilibrium of this exchange was achieved after 94 days with a **36d**:**37d** ratio of 4:1. Under the acid medium of the cyclization reaction, after 24 h, the epimerization of **37d** to **36d** was complete (Table 2, entry 9). As shown in Scheme 7, this epimerization must proceed through the enamine tautomer **40d**, although this tautomer was not detected, probably due to its short lifetime. In the

case of the other aldehyde derivatives bearing higher volume groups (**34**, **35e–h**), the epimer **37**, with the R^1 group towards the *endo*-face, was not obtained, and neither this isomer nor the corresponding enamine tautomer **40** were detected in the reaction mixture.



Scheme 7. Epimerization mechanism for pyrroloimidazoindoles **36d** and **37d**.

In most cases of the aldehyde-derived amino nitriles (**34** and **35d–f** and **h**), the steric volume of the R^1 substituents and their configuration affected their cyclization reaction time and this had an important influence on the stereoselectivity. Thus, the (*R*)-amino nitriles **35**, after the shorter reaction times required for their complete conversion (entries 8, 13, 20, and 27), yielded exclusively the kinetic controlled 2-*exo*-isomer **36** (or **37d** in the case of the acetaldehyde derivatives). However, prolonged reaction times favored the formation of the 2-*endo*-isomer **39** in the more constrained amino nitriles, such as in the phenylacetaldehyde derivative **35e**, where, after 15 days, the isomer **39e** was the major product, in a 3:1 ratio (entry 15). The (*S*)-amino nitriles **34**, which, except for the acetaldehyde and benzaldehyde derivatives **34d** and **34g**, required considerable longer reaction times, also gave the 2-*exo*-isomer **36** as major product of short reaction times (entries 10, 16, and 25), although with low % of cyclization. However, after longer reaction times, the thermodynamic controlled 2-*endo*-isomer **39** was the main reaction product (entries 12, 19, and 26), except for the acetaldehyde- and benzaldehyde-derived amino nitriles, which gave only the 2-*exo*-isomer (**36d** and **36g**, respectively). Interestingly, the epimer of **39** at position 4, **38**, was not obtained in any case. The configurational stability of the 2-*exo*-hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles **36a–36c**, and **36d–36g** was also studied. At room temperature in CH_3CN solution, conditions of the HPLC analysis, samples of all of these compounds remained unaltered after more than 15 days. After 8 days under the cyclization reaction conditions (a solution of each compound in CH_2Cl_2 was stirred at room temperature with a 50% of 85% H_3PO_4), the ketone derivatives **36a–36c**, and the acetaldehyde and benzaldehyde derivatives **36d** and **36g**, retained their 2-*exo*-configuration. However, the phenylacetaldehyde and pivalaldehyde derivatives **36e** and **36f** isomerized slowly to the respective 2-*endo*-isomer **39e** and **39f**, which after 20 days reached a **36**:**39** ratio of 1:4 and 2:3, respectively. In all cases, traces of the corresponding amino nitriles **34** and **35** (3–10%), in a time-independent ratio , were detected in the HPLC analysis of the reaction mixtures. This indicated that, in the acid medium, the α-amino nitriles were in equilibrium with their respective pyrroloimidazoindole derivatives, and, therefore, the cyclization could be considered as an acid-promoted tautomerization reaction. Interestingly, the 2-*exo* (**36**) to 2-*endo* (**39**) isomerization requires both the opening of the fused pyrroloimidazo system and the epimerization at position 4. Although we have not identified any intermediate of this isomerization, we think that it is more probable that the epimerization happens at the pyrroloimidazoindol state, *via* an enamine intermediate similar to **40**, than at the amino nitrile state. In our wide experience in amino acid-derived α-amino nitriles,[2–4] we have not observed epimerizations, either in basic or in acid media.

The configuration assignment of the hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles **36–39** was based on the NOE effects observed in their ^{1}H NOESY 1D spectra, shown in Figure 5. Furthermore, as it has been previously described for hexahydropyrrolo[2,3-*b*]indole derivatives,[31,32a] the *endo*-isomers **39** showed an upfield shift of the MeO signal in their ^{1}H NMR spectra, appearing at 3.02–3.29 ppm, and their coupling constant between 2-H and the 1-*endo*-H (H^a) were 0–2.5 Hz. Besides the 2-*exo*-isomers **36** were significantly more levorotatory than their respective 2-*endo*-isomers **39**.[32a]

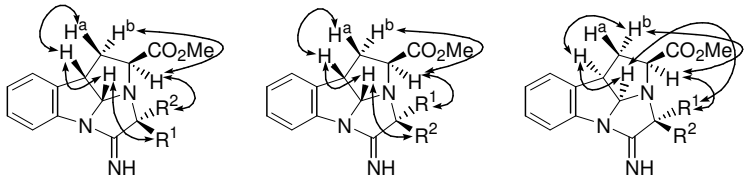


Figure 5. NOE effects observed in the ^{1}H NOESY 1D spectra.

The overall results of the above cyclization and configuration stability studies showed that the 2-*exo*-methoxycarbonyl tautomer **36** was the most stable in the benzaldehyde derivatives (**g**) and in the less hindered compounds [those derived from cyclohexanone (**a**), acetone (**c**) and acetaldehyde (**d**)], while in those more hindered compounds, such as those derived from *N*-benzyl-4-piperidone (**b**), phenylacetaldehyde (**e**), pivalaldehyde (**f**) and *N*-Z-alaninal (**h**), the 2-*endo*-methoxycarbonyl isomer **39** was the most stable. In the case of the aldehyde derivatives the results could be explained in terms of the 3D molecular models for the four pyrroloimidazoindoles **36–39**. Thus, in any case, the 2-*endo* isomer **38** would be the less stable, as both the methoxycarbonyl and the R^1 moieties would project towards the more constrained concave *endo*-face. The relative stability between **36**, **37** and **39** would depend mostly on the steric volume of the R^1 substituent, which, except for small groups, such as Me [acetaldehyde derivatives (**d**)], would have a high preference for an orientation towards the less hindered *exo*-face of the pyrroloimidazoindol framework, as in **36** or **39**. Finally, with the increase in volume of R^1, a destabilizing steric interaction of this group with the 2-methoxycarbonyl moiety, in a relative *cis*-disposition in the 2-*exo* isomer **36**, would displace the equilibrium towards the 2-*endo* isomer **39**, in which those groups would be in a relative *trans*-disposition.

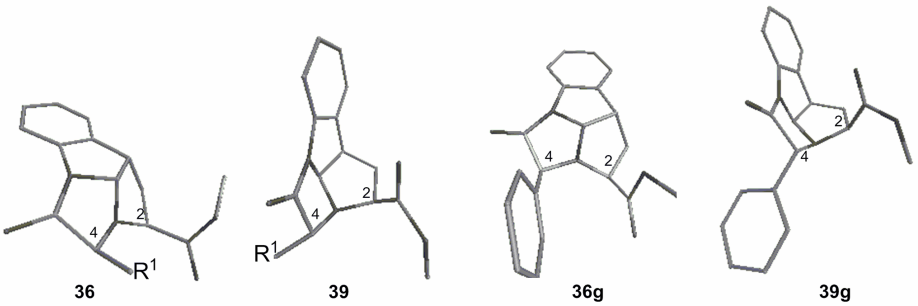


Figure 6. Chem 3D models of 2-*exo*- and 2-*endo*-isomers of the pyrroloimidazoindole derivatives **36** and **39** and those derived from benzaldehyde (**36g** and **39g**).

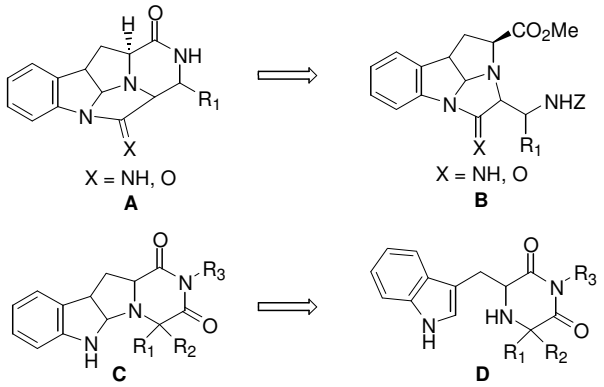
Although the steric volume of the phenyl group is higher than that of the phenylmethyl group,[36] the higher stability of the *exo*-tautomer **36g** versus the *endo* **39g** might be attributed to a possible non-bonding

secondary orbital interaction, possibly of the π–stacking type,[37] between the ester moiety and the 4-phenyl group, which would adopt a parallel *cis*-disposition, as shown in Figure 6.

In the case of the ketone derivatives (**a–c**), the stabilization of the 2-*endo* isomer in the *N*-benzyl-4-piperidone derivatives (**b**), with respect to the cyclohexanone (**a**) and acetone (**c**) derivatives, might also be due to the increase in steric hindrance, but some stabilizing electronic interaction of the *N*-benzyl group with the aromatic part of the pyrroloimidazoindol system cannot be ruled out.

2.5. Exploration toward pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole alkaloid analogues

In view of the growing number of indole alkaloids containing the pyrazino[1',2':1,5]pyrrolo[2,3-*b*]-indole ring system, as commented in section 1.2., we considered of interest to explore the synthesis of analogues of general formulas **A** and **C** shown in the retrosynthetic Scheme 8. Firstly, we undertook the synthesis of imidazopyrazinopyrroloindoles **A** from the *N*-Z-alanine-derived hexahydropyrrolo-imidazoindoles **36h** and **39h**, which required a first step of removing the Z-protecting group. However, several attempts of this deprotection under the usual conditions of Pd(C)-mediated hydrogenolysis were unsuccessful. The 2-*exo*-isomer **36h** was recovered unchanged after 24 h of hydrogenation in MeOH in the presence of 10% Pd(C) either at 1 or 3 atm of H_2, at room temperature or 50 ºC, and in the presence or absence of one equivalent of AcOH.

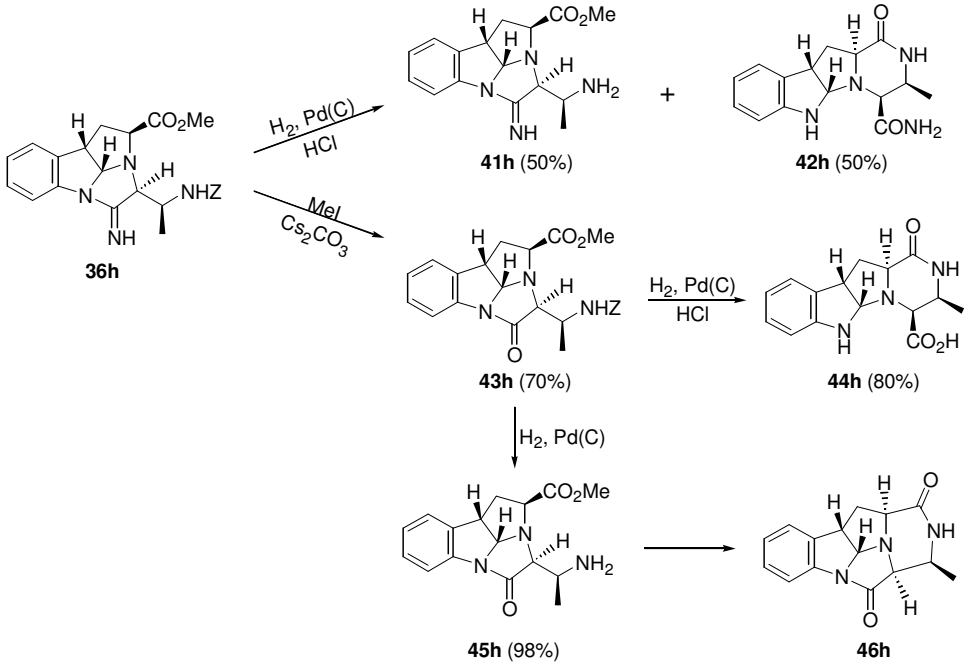


Scheme 8. Retrosynthesis of pyrazino[2'1':5,1]pyrrolo[2,3-*b*]indole derivatives.

Finally, as shown in Scheme 9, the hydrogenation in the presence of one equivalent of HCl led to a (1:1) mixture of the deprotected pyrroloimidazoindole **41h** and the pyrazinopyrroloindole **42h**, which could not be resolved. In the case of the 2-*endo*-isomer **39h**, the hydrogenation in the presence of one equivalent of HCl led to a complex mixture of decomposition.

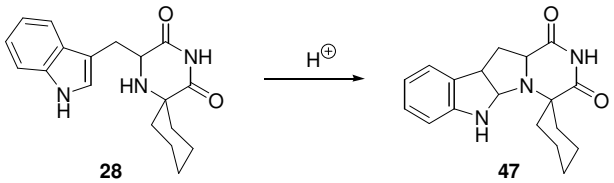
In view of the difficulties for removing the Z-protecting group of **36h** and **39h**, which could be due to catalyst poisoning by the amidine group, next we turned our attention to the lactam analogue **43h**, which was obtained from **36h** in 70% yield by applying the method of alkylative hydrolysis of the amidine group commented in section 2.3. The hydrogenation of the lactam derivative **43h** in the presence of one equivalent of HCl led to the product of imidazole opening **44h**, along with a 20% of the wished deprotected pyrroloimidazoindole **45h**. This unprotected compound was cleanly obtained by 10% Pd(C)-mediated hydrogenolysis of **43h** at 1 atm of H_2 pressure and room temperature. Unfortunately, all attempts of cyclization of **45h** to the fused pyrazine ring of **46h** were unsuccessful. Thus, the treatment of **45h** with saturated solution of NH_3 in MeOH, as described by the Danishefsky's group for the synthesis of

ardeemins,[32b] led to a complex mixture of decomposition. Heating in *n*BuOH in the presence of 10% of AcOH[38] also produced decomposition. Under reflux in xylene, method used in our laboratory for lactamization of amino esters to monocyclic piperazines,[2a] **45h** was recovered unaltered. These unsatisfactory results, which could be due to the highly constrained structure of the proposed pentacyclic ring system of **46h**, discouraged a similar study with the 2-*endo*-pyrroloimidazoindole **39h**.



Scheme 9. Unsuccessful studies on the synthesis of imidazopyrazinopyrroloindole derivatives.

Finally, taking into account the precedents of the cyclative tautomerization of Trp-derived 2,5-dioxopiperazines in acid media,[39] we tried the tautomerization of the 2,6-dioxopiperazine derivative **28** to the corresponding pyrazinopyrroloindole **47** (Scheme 10) by treatment with 85% H_3PO_4 or neat TFA, to explore the synthesis of pyrazino[2'1':5,1]pyrrolo[2,3-*b*]indole derivatives **C** (Scheme 8). However, all attempts of that tautomerization, under different reaction conditions (acid concentration, temperature, and time), were unsuccessful, recovering the starting material **28** unaltered.

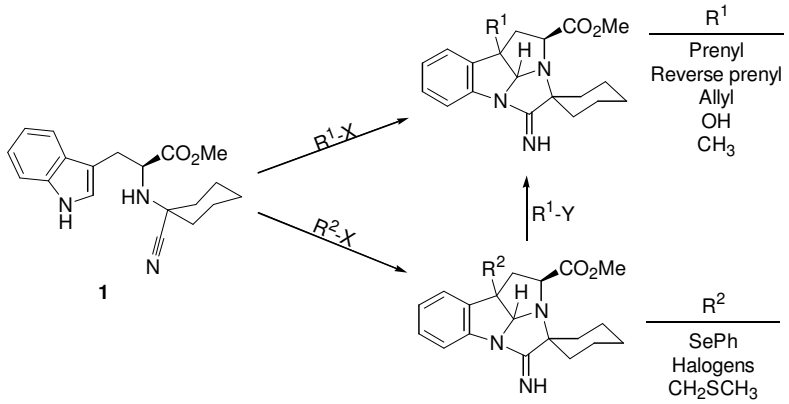


Scheme 10. Unsuccessful synthesis of the pyrazino[2'1':5,1]pyrrolo[2,3-*b*]indole derivative **47**.

3. 10b-Substituted hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles

As shown in Figures 2 and 3, most of indole alkaloids contain substituents at the indoline C_3 position, such as methyl, alkylallyl (prenyl or reverse-prenyl), or hydroxy groups. This fact prompted us to study the incorporation of these substituents (R^1) into the 10b position of 1,2,4,5,10b,10c-hexahydropyrrolo-[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles. As shown in Scheme 11, two alternative strategies were designed to

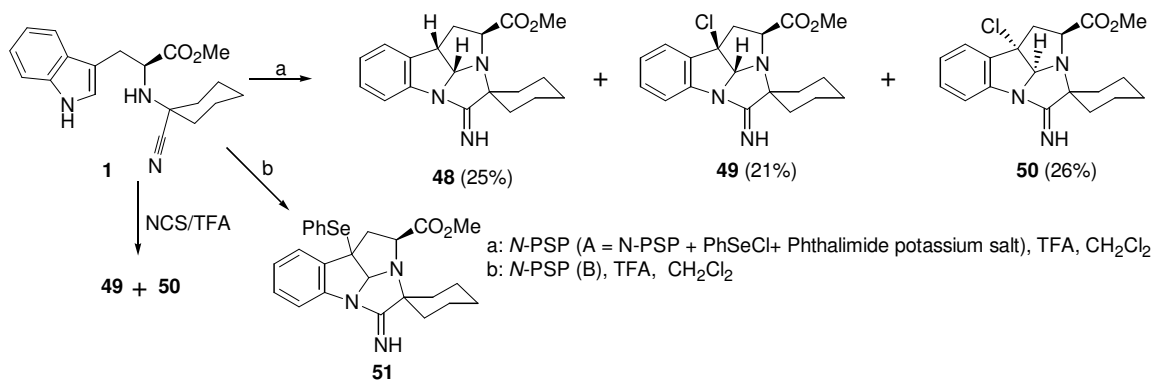
access to these pyrroloimidazoindoles, depending on the substitution at 10b: a) direct introduction of the substituent R^1 upon amino nitrile **1**, by domino electrophile addition-cyclizations; b) introduction of the substituent R^1 upon the preformed 1,2,4,5,10b,10c-hexahydropyrrolo [1',2',3':1,9a,9]imidazo[1,2-*a*]indole scaffold, by the appropriate transformation of substituent R^2 into R^1.



Scheme 11. Alternative strategies for the synthesis of 1,2,4,5,10b,10c-hexahydropyrrolo-[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles substituted at position 10b.

3.1. Halogenation

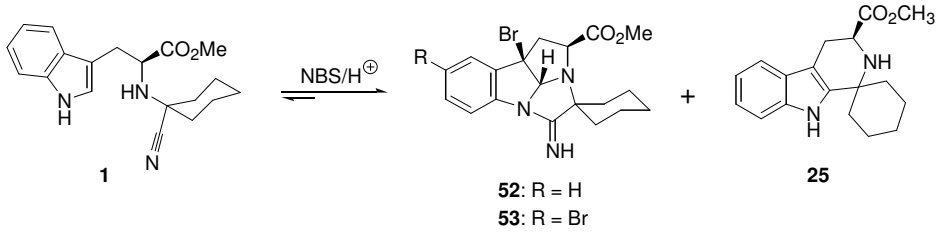
To introduce a prenyl or reverse prenyl group into the 10b position of the hexahydropyrrolo-[1',2',3':1,9a,9]imidazo[1,2-*a*]indole skeleton, we devised a strategy similar to the two-step procedure developed by the Danishefsky's group for the synthesis of hexahydropyrrolo[2,3-*b*]indoles substituted at C_{3a} position.[32b] This strategy involved a first step of domino electrophilic selenation-cyclization of tryptophan derivatives, by treatment with *N*-phenylselenophthalimide (*N*-PSP), followed by the replacement of the phenylselenyl radical by the appropriate functionality. According to this precedent, we initially tried the reaction of amino nitrile **1** (Scheme 12) with commercial *N*-PSP in the presence of *p*-toluenesulfonic acid (*p*-TSA) or pyridinium *p*-toluenesulfonate (PPTS). However, in both cases the amino nitrile was recovered unaltered. Then, we decided to replace *p*-TSA by TFA. Surprisingly, as shown in Scheme 12, after 7 days of treatment with 1.5 equivalents of that commercial *N*-PSP in a (1:4) mixture of TFA/CH_2Cl_2, amino nitrile **1** provided a 47% of an (~1:1) mixture of the 2-*exo*/2-*endo* diastereoisomers of the 10b-chloro-pyrroloimidazoindoles **49** and **50**, along with a 25% of the unsubstituted compound **48**.[40]



Scheme 12. Cyclative chlorination of α-amino nitrile **1**.

An investigation of the origin of the chloro in this reaction led us to the commercial *N*-PSP. The ^{1}H NMR and ES-MS analyses of this reagent showed that it contained important percentages of PhSeCl (~35%) and potassium phthalimide (~50%), which are used as starting materials in the preparation of *N*-PSP.[41] Therefore, the chlorination reagent could have been PhSeCl or *N*-chlorophthalimide, this last could be formed in the reaction medium. When we repeated the reaction, using commercial *N*-PSP from a different supplier, whose purity had been previously checked, the unsubstituted pyrroloimidazoindole **48** was the only reaction product (23%).

Although the unreactivity of **1** toward *N*-PSP closed us the access to 10b-substituted compounds *via* phenylselenyl derivatives, the unexpected chlorination opened a possible alternative access *via* replacement of the halogen. Hence, we studied the optimization of the electrophilic chlorination-ring closing reaction, focusing our attention on its stereocontrol and on the introduction of other halogens. To this aim, *N*-chlorosuccinimide (NCS) was firstly used as chlorination reagent. The treatment of amino nitrile **1** with one equivalent of NCS in 10% TFA in CH_2Cl_2, at room temperature for 30 min, led to 90 % of a (4:1) mixture of the diastereoisomeric chlorides **49** and **50**, which was chromatographically resolved. Interestingly, after 5 days at room temperature, the diastereomeric ratio in the reaction mixture evolved to a (3:2) ratio. However, pure diastereoisomers **49** and **50** in solution of 10% TFA in CH_2Cl_2 were stable at room temperature and no interconversion was observed after 7 days. With the aim of improving the stereocontrol, the chlorination was then carried out under kinetic control conditions (–40 ºC), which led exclusively and quantitatively to the 2-*exo* diastereoisomer **49** after 3 h of reaction. A similar and parallel study was carried out for the bromination-cyclization of **1** with *N*-bromosuccinimide (NBS) also in 10% TFA in CH_2Cl_2. The results were somewhat different. Thus, at room temperature, a complex reaction mixture was obtained from which only a 4% of the 10b-bromo derivative **52**, with a 2-*exo* configuration, and a 25% of the tetrahydro-β-carboline derivative **25** could be isolated (Scheme 13).



Scheme 13. Cyclative bromination of amino nitrile **1**.

Table 3. Optimization of bromination conditions of **1**.

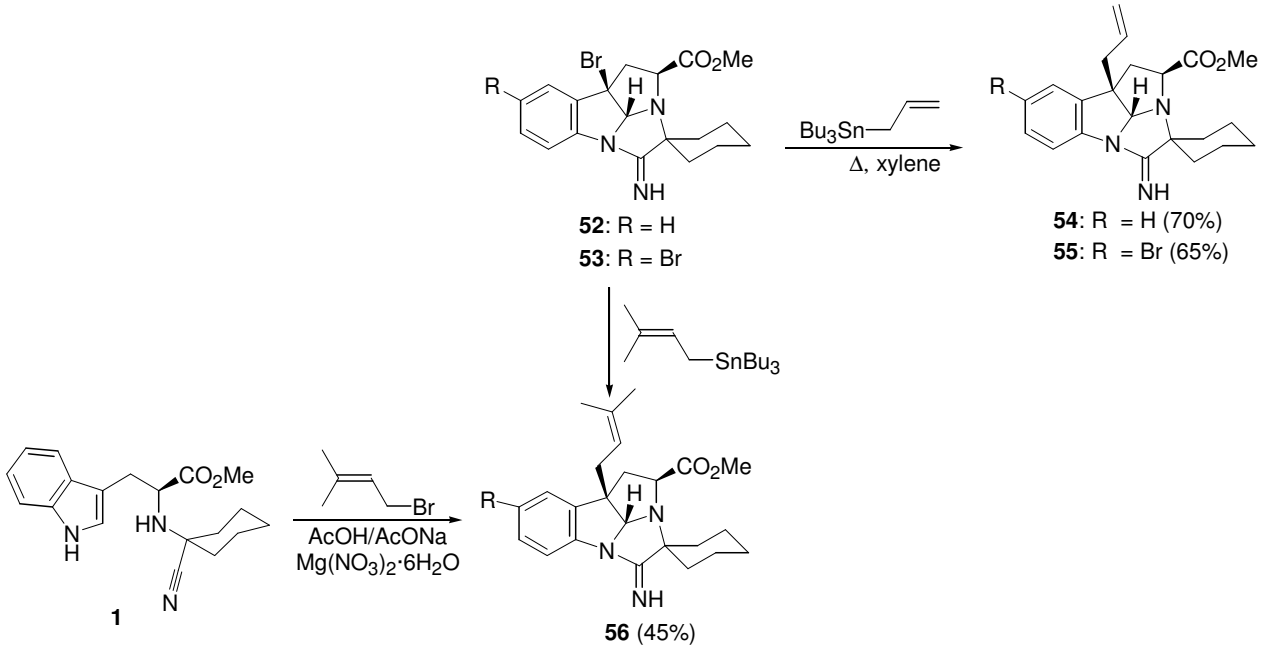
				Yield (%)[a]		
Entry	NBS equiv.	T (ºC)	T (h)	**52**	**25**	**53**
1	1	25	96	4	25	0
2	1	50	24	7	30	0
3	1	–40	3	91	0	0
4	2	–40	3	0	0	94

[a]Isolated yields.

As shown in Table 3, the increase in the reaction temperature, along with the decrease in reaction time, did not improved the bromination yield (entry 2). However, the use of one equivalent of NBS at −40 ºC (entry 3) yielded a 91 % of the monobrominated compound **52**, whereas the use of two equivalents of NBS (entry 4) led to the 9,10b-dibrominated derivative **53** in 94% yield, also with a 2-*exo* configuration. All attempts of similar iodo-cyclization of **1**, by reaction with *N*-iodosuccinimide (NIS), were unsuccessful.

3.2. Allylation and prenylation

In view of the good yields obtained in the synthesis of 10b-bromo-pyrroloimidazoindoles **52** and **53**, we explored the utility of these compounds for the replacement of the 10b-bromo substituent by allyl and alkylsubstituted allyl groups, by reaction with the appropriate allylstannane derivative in the presence of the free radical initiator AIBN. Initially, under the reaction conditions described for the allylation of 3a-bromo-hexahydropyrrolo[2,3-*b*]indoles,[42] **52** and **53** were recovered unaltered after 2 days of treatment with allyltributyltin in refluxing benzene. A similar result was obtained when the benzene was replaced by toluene. However, when this reaction was carried out in refluxing xylene, the corresponding 10b-allyl derivatives **54** and **55** (Scheme 14) were obtained in 70 and 65% yield, respectively. These good results induced us to try these reaction conditions for the introduction of the prenyl or reverse prenyl group, having in mind their possible isomerization,[43] by reaction of the 10b-bromo derivatives **52** and **53** with prenyl tributylstannane.



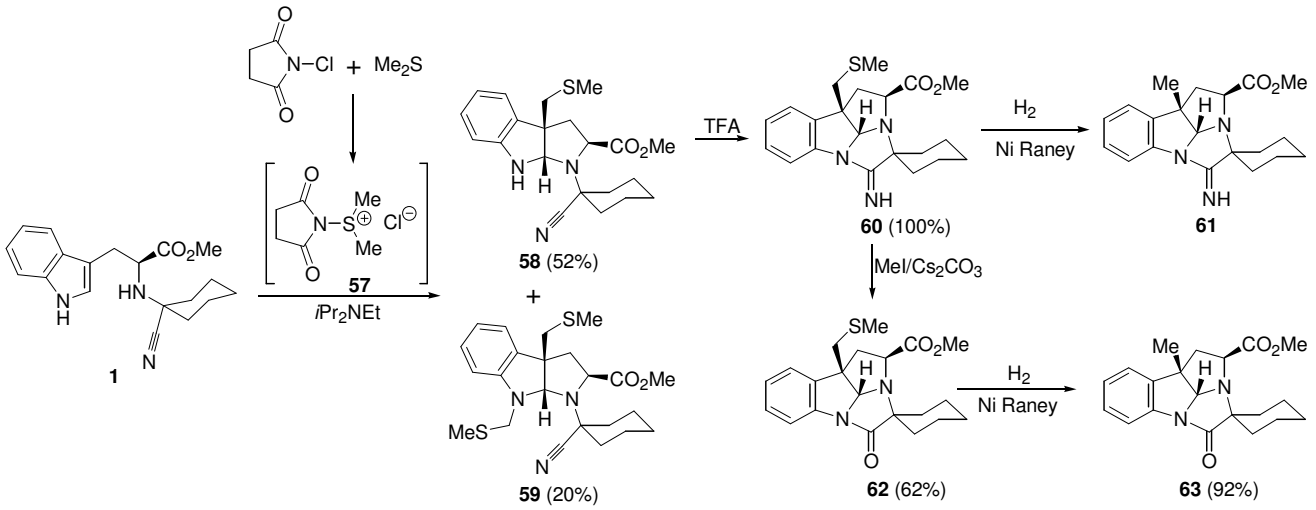
Scheme 14. Synthesis of 10b-allyl- and 10b-prenyl-hexahydropyrroloimidazoindoles.

Unfortunately, as described by D. Crich and co-workers in their report on allylation of 3a-bromo-hexahydropyrrolo[2,3-*b*]indoles,[42] the bromo derivatives **52** and **53** were recovered unchanged. Finally, the procedure developed by the Casnati's group for the insertion of isoprene units into the indole C_3 position[44] was explored as an alternative for the direct introduction of the prenyl group into the α-amino nitrile **1**, by reaction with prenyl bromide in AcOH buffer. In the case of tryptophan or tryptamine derivatives, this methodology leads to 3a-prenyl-hexahydropyrroloindoles, *via* a domino prenylation-cyclization, as

described for the synthesis of pseudophrynaminol[45] and tryprostatin B,[32c] although in low yields. As shown in Scheme 14, the treatment of **1** with prenyl bromide and $Mg(NO_3)_2 \cdot 6H_2O$ in AcOH/AcONa buffer led, with complete stereoselectivity, to the 2-*exo*-10b-prenyl-pyrroloimidazoindole **56** in 45% yield. Interestingly, a similar treatment of **1** with allyl bromide did not give the product of cyclative allylation **54**.

3.3. Methylation

The construction of the 10b-methyl-hexahydropyrroloimidazoindole system was envisaged by applying a strategy similar to that reported by the Nakagawa's group for the synthesis of physostigmine.[32d] This strategy involves the introduction of a methylthiomethyl group into tryptophan derivatives by a cyclative alkylation with the Corey-Kim reagent,[46] followed by reductive desulfurization of the methylthiomethyl to a methyl group. The tryptophan and cyclohexanone-derived α-amino nitrile **1** was used as substrate for the study of this methodology. As shown in Scheme 15, the reaction of **1** with two equivalents of the Corey-Kim reagent (**57**) [prepared *in situ* by reaction of *N*-chlorosuccinimide with dimethyl sulfide in the presence of 2.4 equivalents of diisopropylethylamine (DIEA)] led to a mixture of 52% of the 3a-monoalkylated-hexahydropyrrolo[2,3-*b*]indole **58**, along with a 20% of the 3a,8-dialkylated product **59**.[47] With the aim of avoiding the formation of this dialkylation product, the reaction was also performed using only one equivalent of the Corey-Kim reagent. However, in this case the conversion was very low, obtaining only 16% of **58**, and recovering 53% of the starting amino nitrile. Interestingly, the ring closing alkylation proceeded with complete stereoselectivity toward the 2-*exo*-diastereoisomer, while the Nakagawa's group, under the same reaction conditions, reported an (~1:1) 2-*exo*/2-*endo* diastereoisomeric ratio.[32d] In the next step, the treatment of the 3a-monoalkylated compound **58** with 10% solution of TFA in CH_2Cl_2 quantitatively led to the 5-imino-pyrroloimidazoindole tautomer **60**, which results from the electrophilic cyclization of indole NH onto the protonated cyano group.



Scheme 15. Synthesis of 10b-methyl-hexahydropyrroloimidazoindoles.

All attempts of reductive desulfurization of the methylthiomethyl group of **60**, by heating in the presence of Ni Raney[48] or by catalytic hydrogenation in the presence of this catalyst,[32d] were unsuccessful, recovering the starting material unchanged. As we had previously observed for the hydrogenolysis of the benzyloxycarbonyl-protecting group from the pyrroloimidazoindoles **36h** and **39h** (section 2.5.), the

difficulty of catalytic reductive desulfurization could be due to catalyst poisoning by the amidine group. Hence, we turned our attention from the amidine to the lactam analogue **62**, obtained in 62% yield by alkylative hydrolysis of the amidine group of **60**, carried out by treatment with MeI and Cs_2CO_3 in CH_3CN at 80 ºC for two days. Then, the hydrogenolysis of the methylthiomethyl group of **62** to give **63** was successfully achieved by hydrogenolysis in EtOH at 80 ºC in the presence of Ni Raney under 2 atm of H_2.

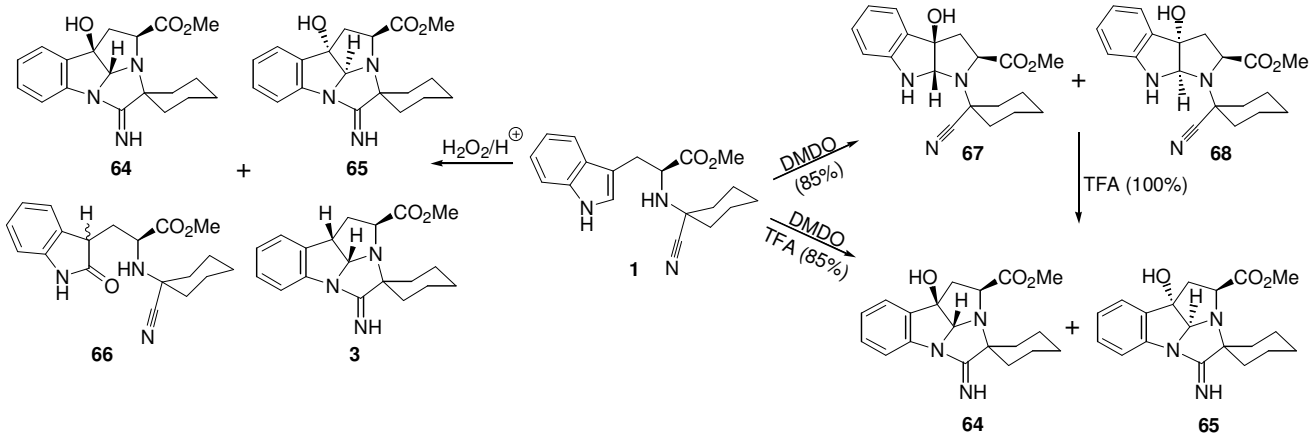
3.4. Oxidation

The synthesis of the 10b-hydroxy-hexahydropyrroloimidazoindole skeleton was first attempted by applying the Crich's methodology of oxidation of hexahydropyrrolo[2,3-*b*]indoles with ceric ammonium nitrate (CAN)[42] to the 10b-unsubstituted hexahydropyrroloimidazoindole **3**. However, this compound was recovered unaltered after three days of treatment with 5 equivalents of CAN. Then, the introduction of the hydroxy group was approached by cyclative oxidation of the corresponding tryptophan-derived α-amino nitrile. As oxidizer, we decided to try first H_2O_2, a commercial, cheap and environmental friendly reagent. Taking into account that, as above mentioned, the cyclization to the hexahydropyrroloimidazoindole system requires the cyano activation by protonation, this oxidation was studied in acid media. As shown in Scheme 16, the treatment of amino nitrile **1**, dissolved in a 10% solution of TFA in CH_2Cl_2, with 4% of H_2O_2 (33% solution in H_2O) at 0 ºC led, after 3 h of reaction, to the two diastereoisomeric 10b-hydroxy-hexahydropyrroloimidazoindoles **64** (54%) and **65** (13%), along with the 2-oxoindolines **66** (11%), traces of the 10b-unsubstituted hexahydropyrroloimidazoindole **3** (1%) and a 21 % of H-Trp-OMe, resulting from the amino nitrile degradation in the acid medium.[47] Diastereoisomers **64** and **65** were chromatographically resolved, however, the epimeric mixture of 2-oxoindolines **66** could not be resolved. To minimize the amino nitrile degradation and the formation of oxoindolines, a reaction condition optimization study was carried out. The results of this study (Table 4) showed that the increase in the H_2O_2 concentration lowered the overall yield of **64** and **65** due to the increase in oxoindolines **66**, while the increase in the TFA concentration or the temperature led to an increase in degradation products. Finally, the replacement of TFA by 85% H_3PO_4 as acid medium (entry 9) produced a significant increase in the overall yield of the desired 10b-hydroxy substituted compounds **64** and **65** (86%).

Taking into account that currently dimethyldioxirane (DMDO), due to its good efficacy and selectivity, is the most used oxidizer of tryptophan derivatives to 3a-hydroxy-pyrroloindoles,[49] we decided to study the oxidation of amino nitrile **1** also with this non-commercial reagent, which was freshly prepared as a 0.05 M solution in acetone.[50] Under the reaction conditions reported by the Danishefsky' group,[49a,b] the treatment of **1**, dissolved in CH_2Cl_2, with 1.2 equivalents of the acetone solution of DMDO at −78 ºC gave an 85% of a (7:1) diastereomeric mixture of the 3a-hydroxy-hexahydropyrrolo[2,3-*b*]indoles **67** and **68**, which could not be separated (Scheme 16). TLC and ^{1}H NMR analysis showed the instability of this mixture and the appearance of degradation products. Therefore, without further purification, it was treated with a 10% solution of TFA in CH_2Cl_2. This treatment quantitatively produced the corresponding 10b-hydroxy-hexahydropyrroloimidazoindoles **64** and **65**. The parallel treatment of amino nitrile **1** with DMDO in the presence of a 10% of TFA at −78 ºC directly led to **64** and **65**, in the same 2-*exo*:2-*endo* diastereomeric ratio (7:1) and in the same overall yield (85%). Interestingly, both H_2O_2 and DMDO gave similar overall yield of 10b-hydroxy-hexahydropyrroloimidazoindoles, although the stereoselectivity of DMDO for the 2-*exo*-diastereoisomer **64** was higher. This higher stereoselectivity is related with the lower reaction temperature,

which favors this kinetic control product. In the case of using H_2O_2, the aqueous phase that contains this reagent froze below 0 ºC and the oxidation did not take place.

The structural assignment of pyrroloimidazoindoles **64** and **65**, as well as that of the other 10b-substituted-pyrroloimidazoindoles commented in previous sections (3.1.–3.3.), was based on their ES-MS and NMR data. The ^{1}H NMR spectra showed the disappearance of the indole NH and 2-H protons and the appearance of a singlet (δ~5.32–6.00 ppm), corresponding to the 10c-H, while the ^{13}C NMR spectra showed the conversion of the nitrile carbon (121.6 ppm) into the amidine or lactam carbon (172–182 ppm) and the transformation of the aromatic indole C_3 and C_2 carbons into the two new aliphatic carbons C_{10b} (49–85 ppm) and C_{10c} (89–96 ppm), respectively. The stereochemistry at these fusion carbons was established on the basis of the NOE correlations observed in the 1D NOESY spectra, as above stated. Furthermore, as it has been described for hexahydropyrrolo[2,3-*b*]indole derivatives,[31,32a] the 2-*endo*-10b-hydroxypyrrolo imidazoindole **65** showed an upfield shift of 0.64 ppm for the MeO signal in its ^{1}H NMR spectrum and it was significantly less levorotatory than its respective 2-*exo*-diastereoisomer **64**.



Scheme 16. Synthesis of 10b-hydroxy-hexahydropyrroloimidazoindoles.

Table 4. Optimization of reaction conditions for the H_2O_2-mediated oxidation of **1**.

		Acid conc.	H_2O_2 conc.			Yield (%)[a]				
Entry	Acid	(%)[b]	(%)[b]	T (ºC)	t (h)	**64**	**65**	**66**	**3**	H-Trp-OMe
1	TFA	10	4	0	3	54	13	11	1	21
2	TFA	10	10	0	2	23	10	19	12	36
3	TFA	10	20	0	3	30	16	24	8	22
4	TFA	10	35	0	3	32	18	50	0	0
5	TFA	10	35	25	1	23	6	46	3	22
6	TFA	20	10	0	2	16	8	13	12	51
7	TFA	40	4	0	2	6	3	17	4	70
8	TFA	40	35	25	1	10	3	8	7	72
9	H_3PO_4	10	4	0	5	56	30	9	1	4

[a]Yields were determined by ^{1}H NMR analysis, except for entries 1 and 9, where yields were of isolated compounds. [b]% in CH_2Cl_2 solution.

4. Conclusions

This review shows once again the high potential of amino acid-derived α-amino nitriles for generating diversity of privileged scaffolds, now, particularly in the field of indole alkaloids. Thus, the acid treatment of tryptophan-derived α-amino nitriles leads, *via* a domino cyclative tautomerization, to the formation of the novel 1,2,4,5,10b,10c-hexahydropyrrolo[1',2',3':1,9a,9] imidazo[1,2-*a*]indole skeleton, which combines in its structure the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*] indole and 2,3,9,9a-tetrahydroimidazo[1,2-*a*]indole ring systems, both present in a growing class of indole alkaloids. Two or three new stereogenic centers are generated in this tautomerization with complete or high stereselectivity, depending on the substituents of the starting amino nitrile. The time and stereoselectivity of this reaction depends mostly both on the steric volume of the substituents at the amino nitrile and on its stereochemistry. Unhindered amino nitriles give exclusively a 2-*exo*-isomer, while, hindered amino nitriles, which require longer reaction times, provide this isomer under kinetic control. Under thermodynamic control, hindered amino nitriles yield a 2-*endo*-isomer as the main reaction product, except for benzaldehyde-derived α-amino nitriles, where a favourable electronic interaction between the phenyl and methoxycarbonyl groups at C_4 and C_2 positions, in a relative *cis*-disposition, might be responsible of the formation of the 2-*exo*-isomer as the only cyclization product.

Similarly, 10b-substituted-1,2,4,5,10b,10c-hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles are obtained by highly stereoselective domino cyclative electrohile additions on tryptophan-derived α-amino nitriles. The complete process of cyclization requires the acid mediated activation of the cyano group, which is transformed into an endocyclic amidine. In absence of acid, addition of the electrohile and partial cyclization to 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole takes place. Acid treatment of this hexahydropyrrolo[2,3-*b*]indole intermediate also produces the corresponding 10b-substituted-1,2,4,5,10b,10c-hexahydropyrrolo [1',2',3':1,9a,9]imidazo[1,2-*a*]indole. The application of this methodology has allowed the introduction of halogens and the prenyl, methylthiomethyl and hydroxyl groups into the 10b position. The 10b-halo derivatives are good intermediates for the introduction of other groups into the 10b position, such as allyl, by replacement of the halogens. Similarly, the methylthiomethyl group can be precursor of the methyl group by catalytic desulfurative hydrogenolysis.

The endocyclic amidine group can be acetylated or benzyloxycarbonyl-proteced under standard reaction conditions. However, the cycle strain does not allows the introduction of the *tert*-butoxycarbonyl-protecting group. Finally, lactam analogues are easily obtained by alkylative hydrolysis of the amidines.

Acknowledgments

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SYNTHESIS OF FUNCTIONALIZED INDAZOLES AND THEIR TRIS(INDAZOLYL)BORATE TRIPODAL DERIVATIVES AS BUILDING BLOCKS FOR THE PREPARATION OF MOLECULAR ROTARY MOTORS

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Abstract. *The synthesis of functionalized indazoles, using a ring-closure reaction or by aromatization of pyrazole-fused cyclohexanes, is surveyed with a special focus on the functionalization at the 6-position of the indazole ring. These building blocks give access to bifunctional tris(indazolyl)borate ligands designed to anchor metallic complexes on various surfaces. These tripodal ligands integrate three pendant ester or thioether groups oriented to anchor complexes onto an oxide or a metallic surface, respectively. They have been subsequently used as stator in a family of single molecular rotary motors.*

Contents

1. Introduction

Although natural compounds bearing an indazole structure are rare,[1] the chemistry of synthetic indazoles is very developed. A number of indazoles possesses important pharmaceutical activity such as

dopamine antagonists, anti-inflammatory, analgesic or antipyretic agents.[2] Other derivatives have herbicide, bactericide, fungicide properties and are also present in the dyes industry.[3] Indazoles and their relative pyrazoles have also been used as ligands in coordination chemistry since the discovery in the late sixties of the tris(pyrazolyl)borate ligand by Trofimenko.[4] This family of tridentate ligands, also known as scorpionate ligands, has been developed in an increasingly wide field of chemistry, ranging from bio-inorganic, organometallic and coordination chemistry to catalysis and material sciences.[5] This last aspect has been extensively studied with a particular interest in the modification of the functional groups connected to the pyrazolyl moiety in order to control or modify the steric and electronic environment surrounding the metal center.

In the last decade, the continuous improvement of near-field microscopy techniques such as Scanning Tunneling Microscopy (STM) and Atomic Force Microscopy (AFM) has led to the imaging and the study of physico-chemical properties of various molecules.[6] These techniques allow the visualization and manipulation of only one molecule and therefore the electrical[7] and mechanical properties[8] of a single molecule deposited on a surface can be investigated. Since single molecule experiments require the control of the shape of the molecule deposited, the design and the synthesis of rigid molecules able to be covalently attached on surfaces with a minimum number of degrees of freedom is an active field of research.[9] In particular, the movement of a molecule can be efficiently restricted by attaching the molecule to a surface with a tripod[10] which not only prevents the translation but also gives a very efficient control on the geometry of the whole architecture thanks to the three points of attachment. Therefore, a structurally rigid bifunctional molecule combining coordinating sites and anchoring groups is of special interest since it would allow the covalent attachment of coordination complexes on a surface, for instance giving rise to surface-mounted molecular gears or motors.[11,12]

The hydrotris(indazolyl)borate (Tp^{4Bo}) ligand, first synthesized in 1995,[13] seems a better candidate than tris(pyrazolyl)borate to perform this role. First it is larger, but the increase in size is not accompanied by a decrease in the rigidity of the molecule. Second, by withdrawing the metal away from the surface, it allows to minimize interferences caused by metal-surface interactions, which is particularly important for near-field microscopy experiments. The rigidity of its indazolyl fragments, conjugated with its tripodal shape, should make it a good candidate for surface deposition of metal complexes.

After a short review of the most common and efficient methodologies to synthesize indazoles, we will present the synthesis of two new scorpionate ligands incorporating functional groups on the indazole rings, designed to interact with metallic or oxide surfaces, and their integration in ruthenium complexes to yield some promising molecular motors.

2. Synthesis of the indazoles

2.1. General aspects

There are three tautomeric forms for indazole. However, unsubstituted indazole only exists as 1*H*-indazole, 2*H*- and 3*H* -indazole (Figure 1) being present in *N*-substituted indazole derivatives.[14]

Tautomeric equilibria between 1*H*- and 2*H*-indazole have been investigated by thermochemical and photophysical techniques as well as by calculations.[15] The results indicate, for example, that 1-methyl-1*H*-indazole is 14.2 kJ more stable than 1-methyl-2*H*-indazole.

In most cases, the synthesis of an indazole ring is conducted using a ring-closure reaction or by aromatization of pyrazole-fused cyclohexanes.

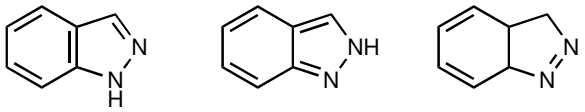
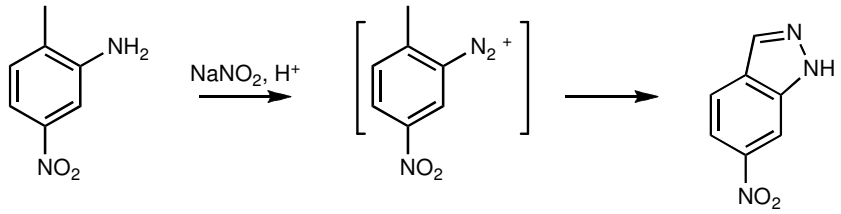


Figure 1. Tautomeric forms of indazole.

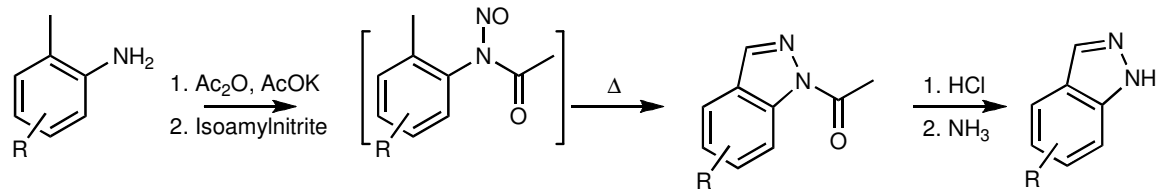
2.2. Synthesis from 2-methylaniline *via* a ring-closure reaction

The standard method for synthesizing indazoles involves ring-closure reactions which form one or two bonds of the pyrazole ring, for which 1,2-disubstituted benzenes of the appropriate type are the most common starting materials.[16] For example, 2-methylaniline (*o*-toluidine) reacts with sodium nitrite in protic solvents under acidic conditions to yield the diazonium derivative which undergoes a spontaneous ring-closure reaction to give access to a wide range of substituted indazoles depending on the substituents present on the starting phenyl ring. However, this synthesis was initially limited to diazonium salts bearing electron-withdrawing groups (*i.e.* bromo or nitro) on the aromatic ring (Scheme 1).[16] This methodology was later extended to diazonium salts with electrodonating groups on the aromatic ring by Bartsch and Yang in 1984, the difference being the use of a phase transfer catalysis.[17]



Scheme 1. Synthesis of electrodeficient indazoles by the diazotation of substituted *o*-toluidines.

The Jacobson indazole synthesis is another method of choice to prepare electron-rich indazoles.[18] The synthesis also starts with an *o*-toluidine, which undergoes acetylation followed by a nitrosation and finally a thermal cyclization to afford 1-acetylindazole. In the last step, the hydrolysis of the acetyl group by treatment with hydrogen chloride and ammonia gives the indazole (Scheme 2).



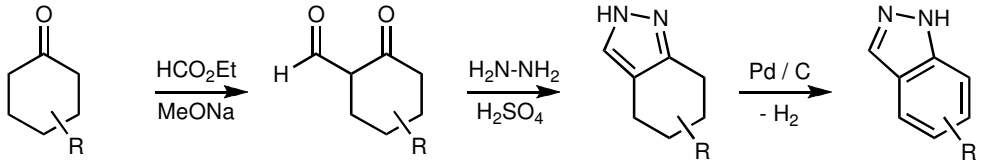
Scheme 2. Jacobson indazoles synthesis *via* acetylation, nitrosation and cyclization of an *o*-toluidine.

The use of isopentyl nitrite as the nitrosation agent in a one-pot reaction avoids the isolation of unstable and explosive *N*-nitroso compounds.

These two synthetic procedures give indazoles in 40–80% overall yield.

2.3. Synthesis *via* the aromatization of a fused pyrazole-cyclohexane

Indazoles can also be obtained by the ring-closure reaction of 2-acylcyclohexanones with hydrazine to yield 4,5,6,7-tetrahydroindazoles directly.[19] These compounds may then be aromatized on palladium/carbon providing a versatile two-step route to indazoles and to ring-fused indazoles. The 2-(hydroxymethylene) cyclohexanone obtained from functionalized cyclohexanone and ethyl formate in basic conditions, reacts with hydrazine hydrate in acidic conditions to give the 4,5,6,7-tetrahydroindazole. Aromatization leads the corresponding indazole (Scheme 3).



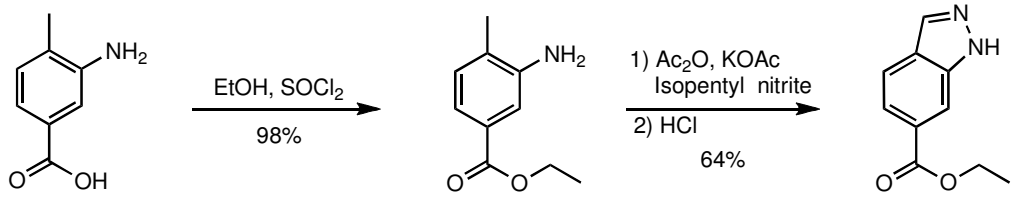
Scheme 3. Synthesis of substituted indazoles by aromatization of a fused pyrazole-cyclohexane.

This strategy is very attractive since it uses the relatively easily accessible pyrazoles as key intermediates. However, the aromatization step is conducted in relatively harsh conditions which are not always compatible with a wide range of functional groups. For instance, the aromatization of the tetrahydroindazole precursor of 7-methylindazole requires a temperature of 280 °C.[19]

2.4. Application to the synthesis of 6-functionalized indazoles

2.4.1. The 6-(ethoxycarbonyl)indazole building block

6-(Ethoxycarbonyl)indazole was synthesized in two steps starting from 3-amino-4-methylbenzoic acid (**1**) (Scheme 4). The protection of the carboxylic acid function was performed *via* an esterification of **1** in ethanol mediated by thionyl chloride following the procedure of Hosangadi and Dave.[20]



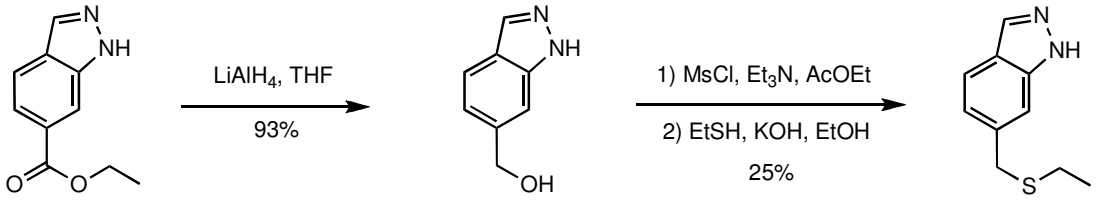
1 **2** **3**

Scheme 4. Synthesis of 6-(ethoxycarbonyl)indazole.

Ethyl 3-amino-4-methylbenzoate (**2**) was obtained quantitatively. The conversion of **2** into 6-(ethoxy-carbonyl)indazole (**3**) was performed using the Jacobson procedure[18] by reaction of **2** with potassium acetate, acetic anhydride and isopentyl nitrite in refluxing toluene to give 1-acetyl-6-(ethoxy-carbonyl)indazole which was deprotected with HCl, followed by neutralization of the crude mixture with ammonia to afford **3** as a colorless precipitate in 64% yield. The formation of the indazolyl ring was demonstrated by ^{1}H-NMR, with a characteristic NH resonance at 11 ppm in $CDCl_3$. This synthesis can be performed on the 5 to 10 gram scale which allowed us to use this indazole as starting material for other purposes.[21]

2.4.2. The 6-[(ethylsulfanyl)methyl]indazole building block

The synthesis of 6-[(ethylsulfanyl)methyl]indazole **5** was achieved in two steps from **3** which is easily accessible in large quantities (Scheme 5). Reduction of the ethylester function using $LiAlH_4$ gave 6-(hydroxymethyl)indazole (**4**) with a 93% yield.[21] Mesylation of the alcohol followed, without purification, by reaction with thioethanol under basic conditions allowed to obtain in a one-pot procedure the thioether-substituted indazole **5** with a yield of 25%. This low yield can be partly explained by the competition during the mesylation reaction between the hydroxyl group and the nucleophilic nitrogen of the indazole. This is illustrated by the formation of a mixture of mono- and di-mesylated products even using one equivalent of mesyl chloride.



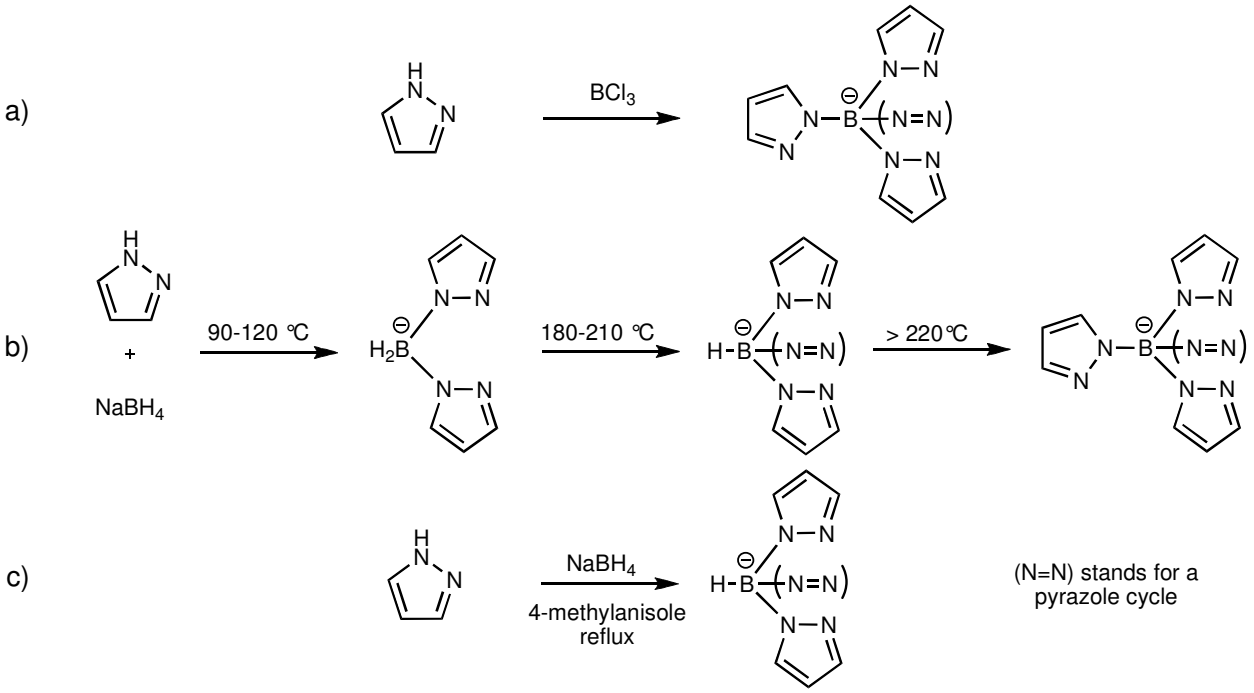
3 **4** **5**

Scheme 5. Synthesis of 6-[(ethylsulfanyl)methyl)]indazole.

3. Synthesis of tris(indazolyl)borate tripodal ligands

3.1. Historical background: synthesis and regiochemistry of the tris(pyrazolyl)borate derivatives: the scorpionates

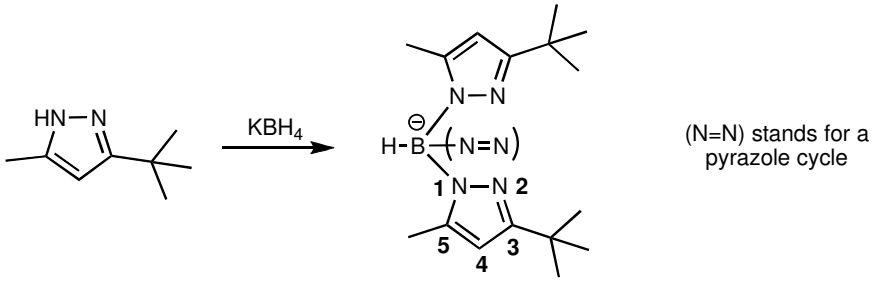
In 1966, Trofimenko reported in a historic paper the first synthesis of a hydrotris(pyrazolyl)borate ligand by reaction of boron trichloride with melted pyrazole (Scheme 6a).[8,22]



Scheme 6. Synthesis of poly(pyrazolyl)borates.

Trofimenko quickly generalized the synthesis of poly(pyrazolyl)borates by reaction of a pyrazole derivative with sodium borohydride without solvent,[8] a milder method compared to the previous one (Scheme 6b). The melted medium allows the reaction to be performed in homogeneous conditions at a controlled temperature. The control of the reaction temperature is a key point since it allows to obtain in a selective way the mono, bis, tris or tetrakis(pyrazolyl)borates. The dihydrobis(pyrazolyl)borate was obtained selectively by heating at 120 °C, the hydrotris(pyrazolyl)borate started to appear at 180 °C and the tetrakis(pyrazolyl)borate if the heating is maintained for a longer period at 220 °C. The presence of functionalized groups on the pyrazole or indazole rings will modulate slightly these temperatures. This methodology is still widely employed for the synthesis of various poly(pyrazolyl)borate derivatives[9a] since it tolerates a broad range of functional groups. We could indeed react ester-functionalized indazoles without any reduction or decarboxylation.[23] A different route, also described recently by Trofimenko, allowed to synthesize selectively hydrotris(pyrazolyl)borates by reaction of pyrazole with a borohydride in refluxing 4-methylanisole (bp 174 °C)[24] (Scheme 6c).

For substituted pyrazoles, the regioselectivity of the boron coordination at the step of formation of the hydrotris(pyrazolyl)borate is under steric control. Therefore, as shown on the example described in Scheme 7, the boron coordinates the less hindered nitrogen.[25]



Scheme 7. Regiochemistry of a substituted hydrotris(pyrazolyl)borate.

3.2. Synthesis and regiochemistry of the unfunctionalized tris(indazolyl)borate tripod

Unfunctionalized potassium hydrotris(indazol-1-yl)borate was synthesized following the strategy described by Janiak.[26] An intimate mixture of indazole (3.2 eq) and potassium borohydride (1 eq) was heated at 220 °C until the hydrogen evolution had stopped. After sublimation of the unreacted indazole, the tripodal ligand was obtained with a yield of 80% as a pale yellow solid.

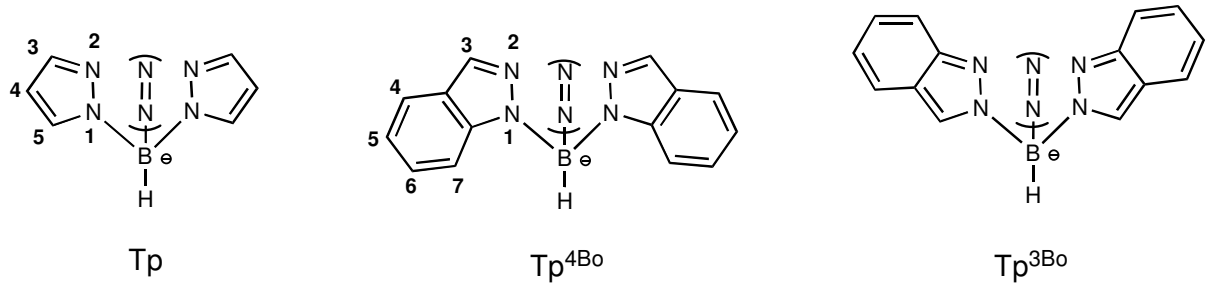


Figure 2. Scorpionate ligands hydrotris(pyrazolyl)borate (Tp) and hydrotris(indazolyl)borates (Tp^{4Bo} and Tp^{3Bo}).

The regiochemistry of the reaction is different from the one obtained in the synthesis of hydrotris(pyrazolyl)borate ligands. Trofimenko has shown that the interplay of steric and electronic factors tilts in favor of the latter, giving a product which is sterically hindered around the boron atom but not on the coordination side. Therefore this reaction affords exclusively the product resulting from the fusion of the benzo ring at the 4-5 position (giving the Tp^{4Bo} product as shown in Figure 2) in which the boron atom is bound to the most hindered nitrogen atom and no trace of the 3-4 fusion product (Tp^{3Bo}). In the case of the poly(indazol-1-yl)borate derivatives, it appears that the electronic effects are predominant compared to the steric effects.[10b]

3.3. Synthesis and regiochemistry of the functionalized tris(indazolyl)borate derivatives

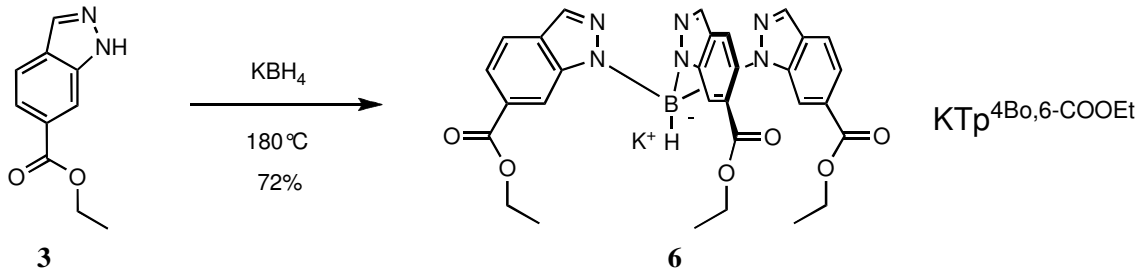
The functionalized borate ligands were designed to have three functional groups pointing on the opposite direction of the coordination site in order not to interfere sterically with it. Each of the three legs of the tripodal unit bears a functional group connected at the 6-position of indazole, which should be, on the basis of the X-ray structures obtained on the cyclopentadienyl model complexes,[21] the optimal orientation for anchoring on a surface without interfering with the metal coordinated since it is at the opposite side of the structure and far enough from the surface to avoid steric hindrance of the surface on the coordination center. The first one incorporates ester-functionalized indazoles to anchor complexes onto the oxide surface used in molecular scale Non Contact Atomic Force Microscope (NC-AFM) experiments. The ester function has been found to strongly interact with oxide surfaces,[27] spontaneous deprotection yielding carboxylic groups which covalently bind the metallic oxide. The second tripod synthesized bears thioether-functionalized indazoles to anchor complexes onto metal surfaces. The thioether function was chosen to alleviate the problem encountered with oxidation sensitive thiols. The thioether group is stable in a wider range of conditions and is also known to interact strongly with a gold surface.[28]

To obtain such tripodal ligands, the strategy consisting in the functionalization of Tp^{4Bo} should be avoided due to the difficulty to perform three times several steps on the 6-position of the borate ligand. In addition to the probable low yield of this non-convergent approach, the purification of these ligands could be problematic. Indeed, classical purification methods used in organic chemistry, such as column chromatography, are not suitable for the purification of these anionic ligands. They are usually purified by crystallization of their thallium salts. Therefore, we followed a convergent strategy which consisted in the synthesis of a functionalized indazole in a first step, and its subsequent reaction with potassium borohydride to yield the potassium hydrotris(indazol-1-yl)borate ligand. Trituration with an apolar solvent can selectively dissolve the indazole precursor and an additional sublimation step provides pure material. In the case of the substituted indazoles scorpionate derivatives, if the substituent is at the 7 position or if a phenyl group is fused with the indazole, the boron center is bound to the less sterically hindered nitrogens. In all the other cases (substitution at the 3, 4, 5 or 6 position), the most sterically hindered nitrogen binds the boron atom. Following Trofimenko's scorpionate nomenclature,[9a] the 6-functionalized ligands can be noted $KTp^{4Bo,6\text{-}COOEt}$ for the ester-functionalized and $KTp^{4Bo,6\text{-}CH2SEt}$ for the thioether-functionalized ligand.

3.3.1. The ester-functionalized tripod ($KTp^{4Bo,6\text{-}COOEt}$)

Reaction of 6-(ethoxycarbonyl)indazole (**3**) at 180 °C with potassium borohydride gave the triester-functionalized hydrotris(indazolyl)borate $KTp^{4Bo,6\text{-}COOEt}$ (**6**) in 72% yield after purification by repetitive

trituration with hot toluene and sublimation of the unreacted 6-(ethoxycarbonyl)indazole (Scheme 8). The reaction can be monitored by the volume of dihydrogen produced and was completed after 5 hours. Mass spectrometry confirmed the absence of side-products such as dihydrobis- or tetrakis(indazolyl)borate ligands. It is noteworthy that by conducting the reaction at 150 °C instead of 180 °C, the bis(indazolyl)borate was the major product. It is also interesting to note that below 200 °C, there is no formation of products arising from the reduction of the ester functions of the indazoles by potassium borohydride. If the temperature is too low, or if the reaction is stopped before the end of the gas evolution, only dihydrobis[6-(ethoxycarbonyl)indazol-1-yl]borate or a mixture of dihydrobis[6-(ethoxycarbonyl)indazol-1-yl]borate and hydrotris[6-(ethoxycarbonyl)indazol-1-yl]borate are obtained. Dihydrobis[6-(ethoxycarbonyl)indazol-1-yl]borate and hydrotris[6-(ethoxycarbonyl)indazol-1-yl]borate are not separable by column chromatography but it is possible to convert the dihydrobis[6-(ethoxycarbonyl)indazol-1-yl]borate into hydrotris[6-(ethoxy-carbonyl)indazol-1-yl]borate, by reacting the disubstituted derivative, pure or as a mixture with the desired tripod, with one equivalent of 6-(ethoxycarbonyl)indazole at 180 °C.



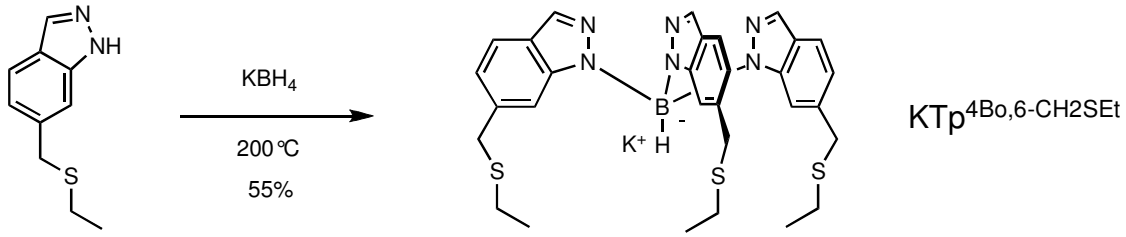
Scheme 8. Synthesis of potassium hydrotris[6-(ethoxycarbonyl)indazol-1-yl]borate.

As described in the literature,[29] the ^{1}H-NMR signal of the BH proton is very broad and difficult to locate due to the quadrupolar relaxation (proton coupled with the nuclear spin of the boron atom) which gave the signal of this proton very wide and difficult to observe. Nevertheless it is very informative to differentiate the bis (signal near 3.5 ppm) from the tris (around 5 ppm) indazolylborate. ^{11}B-NMR also allows to discriminate between the bis derivative (δ = -6.5 ppm in $CDCl_3$) and the tris(indazolyl)borate (δ = -0.9 ppm in $CDCl_3$).

3.3.2. The thioether-functionalized tripod ($KTp^{4Bo,6\text{-}CH2SEt}$)

Thioethers are known to have a good affinity for metallic surfaces such as copper or gold commonly used in AFM experiments.[30] The same procedure used to obtain $KTp^{4Bo,6\text{-}COOEt}$ was applied to **5**, yielding potassium hydrotris{6-[(ethylsulfanyl)methyl]indazol-1-yl}borate ($KTp^{4Bo,6\text{-}CH2SEt}$). After heating 3.4 equivalents of 6-[(ethylsulfanyl)methyl]indazole (**5**) without solvent at 200 °C for 5 hours with one equivalent of potassium borohydride (Scheme 9), sublimation of the unreacted indazole allowed to eliminate this excess. The tripodal $KTp^{4Bo,6\text{-}CH2SEt}$ (**7**) was obtained on the gram scale with a yield of 55%.

The regiospecificity described for the unfunctionalized ligand is maintained with the ester or thioether groups at the 6-position of the indazole, as confirmed by the X-ray structure of the ruthenium complex.[19] These functionalized tris(indazolyl)borates are bifunctional ligands which are able to coordinate a metal on one of their faces and anchor onto a surface on the opposite one.



5 **7**

Scheme 9. Synthesis of potassium hydrotris{6-[(ethylsulfanyl)methyl]indazol-1-yl}borate.

4. Integration of these tripodal ligands as stators in a molecular motor

A mono-molecular motor is a nanoscale machine which consumes energy to produce work *via* a unidirectional and controlled movement of one of its parts. In the bottom-up strategy, artificial molecular machines and motors have recently emerged as a new field of chemistry related to a newly explored dimension of molecular sciences: controlled movement at the molecular scale.[3,31]

Some very elegant examples of molecular rotary motors which have been described so far have been studied collectively and have many degrees of freedom.[32] Their behavior is in general the average behavior of a weak assembly of molecules and not of a single molecule. Moreover, some examples of molecules designed, synthesized and mounted on a surface for single molecule experiment do not undergo a unidirectional rotation: their internal motion is in fact a random oscillation around a given axis.[33] On the contrary, the molecules described here have been designed with the intention to study and manipulate them individually with the tip of a Scanning Tunneling Microscope (STM).[3e] This clearly implies the molecules to be particularly rigid and have minimal degrees of freedom in order to be manipulated on a surface with a maximum control on their movement. With this aim in view, our target molecules incorporate tripodal ligands bearing rigid sub-units.

4.1. Principle of an electron-triggered molecular motor

Looking at the requirements for a true unidirectional rotation, several difficulties can be identified. First, the molecule must be made of rigid parts with a low number of degree of freedom. This requirement is frequently absent in many propositions of molecular motors, which neglect the extreme flexibility of most molecules. In our design of a molecular motor,[21] the source of energy is a tunnel electric current. Our target molecule is supposed to convert the flow of electrons tunneling through the molecule into a directionally-controlled rotary motion. The molecular motor has been designed to be individually interconnected after its deposition to an N-electrode tunnel junction whose nanoelectrodes are separated by a few nanometers. The concept of our electron-fuelled molecular rotary motor is shown in Figure 3.

The electroactive group (EG) closest to the anode would be oxidized (oxidized form EG^+) and pushed back by electrostatic repulsion like it has been shown for a [60]-fullerene between two electrodes.[34] This motion corresponds to a fifth of a turn. As a result, the oxidized electroactive group would approach the cathode and subsequently be reduced. At the same time, a second electroactive group would come close to the anode and a second cycle would occur. A complete 360º turn would be achieved after five cycles, corresponding to the shuttling of five electrons from the cathode to the anode. This would represent the conversion of an electron flow into a movement of rotation, *i.e.* a redox-triggered molecular rotary motor by

the irreversible transport of electrons from the negative to the positive electrode through a tunnel junction. In order for the rotation to be directional, the molecule should be placed in a dissymmetrical environment. This could be achieved either by its positioning in the nanojunction, or for instance by a secondary electric field applied perpendicularly to the nanojunction. The directionality would be obtained because the two senses of rotation are not equivalent: this is clear on Figure 3, as a result of the dissymmetric positioning of the molecule with respect to the electrodes.

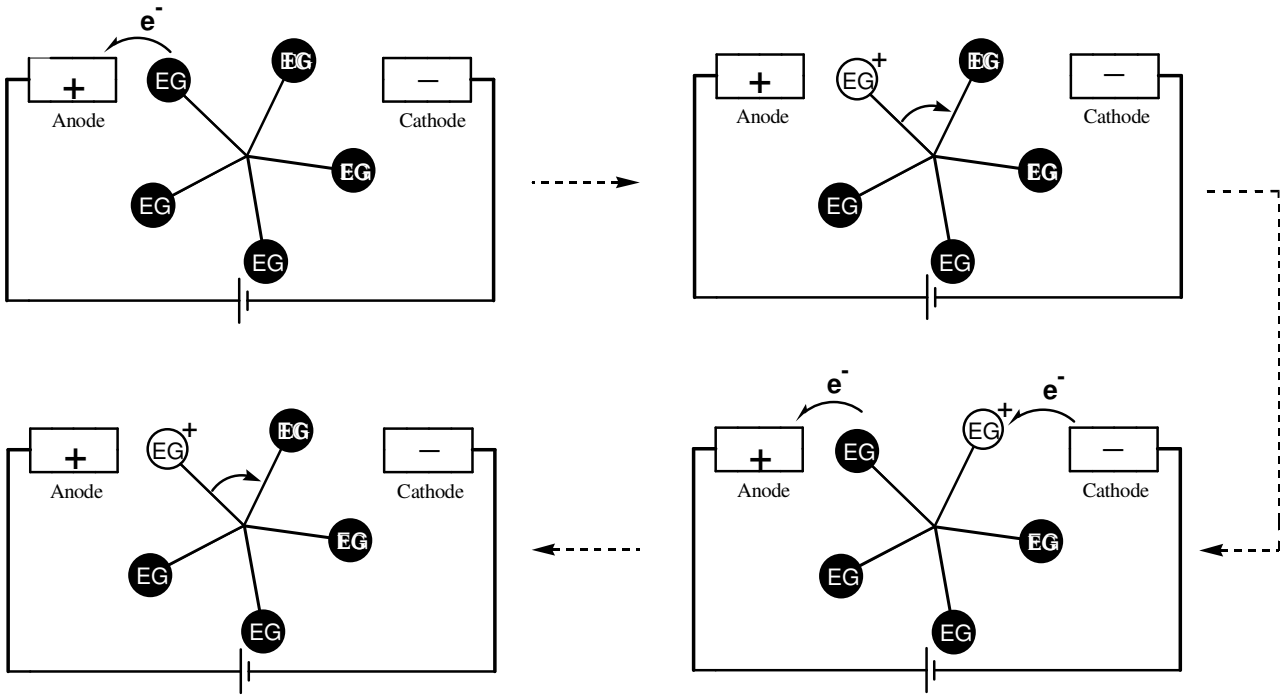
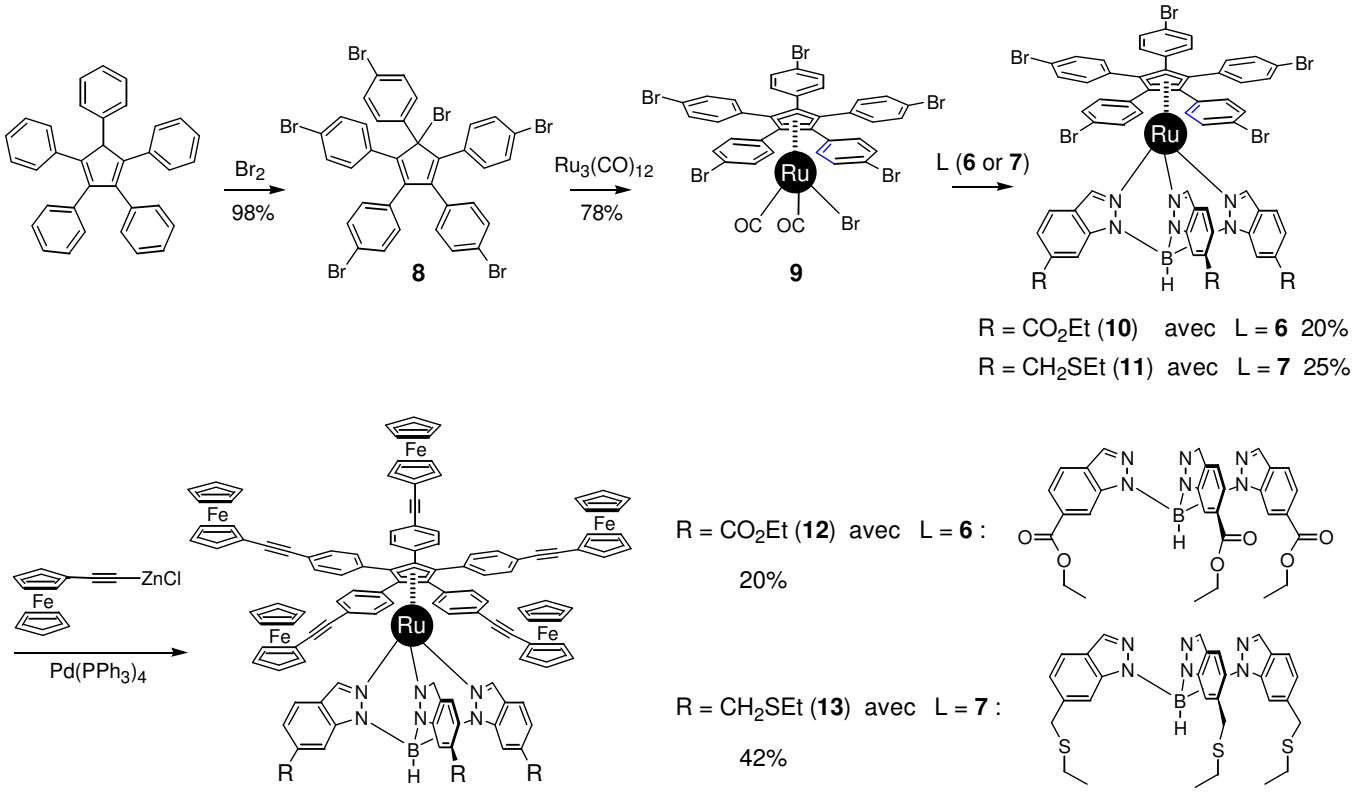


Figure 3. Schematic representation of a molecule placed between the two electrodes of a nanojunction (EG stands for electroactive group). The transfer of electrons from the cathode to the anode through successive oxidation and reduction processes is expected to result in the clockwise rotation of the entire upper part of the molecule. On this figure is represented a fifth of a turn corresponding to the movement induced by the transfer of one electron.

The molecular motors are represented on Scheme 10. It comprises a stator, *i.e.* one part fixed between two electrodes, and on this stator is connected a rotor which should transform a current of electrons into a unidirectional rotation motion. The rotor is a rigid aromatic platform constructed around a cyclopentadienyl ligand (Cp) with five linear and rigid arms, each terminated by an electroactive group. As electroactive group, ferrocene was selected because it exhibits reversible oxidation in various solvents.[35] The stator is a hydrotris(indazolyl)borate ligand described in § 3.

The joint between the rotor and the stator is a ruthenium(II) ion chosen to obtain a kinetically stable molecule bearing zero net charge. Both criteria are essential for surface deposition and hence in view of performing single molecule experiments. The upper part should be free to turn whilst the basis should stay still, anchored on the surface between the two electrodes of the addressing system. In the molecule, there is essentially one degree of freedom: the rotation of the upper part with respect to the lower one. The lower part has a locked conformation.



Scheme 10. Synthesis of the molecular motors.

4.2. Synthesis of the molecular motors

The molecule was synthesized in four steps as shown on Scheme 10, starting from 1,2,3,4,5-pentaphenyl cyclopentadiene which was selectively brominated in the para positions and at the saturated carbon of the cyclopentadiene ring.[36] We obtained 1-bromo-1,2,3,4,5-penta(*p*-bromophenyl)cyclopentadiene (**8**) selectively. The presence of the five bromine atoms in the *para* position of each phenyl ring should be helpful to introduce various groups on the cyclopentadienyl ring. Upon reacting **8** with a solution of $Ru_3(CO)_{12}$ in toluene at reflux, the reaction mixture rapidly turned from yellow to deep green and finally to cherry red, characteristic of a conjugated Cp radical. Column chromatography gave **9** as a yellow solid in 78% isolated yield. Coordination of the scorpionate ligands ($KTp^{4Bo,6\text{-}CO2Et}$ or $KTp^{4Bo,6\text{-}CH2SEt}$) was achieved one pot by substitution of the bromide ligand and CO displacement by heating **9** with 2 equivalents of the ligand. After purification by column chromatography, the ruthenium complexes were obtained as yellow crystals. Reaction time, temperature and solvent have been varied, but none of these changes resulted in an improved yield. Nevertheless, it must be noted that the coordination of the tripodal ligand is the result of two steps and the presence of various ligands (Tp^{4Bo}, Cp, CO, Br) in the reaction mixture may allow numerous side reactions. In the last step, a quintuple coupling of the ethynyl ferrocene electroactive groups occurred with a satisfying overall yield.

The orientation of the three anchoring groups, as shown by the X-ray structures,[21] seems to be ideal for surface deposition of this new family of potential molecular motors. Work is now underway to anchor these complexes on surfaces and address them by the means of two metallic nanoelectrodes. The demonstration of a controlled rotary movement will then need further experimental developments by physical methods such as scanning probe microscopies or the analysis of the time dependence of the current in a two-electrode configuration. Although some progress has been made, it is still a long way to practical applications.

5. Conclusions

In summary, after an overview of the existing efficient methodologies to synthesize indazoles and substituted indazoles, we have shown the synthesis of new functionalized indazoles which have been trimerized to prepare some tripodal tris(indazolyl)borate ligands designed to interact with metallic or oxide surfaces. Their incorporation in ruthenium complexes yielded some promising ruthenium complexes which are potential molecular motors.

Acknowledgments

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ANALOGUES OF TRÖGER'S BASE: RECENT DEVELOPMENTS AND CONTROVERSIES

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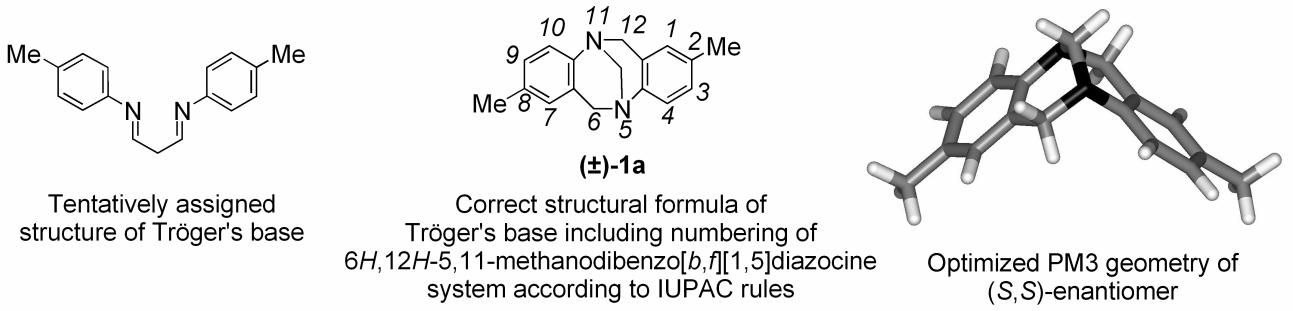
Abstract. *Tröger's base is a well-known chiral molecule with a few unusual structural features. Synthetic chemistry of analogues of Tröger's base has been greatly developed and some of these molecules have found interesting applications in supramolecular chemistry and in molecular recognition. Since a few excellent, comprehensive reviews and book chapters devoted to various aspects of Tröger's base chemistry have been published relatively recently, a complete coverage of the related topics and of the relevant literature was not the purpose of this account. Instead, we have tried to give a short overview of historical developments, to cover the most important aspects of the chemistry of Tröger's base and its analogues and to focus on the recent achievements and on the accompanying controversies that have been revisited in recent years. We have attempted, however, to provide a possibly complete coverage of the scientific literature published in the last two years and therefore not cited by the previous reviews and accounts.*

Contents

1. Introduction

Tröger's base ((±)-**1a**, Scheme 1) is a polycyclic diamine with a few unusual structural features. Its two aromatic rings are nearly perpendicular to each other, creating a rigid, V-shaped molecular scaffold with a distance of *ca.* 1 nm between the two extremities. The two tertiary bridgehead nitrogen atoms of this C_2-symmetrical molecule are stereogenic centers. In general, enantiomers of chiral tertiary amines with

asymmetric nitrogen cannot be resolved because of a rapid inversion at ambient temperature. However, inversion of the bridge-head nitrogen atoms in the molecule of Tröger's base is greatly hindered since it would impose a very high ring strain. Consequently, enantiomers of Tröger's base are stable to the extent that they can be sublimed without noticeable racemization.



Tentatively assigned structure of Tröger's base

Correct structural formula of Tröger's base including numbering of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine system according to IUPAC rules

Optimized PM3 geometry of (*S*,*S*)-enantiomer

Scheme 1

It is therefore both unsurprising and surprising that interests of organic chemists in increasingly complex derivatives of Tröger's base has greatly grown over the last two decades (see recent comprehensive reviews).[1,2] It is certainly unsurprising as Tröger's base offers itself as a unique, nanometer-sized building block for unusual molecular designs. For instance, various functional groups capable to the formation of hydrogen bonds were installed at the extremities of the V-shaped skeleton of Tröger's base to create synthetic receptors for recognition of adenine, pyrimidine, biotin derivatives[3] and dicarboxylic acids.[4] Water-soluble cyclophane-like analogs of Tröger's base have been suggested as chiral receptors for small, neutral organic molecules.[5] Enantiomerically pure Tröger's base was used as a chiral solvating agent for chiral alcohols[6] and acetals.[7] What is surprising about this "renaissance" of Tröger's base is that it only happened some 100 years after the first published synthesis of this fascinating molecule!

2. Synthetic chemistry of Tröger's base and its analogues

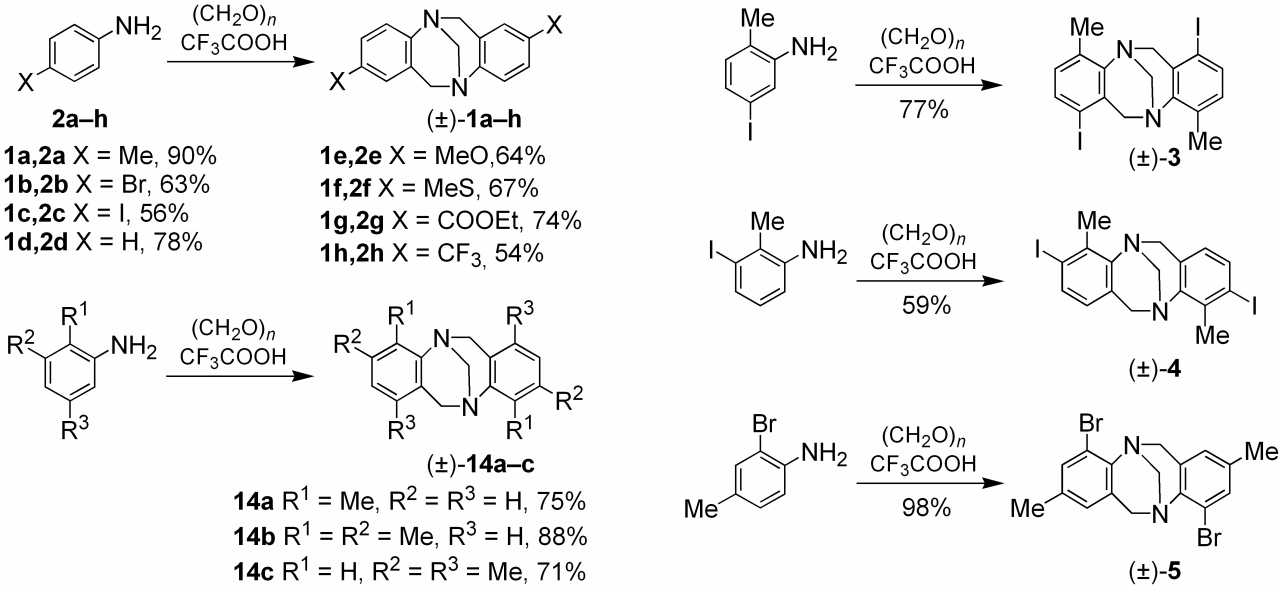
2.1. Synthesis of symmetrical analogues of Tröger's base

Since the early publications dealing with the chemistry of Tröger's base and until today, the history of this unusual molecule has been full of controversies and has actually begun with an unintentional synthesis. In 1887, a German chemist Julius Tröger set out to prepare an acridine derivative from *para*-methylaniline and formaldehyde (generated *in situ* by the hydrolysis of methylal, $CH_2(OMe)_2$ in aqueous HCl). Instead, he isolated an unwanted product, which he described as a "base $C_{17}H_{18}N_2$" and which later became commonly known as Tröger's base.[8] However, although Tröger correctly identified the molecular formula of this base, his suggested structure was erroneous (Scheme 1). It was only considerably later that the accurate structural formula of Tröger's base featuring the central bicyclic unit and two bridgehead nitrogens was elucidated and a plausible mechanism for its formation was suggested.[9] Tröger's base thus represents a 2,8-dimethyl derivative of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine. However, it took another 50 years, that is, almost a century after the pioneering work of Tröger, before Wilcox unambiguously confirmed the molecular structure of Tröger's base with the aid of single crystal X-ray analysis – a surprisingly long gap for an air-stable, soluble, easily available molecule with a molecular weight of only 250.[10]

Considerable controversies are related to the synthesis of analogues of Tröger's base **1**, that is, derivatives of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine bearing various substituents in different

positions of the aromatic rings.[11] The general approach to these molecules actually comprises relatively minor variation of the good old method developed by J. Tröger, namely, the condensation of formaldehyde (or of its synthetic equivalent) with suitably substituted anilines **2** (Scheme 2). The reaction is catalyzed by HCl in ethanol, water, or in the mixture of both, by acetic, trifluoroacetic, methanosulfonic acids and, as recently demonstrated, also by Lewis acids.[12] Since gaseous formaldehyde is dangerous and inconvenient to handle, it is either used as a commercial water solution (formaline) or generated *in situ* from methylal $(MeO)_2CH_2$, hexamethylenetetramine $(CH_2)_6N_4$ or paraformaldehyde.

The scope and limitations of this condensation relative to the structure of aniline derivatives have been examined in detail.[13] It has been accepted that, regardless of the experimental conditions and reagents, the *para*-position of aniline **2** should be blocked in order to avoid polymerization. On the contrary, substituents such as methyl groups in other positions are not crucial and often even improve the yield of the condensation. Furthermore, it was believed that the substituents on the aromatic ring should have the electron-donating nature to allow electrophilic substitutions that represent key steps in the formation of the Tröger's base framework.

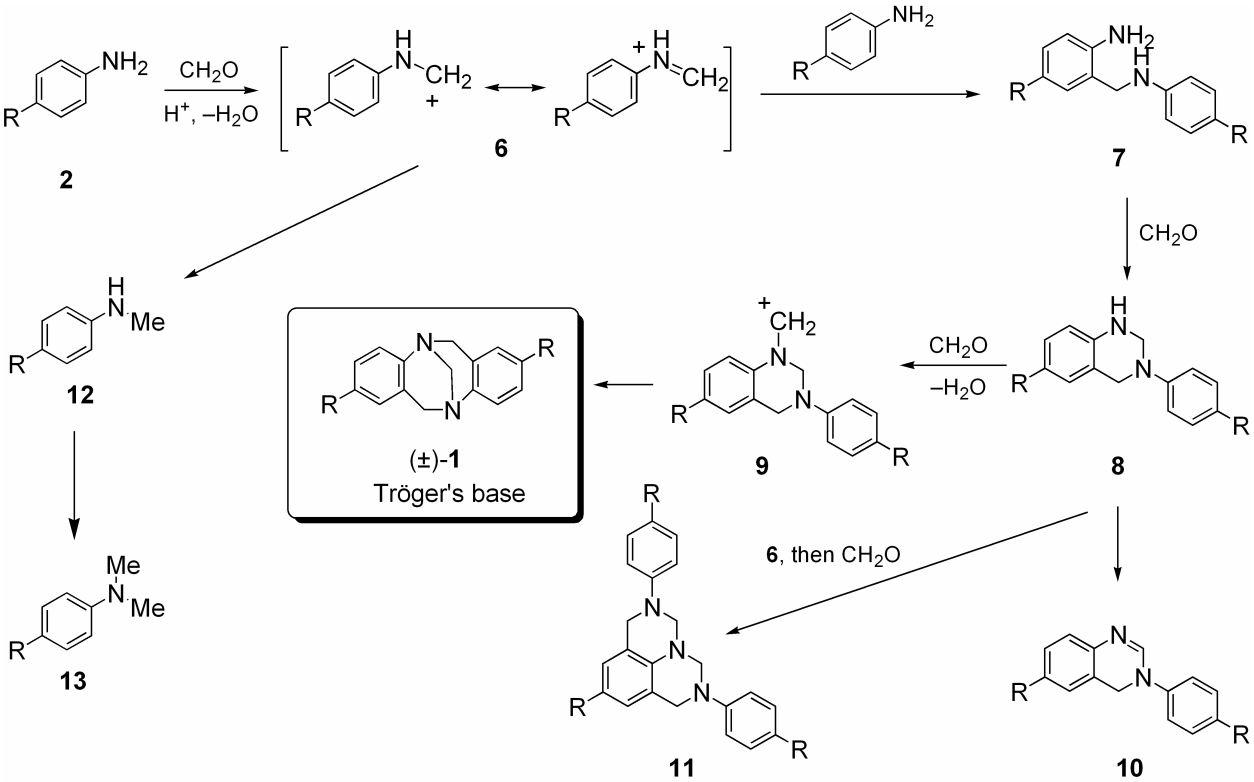


Scheme 2

However, in the recent years these limitations have been considerably adjusted. Thus, Wärnmark and coworkers demonstrated the feasibility of condensation of anilines bearing moderately electron withdrawing halogens in the *para*-position (such as **2b** and **2c**) to give 2,8-dihalo derivatives of Tröger's base (such as (±)-**1b** and (±)-**1c**) in fair to excellent yields.[14] The reaction was performed in trifluoroacetic acid (CF_3COOH) with paraformaldehyde as a source of reactive CH_2=O. This method can also be extended to the synthesis of Tröger's base derivatives with halogens in other positions of the aromatic rings (such as (±)-**3**, (±)-**4** and (±)-**5**, Scheme 2).[15–17] Furthermore, as a study in our laboratory has shown,[18] a number of Tröger's base analogues with both electron-donating (*e.g.* MeO, MeS, (±)-**1e,f**) and electron withdrawing (*e.g.* COOEt, CF_3, (±)-**1g,h**) substituents can be successfully prepared from the corresponding anilines and paraformaldehyde in CF_3COOH (for yields, see Scheme 2). However, anilines bearing very strong acceptor groups (such as 4-cyano- and 4-nitroanilines) do not react.[19] At the same time, when NO_2 and

electronodonating group(s) (Me and/or MeO) are present together, they counterbalance each other and the aromatic ring may become sufficiently activated for the formation of Tröger's base derivatives.[20,21]

In order to explain different courses of reaction depending on the experimental method, it is appropriate to consider the accepted mechanism of formation of Tröger's base derivatives from anilines. It involves an electrophilic substitution in the position *ortho* to the NH_2 group upon the attack of the iminium intermediate **6** (formed from CH_2O and another molecule of aniline) to give diamine **7**. Subsequent steps involving the second and the third molecules of formaldehyde lead to the formation of tetrahydroquinazoline **8** and iminium ion **9**. Finally, an intramolecular electrophilic substitution in **9** gives Tröger's base (±)-**1** (Scheme 3). Recently, this mechanism was revisited with the aid of online ESI-MS monitoring and direct experimental evidences for the formation of reactive intermediates **6**, **8**, and **9** were obtained.[22] Another confirmation of this mechanism is the synthesis of highly reactive, moisture sensitive iminium salts **6** (R = H, Me, OMe) by a gas-solid reaction between 2,4,6-triaryl-1,3,5-hexahydrotriazines and HCl. Upon treatment with CF_3COOH these salts gave the corresponding derivatives of Tröger's base in 79–90% yield.[23]

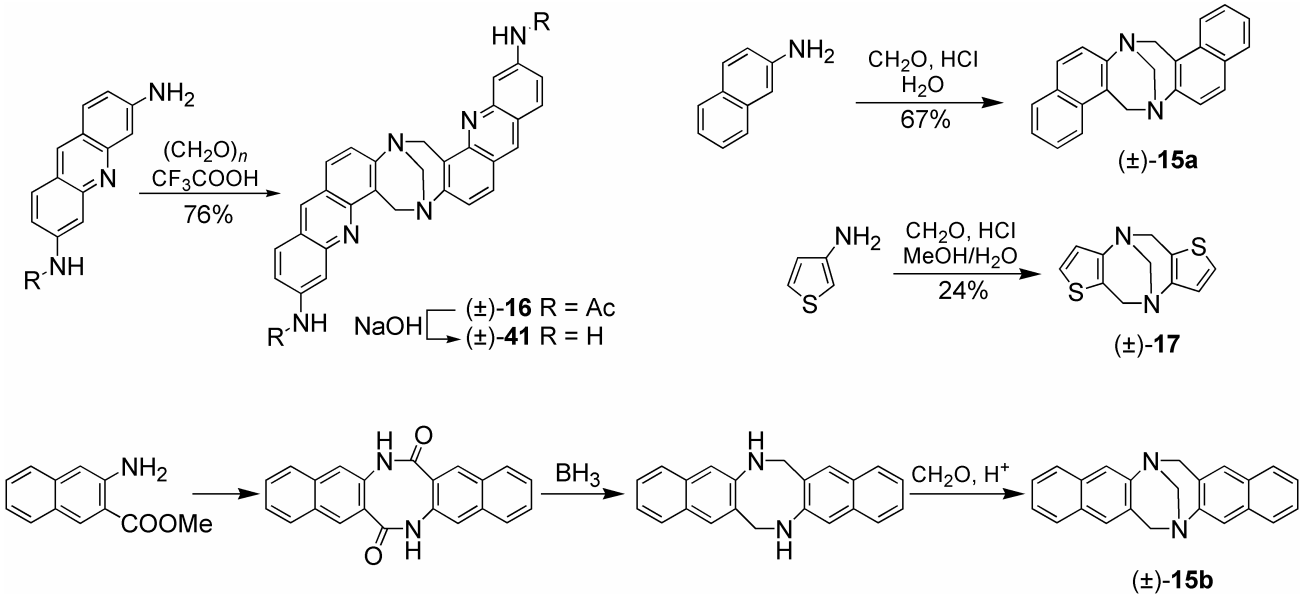


Scheme 3

In addition to the derivatives of Tröger's base (±)-**1**, formation of various side products was documented. Oxidation of tetrahydroquinazoline **8** leads to the formation of dihydroquinazoline **10**. A derivative of pyrimidoquinazoline **11** results from the attack of the second molecule of iminium ion **6** at the free *ortho*-position of **8** followed by cyclization to furnish a tricyclic system. Thus, **11** represents a product of a seven-component reaction that involves three molecules of aniline **2** and four molecules of CH_2O. Finally, we have observed the formation of *N*-methyl and *N*,*N*-dimethyl derivatives of the starting aniline (**12** and **13**, respectively) *via* the hydrogen transfer reduction of **6** with formaldehyde (similar *N*-methylation of amines in formaldehyde and formic acid is well-known as Eschweiler-Clark methylation).[24]

It was speculated that anilines with electron-withdrawing substituents do not give the corresponding Tröger's base derivatives because in the often-used aqueous reaction media, nucleophilicity of nitrogen in **8** is insufficient to attack formaldehyde. Reaction thus stops at the formation of tetrahydroquinazoline **8** or leads to side products **10** or **11**. It was accordingly suggested that various factors are crucial for the successful condensation in CF_3COOH. First of all, concentrations of electrophilic species (protonated formaldehyde as well as iminium ions **6** and **9**) are believed to increase in highly ionisable CF_3COOH compared to aqueous media. In addition, the formation of dihydroquinazoline **10** is greatly diminished due to its reduction back to tetrahydroquinazoline **8**. The latter hypothesis is in perfect agreement with the formation of *N*-methylated anilines **12** and **13** observed by us, which involves a similar hydride-transfer reduction of an iminium cation. It should be noted that reaction of 4-halosubstituted anilines with paraformaldehyde in some other non-aqueous media (*e.g.*, in $MeSO_3H$) does give the corresponding derivatives of Tröger's base, but the yields are lower than in CF_3COOH.

It is worth mentioning that the reaction between unsubstituted aniline and paraformaldehyde in CF_3COOH smoothly provides 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine ((±)-**1d**) in 78% yield (Scheme 2).[25] The one-step synthesis of (±)-**1d** makes this molecule an attractive intermediate for the synthesis of other derivatives of Tröger's base (see Scheme 10, Section 2.4. below). We have also demonstrated that 2-methyl, 2,3- and 3,5-dimethyl anilines gave the corresponding analogues of Tröger's base (±)-**14a–c** in 71–88% yield (Scheme 1). These findings clearly show that the absence of substituent in *para*-position of the starting aniline does not necessarily lead to polymerization, as was widely accepted.



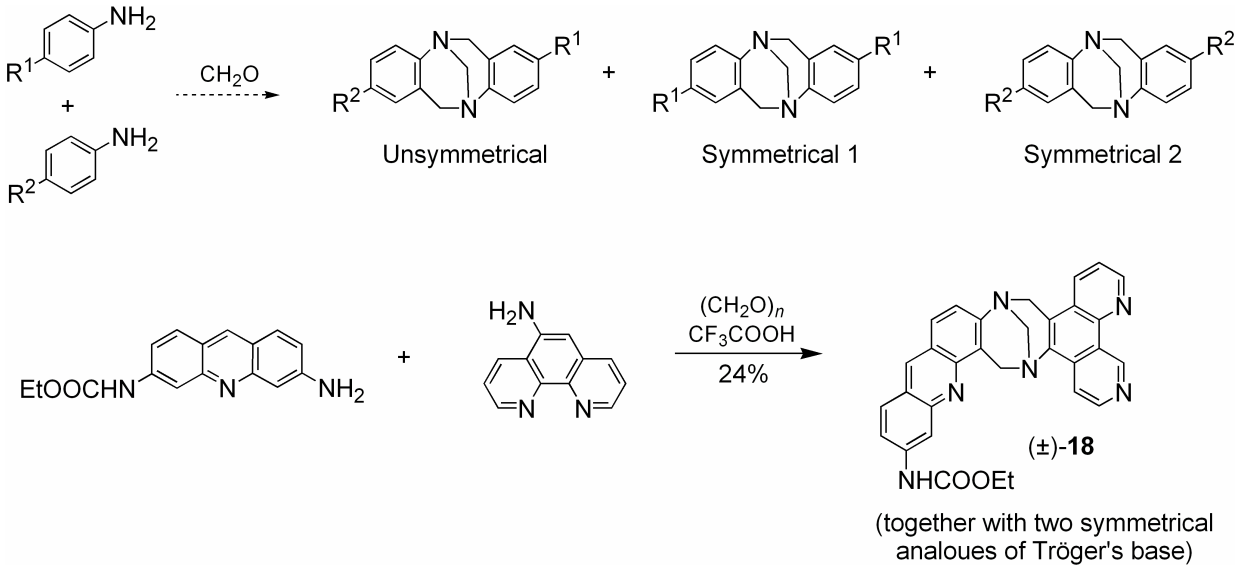
Scheme 4

In all discussed examples, either both *ortho* positions in the starting aniline are equivalent (in unsubstituted, 4-substituted and 3,5-disubstituted anilines) or one of them is blocked by a substituent. Therefore, the formation of only one derivatives of Tröger's base is possible. Anilines with other substitution patterns (*e.g.*, 3-substituted or 3,4-disubstituted) have two non-equivalent positions available for the attack of an electrophile and give a mixture of three regioisomers, although not necessarily in statistical ratio. Examples of such condensations are known, but separation of isomeric products was not performed.[17]

Finally, a number of non-benzenoid aromatic and heteroaromatic amines, including derivatives of naphthalene, acridine, phenanthroline, carbazole, pyrazole, benzothiazole, pyrimidine, pyrrole and thiophene gave Tröger's base derivatives *via* the condensation with CH_2O, though yields vary very strongly. A recent communication reports on the use of ionic liquids for the synthesis of some carbo- and heterocyclic analogues of Tröger's base in excellent yields.[26] For many of non-benzenoid systems, the formation of regioisomeric products is *a priori* possible. However, these condensations are typically perfectly regioselective, mirroring the usual reactivity of non-benzenoid aromatics towards electrophiles. Thus, 2-aminonaphthalene[27] and a derivative of 2-aminoacridine[28] give exclusively analogues of Tröger's base (±)-**15a** and (±)-**16** resulting from the substitution in position 1 and 3-aminothiophene[29] undergoes exclusively substitution in position 3 to give (±)-**17** (Scheme 4). Due to lower reactivity of the β-position in naphthalene, a "linear" naphthalene analog of Tröger's base (±)-**15b** cannot be prepared from 1-naphthylamine. However, it was successfully synthesized in 3 steps from the methyl ester of 3-amino-2-naphthalenecarboxylic acid.[30]

2.2. Synthesis of unsymmetrical analogues of Tröger's base

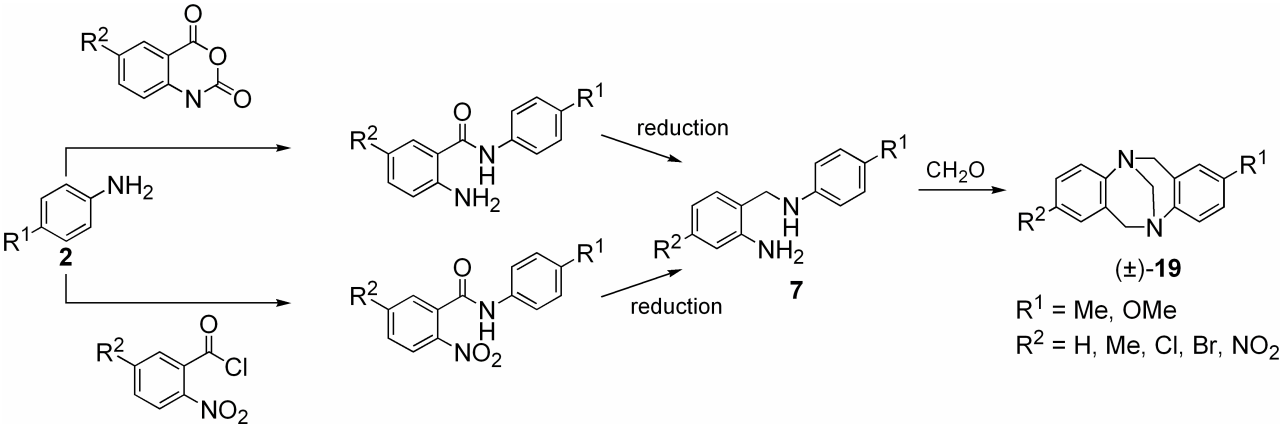
The direct condensation of anilines with formaldehyde gives access only to symmetric derivatives of Tröger's base. In theory, it should be possible to obtain non-symmetric derivatives in a single synthetic step from a mixture of two anilines (Scheme 5). However, such an approach must lead to a mixture of the desirable product with two symmetric compounds and thus appear rather impractical. To the best of our knowledge, such a synthesis has been documented only once and gave an unsymmetrical derivative (±)-**18** with acridine and phenanthroline aromatic systems in 24% isolated yield.[31]



Scheme 5

At the same time, diamines **7** that appear as key intermediates in the synthesis of Tröger's base from anilines (see Scheme 3 above), can also be prepared by other, multi-step methods, *e.g.*, starting from anilines **2** and derivatives of either isatoic anhydride (2*H*-3,1-benzoxazine-2,4(1*H*)-dione) or of 2-nitrobenzoyl chloride (Scheme 6). Obviously, this method would also yield diamines **7** with non-identical substituents R^1 and R^2. Subsequent treatment of **7** with formaldehyde in HCl/H_2O/EtOH afforded (in case of $R^1 \neq R^2$) the corresponding non-symmetric analogues of Tröger's base (±)-**19**.[32,33] Similarly to the synthesis of

symmetrical analogues of Tröger's base from anilines, this condensation tolerates only electron-donating substituents R^1. It is reasonable to suggest that condensation with paraformaldehyde in CF_3COOH may extend the scope of this method. However, an attempt to prepare an analogue of (±)-**19** with R^1 = Br, R^2 = H resulted in a disappointingly low 25% yield.[34] This methodology is nevertheless very valuable, since it provides access to complex unsymmetrical derivatives of Tröger's base, such as "molecular torsion balances" of Wilcox and co-workers (see Scheme 17 below).[33,35,36] Alternative approaches to non-symmetrical derivatives of Tröger's base, involving either desymmetrization of symmetrical dihalo derivatives, or electrophilic substitution in the aromatic rings of unsubstituted 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, will be discussed below (see Sections 2.3. and 2.4., respectively).



Scheme 6

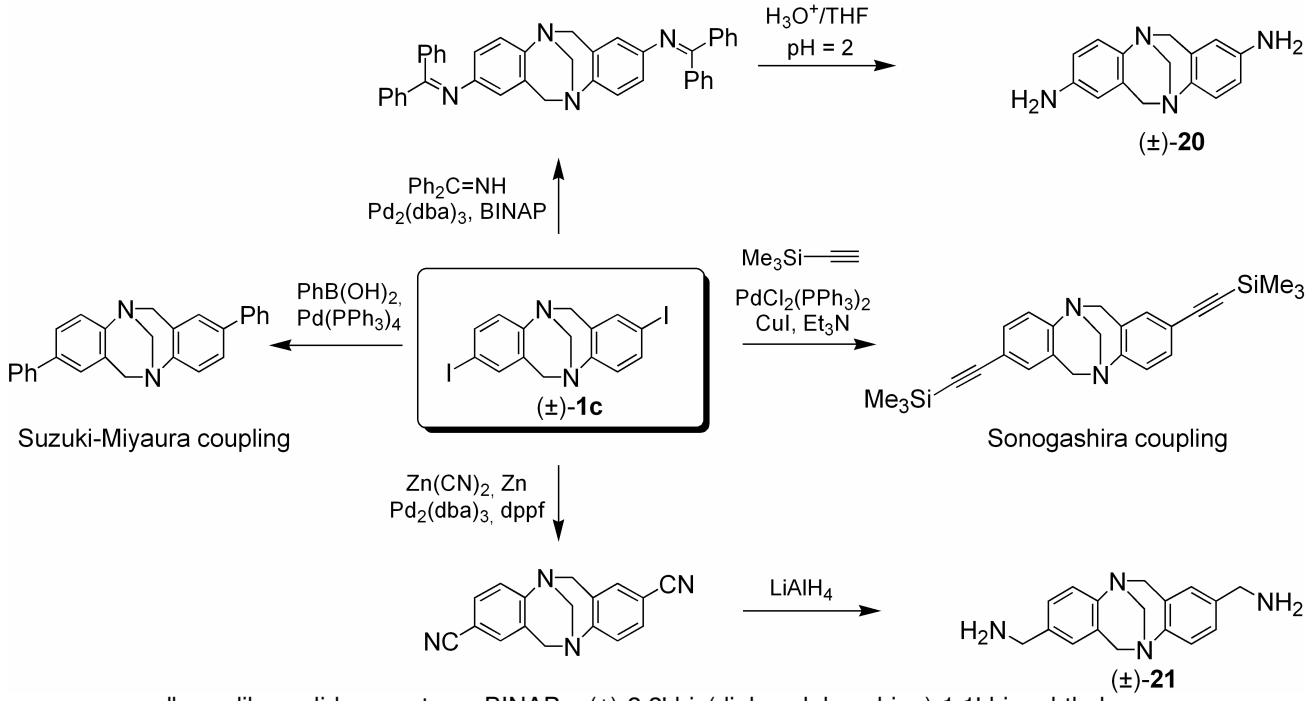
2.3. Transformations of functional groups attached to the aromatic rings of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Chemistry of functional groups attached to the aromatic rings of Tröger's base analogues has been extensively explored. These are standard synthetic transformations, which are not specific to Tröger's base but are rather common for various aromatic derivatives.

The halogen derivatives of Tröger's base, first introduced by Wärnmark in 2001,[14] are particularly important synthetic intermediates since they allow access to many other functional derivatives *via* transition metal catalyzed cross-coupling reactions such as Suzuki-Miyaura[37] or Sonogashira[38] coupling (Scheme 7). Recently, we have reported[39] the synthesis of symmetrical amino derivatives of Tröger's base either *via* Buchwald-Hartwig amination with benzophenone imine (Ph_2C=NH) followed by mild acidic hydrolysis or *via* Pd-catalyzed cyanation followed by reduction of CN to CH_2NH_2 (Scheme 7). These two methods provide access to derivatives of Tröger's base such as (±)-**20** and (±)-**21** bearing NH_2 or CH_2NH_2 groups, respectively, in the different positions of the aromatic rings. These molecules are undoubtedly very promising as ligands for supramolecular architectures based on transition metal coordination[20,40] and for catalysis with transition metal complexes. On the other hand, these diamines can be further elaborated in a variety of ways and converted into other derivatives such as amides, carbamates, sulfonamides, ureas or thioureas.[39]

Metal-catalyzed cross-coupling reactions were also used for the synthesis of unsymmetrically substituted Tröger's base derivatives. Non-selective substitution of only one iodine atom in the molecule of diiodide (±)-**1c** provides the corresponding unsymmetrical derivatives with iodine in one aromatic ring and a

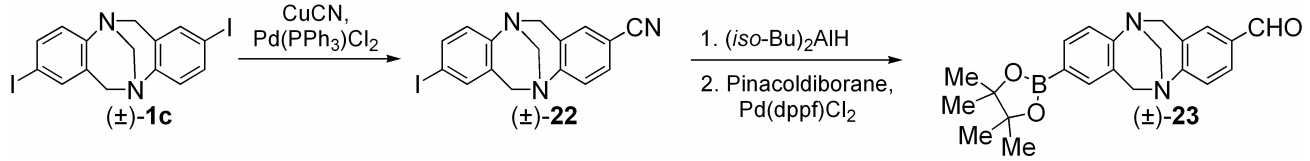
different functional group in another one. In spite of modest yields, this approach is of great synthetic value since it allows the preparation of otherwise hardly available functionalized analogues of Tröger's base.[37]



dba = dibenzylideneacetone; BINAP = (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene; dppf = 1,1'-bis(diphenylphosphino)ferrocene.

Scheme 7

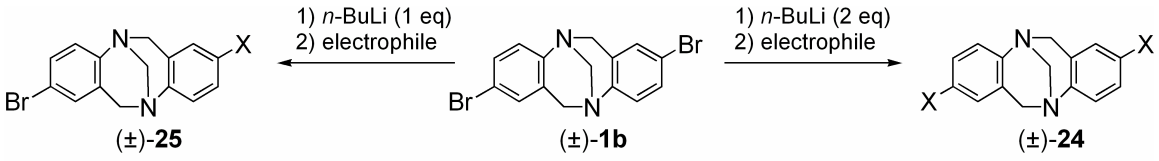
Desymmetrization of diiodide (±)-**1c** by Pd-catalyzed cyanation and example of subsequent elaboration of both functionalities in 2-cyano-8-iodo derivative (±)-**22** are shown in Scheme 8. Boronate (±)-**23** was used by Diederich and co-workers in the construction of "molecular torsion balance" for the quantification of weak interactions between organic fluorine and C=O bond of an amide group (see below, Section 5.).[41]



Scheme 8

Another very useful methodology that takes advantages of dihalo derivatives of Tröger's base was introduced by Wärnmark and co-workers.[42] It involves double halogen-lithium exchange upon the action of *n*-BuLi followed by the reaction of the lithium intermediate with a range of electrophiles. A number of synthetically valuable Tröger's base derivatives (±)-**24** with functional groups that are incompatible with conditions of the condensation of anilines with formaldehyde can be prepared by this method (Scheme 9). Moreover, upon careful optimization of the reaction conditions, it was also possible to perform a single halogen-lithium exchange. Subsequent reaction with an electrophilic reagent afforded unsymmetrical derivatives (±)-**25**. The remaining halogen atom in (±)-**25** can also be used in a second halogen/lithium exchange followed by reaction with a different electrophile. This desymmetrization is complementary to the

above described Wilcox and Diederich syntheses. Altogether, these three methodologies constitute a powerful method for the synthesis of complex unsymmetrical derivatives of Tröger's base.



24,25: X = Me_3Si, CHO, COOH, Bu_3Sn, N_3

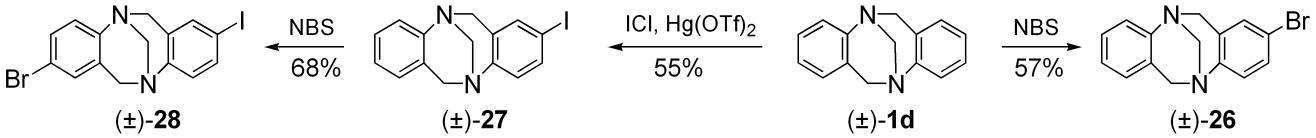
Scheme 9

A number of other transformations of functional group attached to the Tröger's base framework have been reported. They include reduction of nitro, nitrile, aldehyde or ester functions, hydrolysis of nitrile and ester groups, addition of Grignard reagents to carbonyl group, transformation of COOH into amide or ester functionalities, oxidation of secondary alcohol and aldehyde functions (see review[2] and references cited therein). It is worth mentioning that in the course of these reactions, Tröger's base skeleton demonstrates stability towards various reagents and conditions, including organolithium[42] and Grignard[37] reagents, $LiAlH_4$[15], sodium in refluxing ethanol,[2] BBr_3 in CH_2Cl_2,[43] MnO_2 and $KMnO_4$ at temperatures up to 80 °C[37] and catalytic heterogeneous reduction.[38]

2.4. Reactivity of the aromatic rings of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

As discussed above, the chemistry of functional groups attached to the aromatic rings of Tröger's base has been extensively studied. However, the reactivity of the parent heterocyclic system, 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine ((±)-**1d**) has never been explored, in spite of the fact that its first four-step synthesis from *para*-aminoethyl benzoate was reported more than 50 years ago.[44] In fact, (±)-**1d** can be viewed as a structural analogue of *N,N*-dimethylaniline and should therefore be prone to aromatic electrophilic substitutions, in particular in the *para*-position to the nitrogen atom.

We have recently demonstrated the feasibility of electrophilic brominations (with *N*-bromosuccinimide, NBS) and iodinations (with ICl) of (±)-**1d** in positions 2 and/or 8.[25] Although the *para*-positions of both aromatic rings are available for the substitution, it was possible to obtain selectively monosubstituted bromo and iodo derivatives (±)-**26** and (±)-**27**, respectively, in 55–57% yield (Scheme 10).



NBS = *N*-bromosuccinimide; DMF = *N,N*-dimethylformamide.

Scheme 10

These halogenations represent the first example of electrophilic substitution in the 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine system. Although our study revealed relatively low reactivity of this heterocyclic system compared to *N,N*-dialkylanilines, it clearly demonstrated the perfect regioselectivity of substitution in the *para*-position to the nitrogen atom. Therefore, methanodibenzodiazocine (±)-**1d** probably has an even greater synthetic potential as a substrate for other electrophilic substitutions. Preparative utility of (±)-**1d** can certainly be limited by its diminished reactivity caused by the poor conjugation between the

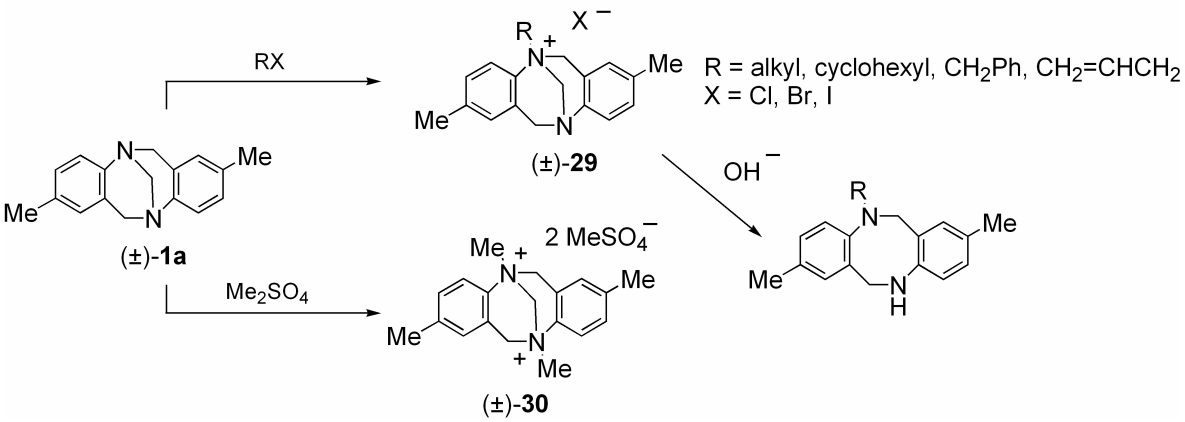
aromatic ring and the nitrogen atom. Thus, attempted Vilsmeier-Haack formylation of (±)-**1d** with DMF/$POCl_3$ gave no aldehyde.[45] Nevertheless, we are currently examining other electrophilic substitutions of (±)-**1d** that may result in interesting building blocks and intermediates.

Finally, an interesting derivative (±)-**28** bearing bromine and iodine atoms in the two different aromatic rings of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, which is inaccessible by other synthetic routes, was prepared in 68% yield by bromination of iodide (±)-**27** with NBS in DMF (Scheme 10). As discussed above, both bromine and iodine can serve as leaving groups in many cross-coupling reactions. At the same time, the difference in their reactivity allows the selective substitution of iodine, leaving bromine intact for subsequent transformations. This synthetic strategy will hopefully uncover its potential in upcoming years to provide shorter and more convergent access to sophisticated, unsymmetrical derivatives of Tröger's base such as "molecular torsion balances"[33] or "oligo-Tröger's bases"[46] (see Section 5.1.).

2.5. Reactivity of the aliphatic bicyclic system of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

The central, aliphatic bicyclic system of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine also offers potential for certain synthetic transformations. First of all, a possibility to prepare quaternary salts of Tröger's base was explored and the outcome is controversial. Results of several independent studies[47] have shown that quaternary monocationic derivatives such as (±)-**29** can easily be prepared upon the action of a suitable alkylating agent such as alkyl, cycloalkyl, benzyl or allyl halides (Scheme 11). At the same time, quaternization of both nitrogen atoms was not feasible even in the presence of a large excess of alkylating agent. This may be explained by the negative inductive effect of the positively charged quaternary nitrogen atom in (±)-**29** that greatly reduces the nucleophilicity of the tertiary nitrogen atom. However, Kostyanovsky and co-workers have recently reported the preparation of the dicationic derivative (±)-**30** in nearly quantitative yield in the reaction between Tröger's base ((±)-**1a**) and dimethyl sulfate (Me_2SO_4). The structure of (±)-**30** was confirmed by single crystal X-ray diffraction analysis.[48]

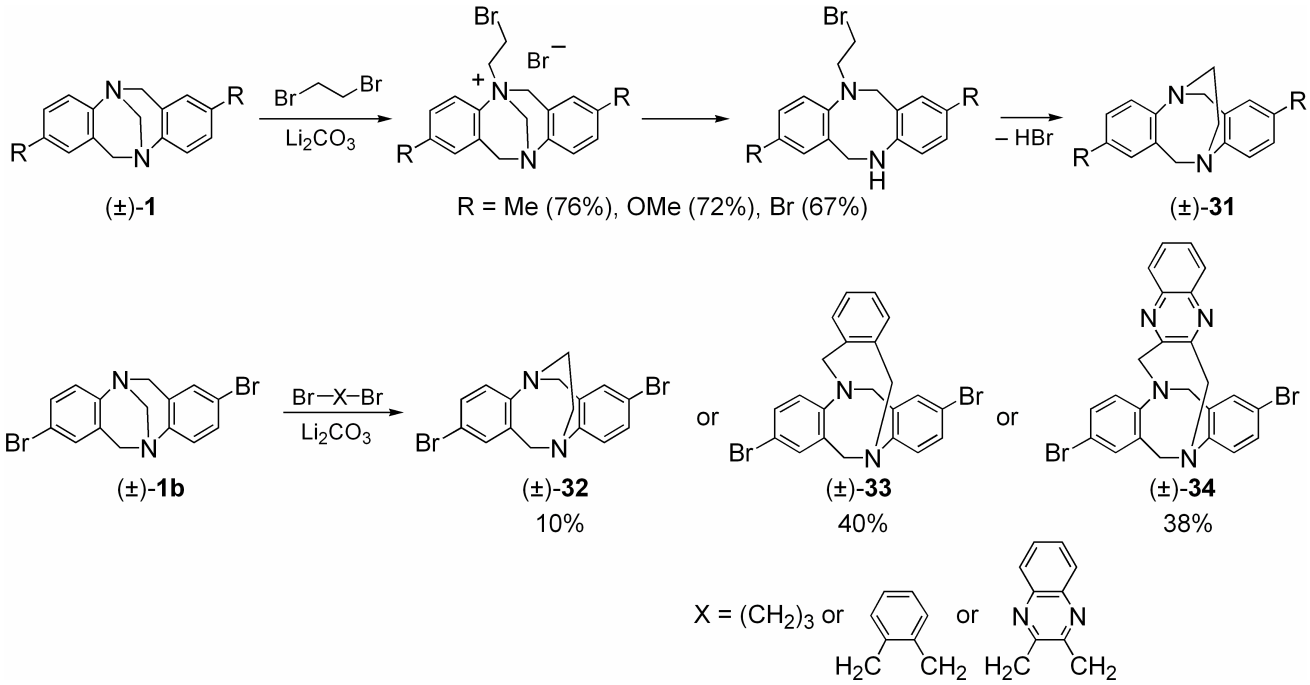
Analogues of Tröger's base can be viewed as aminals of formaldehyde. They are rather stable towards action of bases. However, quaternization of one nitrogen atom facilitates cleavage of the NCH_2N bridge: upon the action of strong bases, mono-quaternary salts (±)-**29** easily undergo loss of formaldehyde (Scheme 11).



Scheme 11

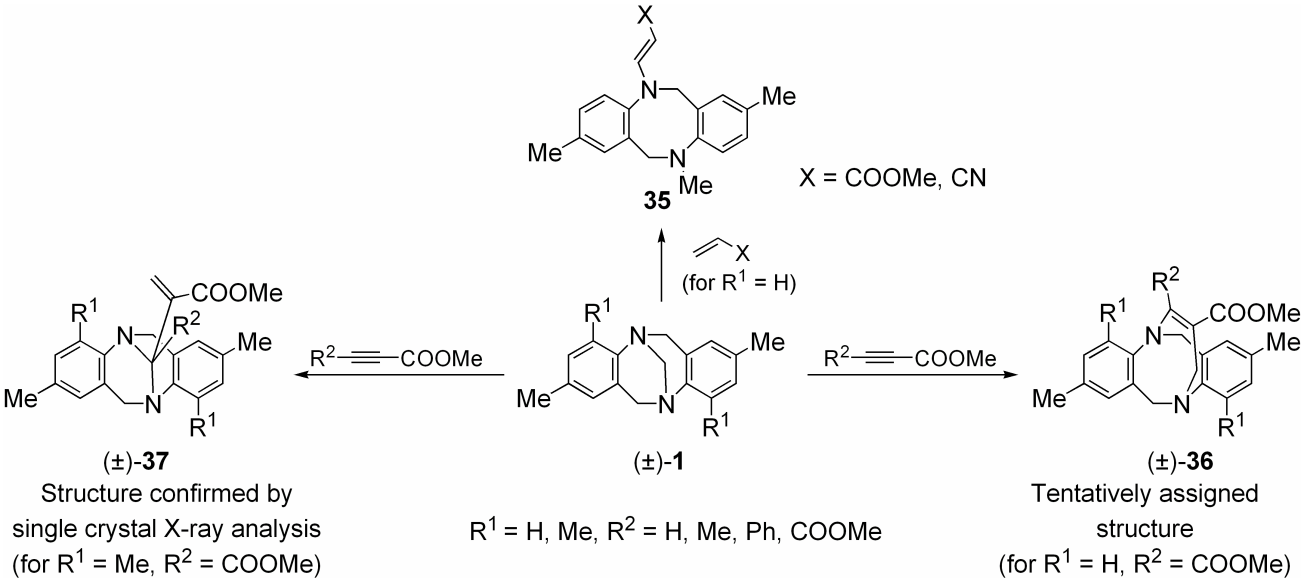
Formation of a quaternary salt and subsequent NCH_2N-bridge cleavage probably represent the two first steps in the reaction between analogues of Tröger's base and 1,2-dibromoethane (Scheme 12). In the

final step, intramolecular nucleophilic substitution of the second bromine atom with the secondary amino group leads to the unusual "bridge replacement" transformation to give an analogue of Tröger's base (±)-**31** featuring NCH_2CH_2N bridge. The analogous reaction with 1,3-dibromopropane proceeds only sluggishly (10% of (±)-**32**) and 1,4-dibromobutane gives no bridged product at all. These observations are not surprising, since the incorporation of $N(CH_2)_2N$ bridge implies the formation of a 7-membered ring, while $N(CH_2)_3N$ bridge requires formation of a less thermodynamically favored 8-membered ring, and $N(CH_2)_4N$ bridge of a highly strained 9-membered one. In addition, bridged derivatives (±)-**33** and (±)-**34** were prepared starting from *ortho*-bis(bromomethyl) derivatives of benzene and quinoxaline. While (±)-**31** with NCH_2CH_2N bridge maintains the V-shape similar to that of Tröger's base, molecules (±)-**32**–(±)-**34** with longer bridges adopt "flattened" conformations with two aromatic rings in a propeller-like orientation with respect to each other.[49]



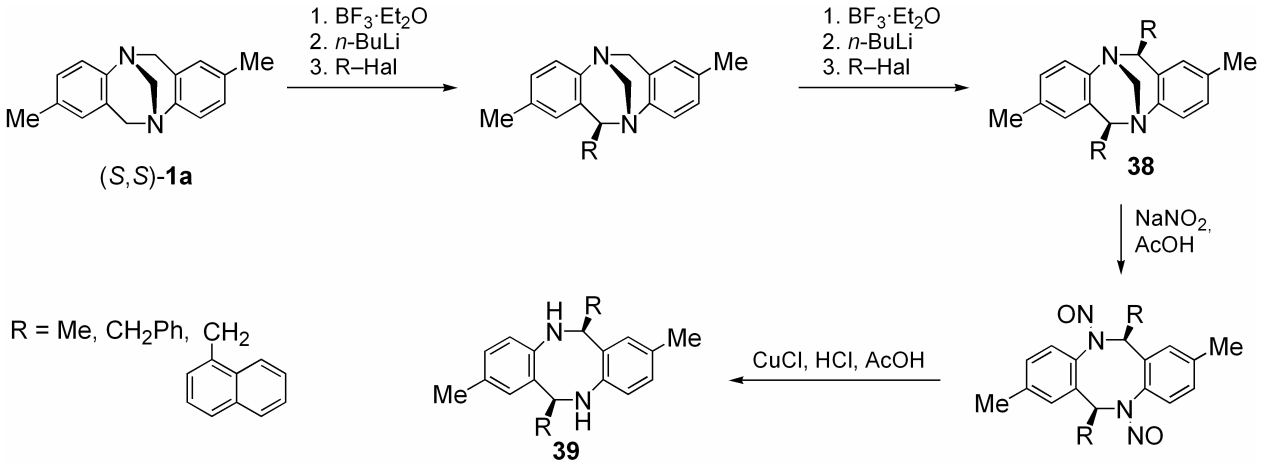
Scheme 12

Interesting products were recently obtained from the reaction between Tröger's base and some activated alkenes and alkynes. Reaction of Tröger's base ((±)-**1a**) with acrylonitrile or acrylates in the presence of Lewis acids gave dibenzodiazocines **35** (Scheme 13).[50] On the contrary, reaction of analogues of Tröger's base (±)-**1** with activated acetylenes afforded products with a central bicyclic moiety. Originally they were identified as enaminones (±)-**36** featuring three-carbon bridge between two nitrogen atoms. However, a later study of Kostyanovsky and co-workers revealed the structure (±)-**37** with an exocyclic $C{=}CH_2$ bond and a methylene bridge between the two nitrogen atoms, as was unambiguously confirmed by a single crystal X-ray analysis. The mechanism of this transformation is not fully clear and might include a rearrangement of **36** into **37**.[51] It is also worth mentioning that in these two studies, somewhat different substrates ((±)-**1**, R^1 = Me[51] *vs.* R^1 = H[50], Scheme 13) were used, and therefore, this issue might require further clarifications.



Scheme 13

Harmata and co-workers demonstrated the possibility of selective deprotonation of benzylic CH_2 in non-racemic Tröger's base (*S*,*S*)-**1a** with *n*-BuLi in the presence of $BF_3{\cdot}Et_2O$ followed by alkylation of the carboanion with alkyl halides.[52] Alkylation of two benzylic CH_2 groups can be performed in a stepwise manner without affecting the configuration of the Tröger's base skeleton to give **38** (Scheme 14). Subsequent cleavage of the methylene bridge between two nitrogen atoms by nitrosation followed by treatment with CuCl in HCl gives access to a new class of C_2-symmetrical diamine ligands **39** that may be useful in metal-catalyzed or organocatalytic transformations.

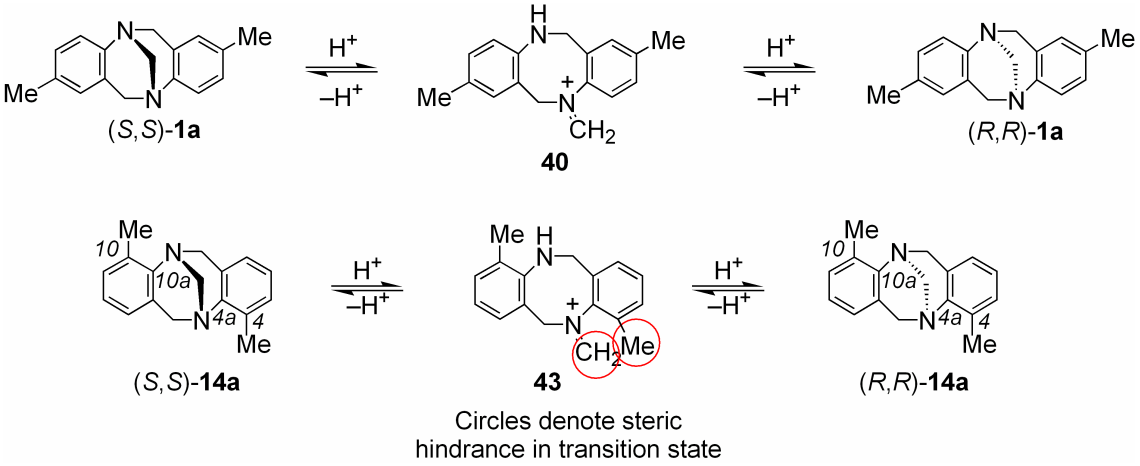


Scheme 14

3. Enantioseparations of Tröger's base and its analogues

Perhaps the most controversial chapter in the history of Tröger's base is related to separations of its enantiomers. As early as 1944, Prelog recognized the chiral nature of Tröger's base due to the hindered inversion of the bridge-head nitrogen atoms.[53] He also performed the separation of the enantiomers on specially prepared lactose. This was a truly pioneering work, representing the first separation of a chiral amine and at the same time, the first application of chromatography on a chiral stationary phase. It was also

Prelog who reported on the slow acid-catalyzed racemization of Tröger's base. It was postulated later that the inversion of configuration occurs *via* a reversible formation of an achiral iminium intermediate **40** that can with equal probability close back to either of the two enantiomers (Scheme 15). Although this racemization model appears very plausible, no spectroscopic evidence of iminium intermediate **40** has ever been obtained.[54] It should therefore be suggested that this intermediate is present in concentrations too low to be detected spectroscopically. Formation of **40** from the bicyclic structure **1a** should be much slower than the reverse process. This is also consistent with the fairly slow rate of racemization of Tröger's base in solution: racemization half-time of Tröger's base **1a** at 25 °C and pH 1 was found to be 6.4 h.[55]



Scheme 15

In accordance with observed acid-promoted racemization, it was postulated that chiral resolution of Tröger's base by the classical way, *i.e.*, *via* crystallization of diastereoisomeric salts with chiral acids is not feasible. Some unsuccessful attempts were indeed documented to confirm this assertion. However, a few "special cases" have been reported. An important exception is the isolation of enantiomerically pure (ee > 98%) Tröger's base (+)-**1a** with the aid of (–)-1,1´-binaphthalene-2,2´-diyl hydrogen phosphate described by Wilen and coworkers.[6] In these very special circumstances, a strongly acidic resolving agent does induce the racemization *in solution*, but only one enantiomer of Tröger's base *crystallizes* from solution as a stable salt. It should also be stressed that a *strongly acidic* resolving agent has been deliberately chosen to facilitate formation of a salt. Furthermore, the yield of (+)-**1a** from racemate was up to 93%, that is, 186% based on the amount of (+)-**1a** initially present in the racemate. This clearly implies that essentially all (–)-**1a** initially present in racemate has been isomerized to (+)-**1a**. Hence, this experiment cannot really be considered as a separation of enantiomers but rather as a crystallization-induced asymmetric transformation of one enantiomer into another. In another particular case, an aminoacridine analogue of Tröger's base (±)-**41** (see Scheme 4 above) was resolved by crystallization of its dibenzoyltartrate salts.[28] This separation was only possible because protonation of the more basic nitrogen atoms of the acridine rings, rather than the bridgehead atoms of Tröger's base moiety, prevented racemization *via* the formation of iminium intermediate.

However, some other reported cases of successful resolution do not fit into the above-described picture. Thus, a naphthyl analogue of Tröger's base (±)-**15a** (see Scheme 4 above) has been successfully resolved with the aid of either (+)- or (–)-di-*p*-toluoyl tartaric acid in dry acetone.[27] However, there should

be no considerable difference in the stability towards racemization of Tröger's base **1a** and its naphthyl analogue **15a**. Indeed, in a very recent communication the resolution of Tröger's base itself with the aid of (–)-(*R*,*R*)-dibenzoyltartaric acid ((–)-(*R*,*R*)-**42**) has been revisited.[12] Quite surprisingly, a salt (–)-(*R*,*R*)-**1a**·(–)-(*R*,*R*)-**42** was obtained after precipitation from acetone, and its neutralization afforded one enantiomer of Tröger's base (–)-(*R*,*R*)-**1a** with 91% ee (98% ee after a single crystallization). Structure of (–)-(*R*,*R*)-**1a**·(–)-(*R*,*R*)-**42** was confirmed by single crystal X-ray diffraction analysis. The bond lengths of the carboxylic groups and OH–N distances clearly indicate non-dissociated COOH and an efficient hydrogen bond O–H···N. Therefore, (–)-(*R*,*R*)-**1a**·(–)-(*R*,*R*)-**42** does not actually represent a salt, but a hydrogen-bonded aggregate. This observation is consistent with the information that "*resolution of (±)-**15a** failed in the presence of trace amounts of water*".[27] It seems reasonable to suggest that H_2O efficiently competes for the formation of hydrogen bonds and therefore prevents crystallization. On the contrary, in the absence of water crystallization induced by H-bonding occurs.

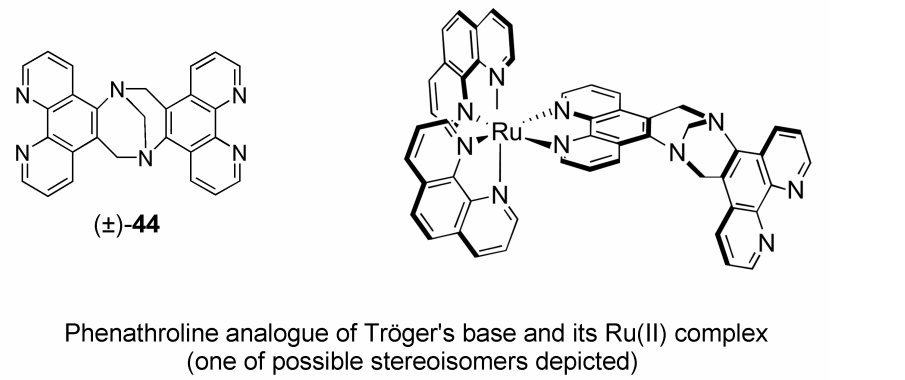
In another recent and interesting work, Kostyanovsky and co-workers reported considerable increase in the racemization energy barrier of Tröger's base analogues upon substitution in the *ortho*-positions relative to the nitrogen atoms (ΔG of enantiomerization was found to be 130.4 kJ mol^{-1} for (*S*,*S*)-**14a** *vs.* 101.4 kJ mol^{-1} for Tröger's base (*S*,*S*)-**1a**).[55] This observation has been rationalized in terms of the iminium intermediate **43**. For the isomerization of (*S*,*S*)-**14a** to (*R*,*R*)-**14a** (or *vice versa*) to happen, the methylene group of the iminium intermediate **43** formed from (*S*,*S*)-**14a** has to pass through the plane of the aromatic ring followed by back closure on the opposite side to give (*R*,*R*)-**14a** (Scheme 15). For this, a rotation around the C4a–N (or C10a–N) bond should occur. It is therefore predictable that the substitution of *ortho* hydrogens (in positions 4 and 10) by bulkier groups should increase the energy barrier of this process and consequently, slow down the enantiomerization. Although the resolution of racemic **14a** with the aid of chiral acids was not reported, it seems reasonable to suggest that derivatives with substituents in the *ortho* position respective to nitrogen atoms should be good candidates to test this approach.

All the cited above communications should prompt us to reconsider the (un)feasibility of resolution of Tröger's base derivatives with the aid of chiral, optically pure acids. An up-to-date statement concerning such a resolution should probably be moderated to the following one: "*Resolution of Tröger's base and its analogues via diastereomeric salts is in general feasible, but requires the careful choice of resolving agents and of experimental conditions. In particular, anhydrous aprotic solvents seem to be crucial. In addition, stability of Tröger's base analogues towards racemization in acidic medium considerably depends on the substitution pattern of the aromatic rings*".

Another convenient method for the enantioseparation of Tröger's base analogues is HPLC on chiral stationary phases (CSP). Here we are again confronted with a paradox: on the one hand, Tröger's base (±)-**1a** was the first substance ever resolved by a chromatography technique and later it became a standard probe for the evaluation of various newly designed CSPs. On the other, separations of functionalized derivatives of Tröger's base were not known until the last decade and still remain rather scarce. Thus, diamino derivative (±)-**21**[56] and a "trögerophane"[57] containing an oligoether linker between the two aromatic rings of the methanodibenzodiazocine scaffold have been separated on commercially available Chiralcel OJ (Daicel). Sergeyev and Diederich have published a communication describing successful analytical and semipreparative enantioseparations of a few Tröger's base analogues bearing ester or aldehyde functionalities.[16] In this study, cellulose-based Chiralcel OJ (Daicel) and Whelk O1 (Regis) with covalently

bound tetrahydronaphthalene derivative as chiral selector were demonstrated to be complementary in their scope.

These recent communications undoubtedly indicate the growing popularity of chiral HPLC that seems to become a method of choice for the enantioseparation of relatively small amounts of Tröger's base analogues. Typically, few milligrams to few grams of racemate can be separated in a single run on an appropriately sized column. Among further advantages of chiral HPLC, availability of both enantiomers from one experiment and very easy recovery of purified material by simple removal of solvents are worth mentioning. It should also be noted that derivatives of Tröger's base often demonstrate extraordinary quality of separations, thus providing easy access to materials with 100% ee and/or enabling the separation of unusually large quantities in a single run on overloaded columns. Chiracel OJ with cellulose tris(4-methyl-benzoate) as a chiral selector clearly remains the most succesful CSP (for Tröger's base (±)-**1a**, separation factor α = 4.81 and resolution R_s = 4.20 have been reported,[16] and even higher enantioselectivity was claimed by the manufacturer). Much better performance of Chiralcel OJ over other structurally related oligosaccharide phases suggests strong site-dependent chiral recognition. Undoubtedly, more examples of the separation of increasingly complex Tröger's base derivatives by chiral HPLC are to appear in the future.



Phenathroline analogue of Tröger's base and its Ru(II) complex
(one of possible stereoisomers depicted)

Scheme 16

Finally, an interesting example of resolution concerns a phenanthroline analogue of Tröger's base (±)-**44** that was used to prepare complexes $[Ru(phen)_2 \cdot \mathbf{44}]^{2+}$ (phen = phenanthroline) with an octahedral hexacoordinated Ru(II) center (Scheme 16). This creates an interesting stereochemical situation when elements of chirality originating from (±)-**44** and from Ru(II) center are combined in one molecule. When an optically pure precursor complex Λ-cis-$[Ru(phen)_2(Py)_2]^{2+}$ (Py = pyridine) was used, the resulting diastereoisomeric complexes Λ-(*R*,*R*)-$[Ru(phen)_2 \cdot \mathbf{44}]^{2+}$ and Λ-(*S*,*S*)-$[Ru(phen)_2 \cdot \mathbf{44}]^{2+}$ were isolated by fractional crystallization.[58]

To conclude this section, we would like to stress that both crystallization of diastereoisomeric salts with chiral acids and chiral chromatography proved useful to access enantiomerically pure derivatives of Tröger's base on preparative scale. These achievements undoubtedly pave the way for applications of Tröger's base analogues in asymmetric synthesis and catalysis, a nearly unexplored field.

4. Assignment of the absolute configuration of Tröger's base and its analogues

Determination of the absolute configuration of a chiral molecule is a common issue chemists have to tackle. Unless a crystal structure of a molecule featuring at least one stereochemical element with configuration unambiguously known from independent studies is available, such assignments rely on

indirect methods and are therefore not unmistakable. Determination of the absolute configurations of Tröger's base enantiomers serves as an excellent illustration of this problem. The first assignment of the absolute configuration published by Mason *et al.* was based on the analysis of circular dichroism (CD) data by the exciton chirality method.[59] According to these calculations, a dextrorotating enantiomer (+)-**1a** was determined to have (*R*,*R*) configuration. This assignment has been cited in the literature since 1967. However, in 1991 Willen and co-workers unequivocally proved by single crystal X-ray diffraction analysis of the salt of (+)-**1a** with (–)-1,1´-binaphthalene-2,2´-diyl hydrogen phosphate that this assignment was incorrect and should be inverted to (+)-(*S*,*S*)-**1a**/(–)-(*R*,*R*)-**1a**.[6] Another recently published single crystal analysis of salt (–)-**1a**·(–)-**42**[12] is also in agreement with this assignment. Rather confusingly, catalogues of some major chemical companies keep on quoting the erroneous absolute configurations of Tröger's base enantiomers. That, in turn, results in the citation of incorrect configurations even in the most recent scientific literature.[60] It is worth mentioning that CD spectroscopy should not be underestimated as a reliable method to obtain sufficiently accurate information on the absolute configuration of Tröger's base derivatives. Thus, Kostyanovsky and co-workers have demonstrated (by independent X-ray diffraction and CD spectroscopy studies on three variously substituted analogues of Tröger's base) a correlation between their absolute configuration and the sign of the absorption band corresponding to the transition from the ground state to the lowest-energy excited state.[61]

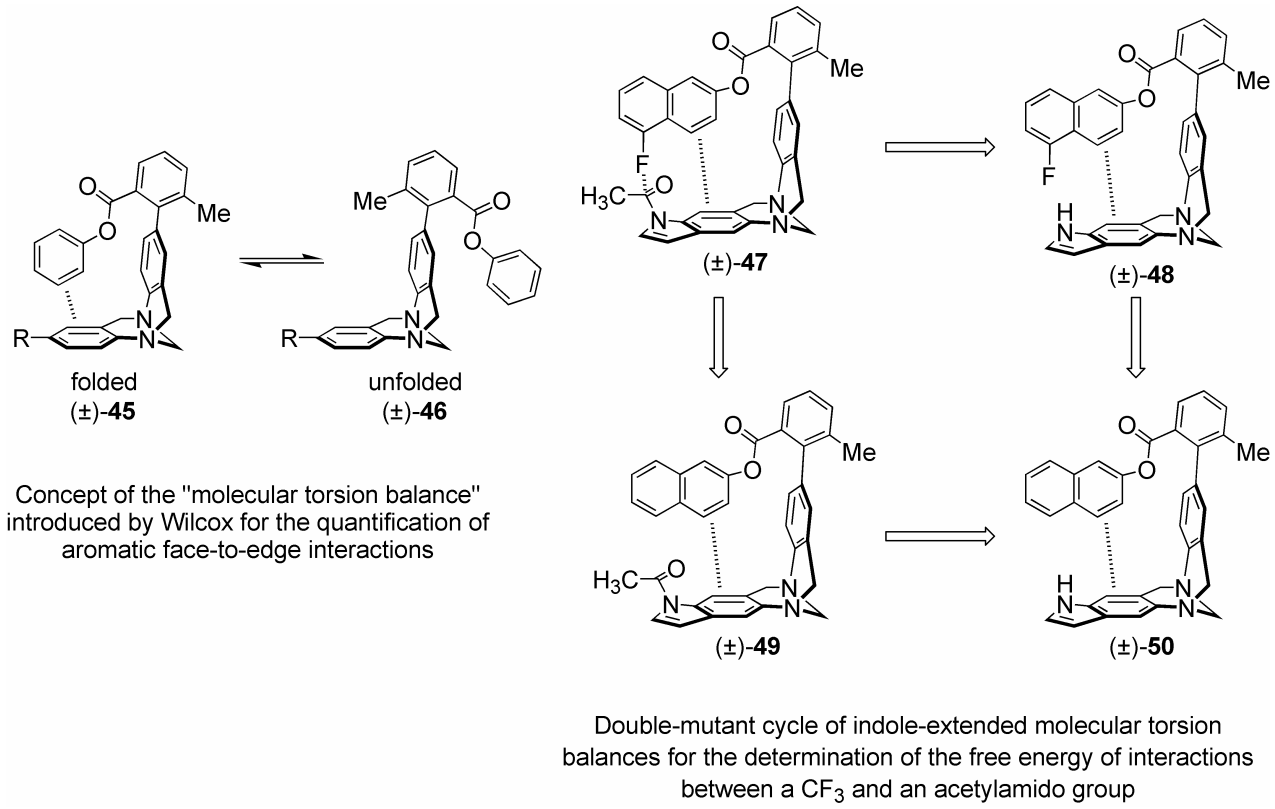
An interesting remark concerns very high values of specific optical rotation for analogues of Tröger's base containing expanded, fused aromatic systems. Thus, for naphthalene analogue (*S*,*S*)-**15a**[27] $[\alpha]_D = -1166$ 10^{-1} deg cm^2 g^{-1}, and for acridine derivative (*S*,*S*)-**41**[28] $[\alpha]_D = +4650$ 10^{-1} deg cm^2 g^{-1}. For comparison, $[\alpha]_D$ +280 10^{-1} deg cm^2 g^{-1} was reported for Tröger's base (*S*,*S*)-**1a**. In fact, among other organic molecules, only some helicenes outperform these values (*cf.* $[\alpha]_{589} = 3640$ 10^{-1} deg cm^2 g^{-1} for [6]helicene, $[\alpha]_{579} = 5900$ 10^{-1} deg cm^2 g^{-1} for [7]helicene, and $[\alpha]_{579} = 8100$ 10^{-1} deg cm^2 g^{-1} for [9]helicene).[62] It is interesting to note that similarly to helicenes, there is a growth of $[\alpha]_D$ value with an increase of the number of fused aromatic rings. One might therefore expect that further expansion of the fused aromatic system in analogues of Tröger's base might set a new world record in the value of specific optical rotation for small organic molecules.

5. Uses and applications of Tröger's base and its analogues

The unusual geometry of Tröger's base has encouraged a number of interesting molecular designs. In particular, numerous receptors bearing various functionalities attached to the V-shaped framework have been reported. Since these applications have been extensively covered by a few earlier comprehensive reviews,[1,2,63] we will largely focus on two categories of applications. Firstly, a review of still relatively scarce applications that take advantage not only of the geometry, but also of the chirality of Tröger's base will be given. Secondly, we will attempt to provide a full account of publications that appeared since the beginning of the year 2006 and were not covered by the most recent review.[2]

5.1. Overview of recent applications of Tröger's base analogues

Perhaps the most elegant and at the same time the most fundamentally important molecular design using Tröger's base motif is the "molecular torsion balance" (Scheme 17) originally designed by Wilcox *et al.*[35] and further developed by Diederich *et al.*[41]



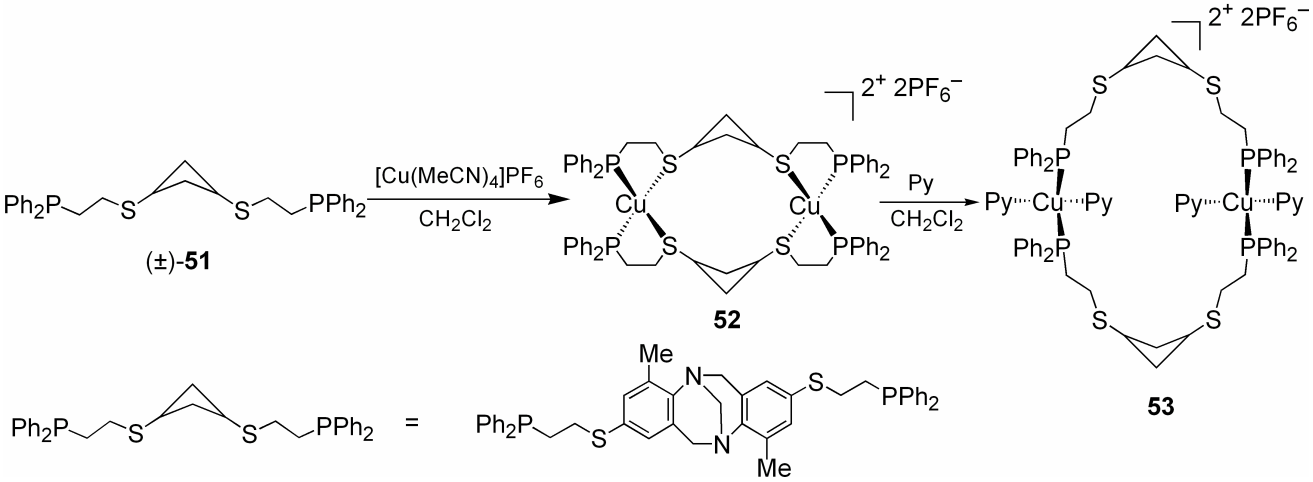
Scheme 17

Small differences in free energy between "folded" and "unfolded" conformers such as (±)-**45** and (±)-**46** can be measured from NMR experiments and used for the quantification of weak forces such as aromatic edge-to-face interactions,[35] CH-π interactions,[35] or weak attractions between organic fluorine and an amide group.[41] Characterization of such forces is of primary importance for the understanding of protein folding and for the rational design of enzyme inhibitors. It is therefore unsurprising that groups of Wilcox and Diederich have revisited this concept very recently. An improved design of Wilcox's molecular balance offers solubility in water and allows to avoid corrections for the change of dipole moment between folded and unfolded conformers.[33] The last generation of Diedrich's molecular balance (±)-**47**–(±)-**50** comprising an indole fragment required considerable efforts (up to 21 synthetic steps from commercially available materials), but in return, provided a final proof for the existence of attractive orthogonal dipolar interactions between a C_{sp2}–F bond and an amide carbonyl group.[64] Since fluorine has become a widespread and important component of many drugs and drug candidates, this type of interactions represents a new, important tool to tune protein–ligand interactions in medicinal chemistry research.[65]

In the two recent years, some new ideas exploring the unusual V-shaped geometry of Tröger's base have emerged. Thus, Bew *et al.* have suggested Tröger's base as a scaffold to induce *ca.* 90° turn in synthetic peptides.[38] Lützen and co-workers have developed extended ligands with 2,2'-bipyridine or 2-pyridylmethanimine functions appended to the Tröger's base scaffold. Upon coordination to Cu^+ or Ag^+ cations, these ligands undergo a diastereoselective self-assembly into double-stranded helical superstructures.[20] In a similar fashion, ligands with catechol end-groups were shown to self-assemble into triple-stranded helicates around Ti(IV) ions. However, the latter process was not diastereoselective.[40]

The structural motif of Tröger's base was incorporated into a phosphine/thioether chelating ligand (±)-**51**, that was reacted with Cu(I) or Rh(I) complexes. Due to different preferred coordination geometries

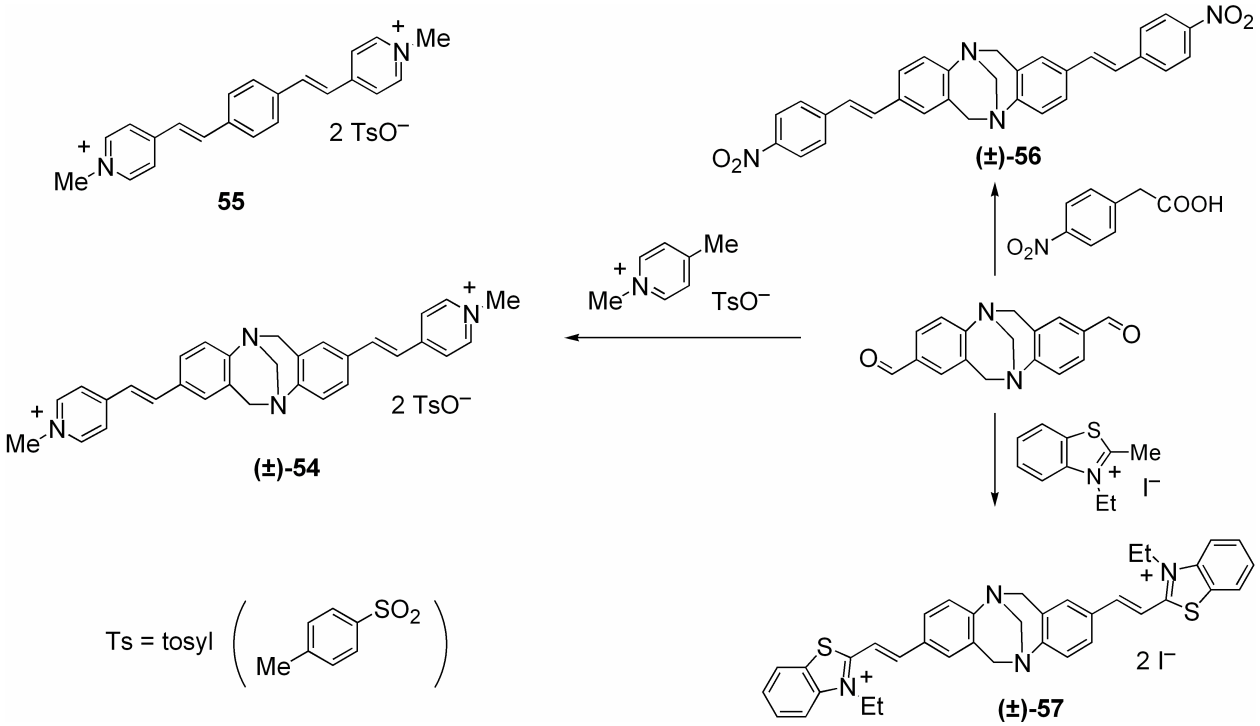
of Cu(I) and Rh(I), different types of metallomacrocycles were obtained. In the case of Cu(I), that has a tendency to form complexes with tetrahedral geometry, a dimeric macrocycle **52** was quantitatively formed upon the ligand exchange in $[Cu(CH_3CN)_4]PF_6$ through phosphine/thioether chelating functions of (±)-**51**. Upon addition of pyridine, the weaker coordination bond between Cu and S was cleaved while the stronger Cu–P bond was retained to give an expanded dimeric macrocycle **53** (Scheme 18). In case of a Rh(I) complex, with preferred square planar geometry, a more complicated situation was observed, namely, the formation of a mixture of di- and trimeric metallomacrocycles.[66]



Scheme 18

Very recently, the first examples of molecular designs directed towards materials for optical applications and combining rigid scaffold of methanodibenzodiazocine with (hetero)aryl vinylene motifs have been suggested. Thus, quaternary bis-pyridyl derivative (±)-**54** demonstrated unusually efficient aggregation-induced light emission in solid state, while luminescence in solution was quenched.[67] This behavior is strikingly different to that of a planar analog **55** comprising the same chromophores as (±)-**54** but with V-shaped Tröger's base scaffold replaced with a flat 1,4-phenylene moiety. Solid-state fluorescence was thus attributed to the solid state packing features that result from the V-shape of (±)-**54**. In addition, we have recently reported on the synthesis and optical properties of similarly designed bichromophoric systems with two para-nitrophenylene or benzothiazolium moieties ((±)-**56** and (±)-**57**, respectively, Scheme 19).[45] Combination of donor-π-acceptor design and inherent chirality of the molecule may prove promising in the design of novel non-centrosymmetric materials for NLO applications.

The framework of Tröger's base has been extensively used, first by Wilcox and then by others in the design of synthetic H-bonding receptors with various recognition elements for functionalized molecules.[2] A great deal of attention has recently been given to "bis-, tris- and oligo-Tröger's bases", that is, molecules comprising two, three or more methanodibenzodiazocine units fused in such a way that an aromatic ring of one methanodibenzodiazocine unit constitutes a part of a neighboring one. Interest in these molecules arose from the challenge to create relatively unfunctionalized molecular tweezers or molecular clefts with extended concave surfaces. These molecular shapes are important for the understanding of recognition processes on concave surfaces that are governed largely by non-directional solvophobic effects and van der Waals interactions as well as, in relevant cases, by π-stacking and cation-π interactions.



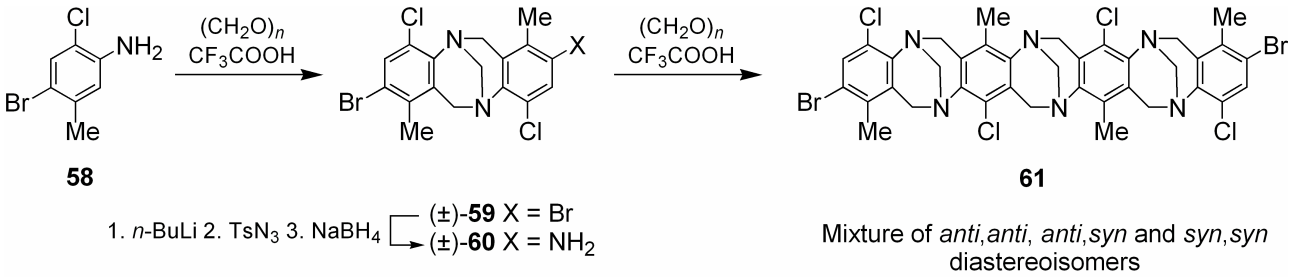
Scheme 19

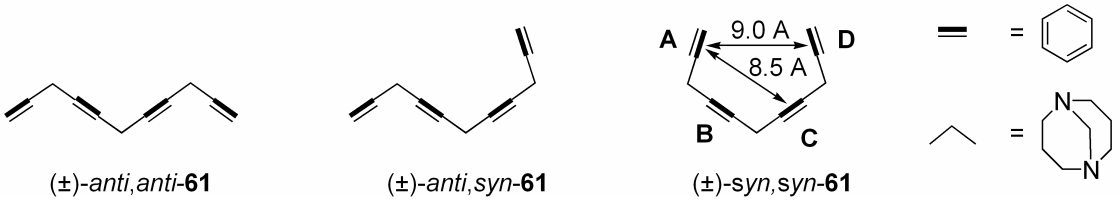
For "oligo-Tröger's bases", multiple regioisomers are possible depending on the pattern in which benzene rings and methanodiazocine bicycles are fused. Various synthetic methodologies have been developed in order to overcome regio- and diastereoselectivity issues, which become more and more complex with the increasing number of fused methanodibenzodiazocine cores. This subject was extensively covered by the excellent review of Král, Elguero and co-workers[2] (see also the most recent publications from one of these groups).[68]

Here, let us consider as an illustrative example the recently published synthesis of a "linear tris-Tröger's base" (Scheme 20).[46] Dibromo derivative of Tröger's base (±)-**59** was prepared from the corresponding aniline **58** by a standard method and then subjected to desymmetrization according to discussed above Wärnmark's lithiation methodology to give amine (±)-**60**. In a key step, the central methanodiazocine unit in the "linear tris-Tröger's base" **61** was assembled by the condensation of (±)-**60** with paraformaldehyde. Since (±)-**61** has a bromine atom in each terminal benzene ring, this desymmetrization followed by condensation can be repeated to synthesize higher generations of "linear oligo Tröger's bases" comprising 2*n*+1 methanodiazocine bicycles (where *n* is a number of methanodiazocine bicycles in the previous generation; *n* can thus be equal to 3,7,15...).

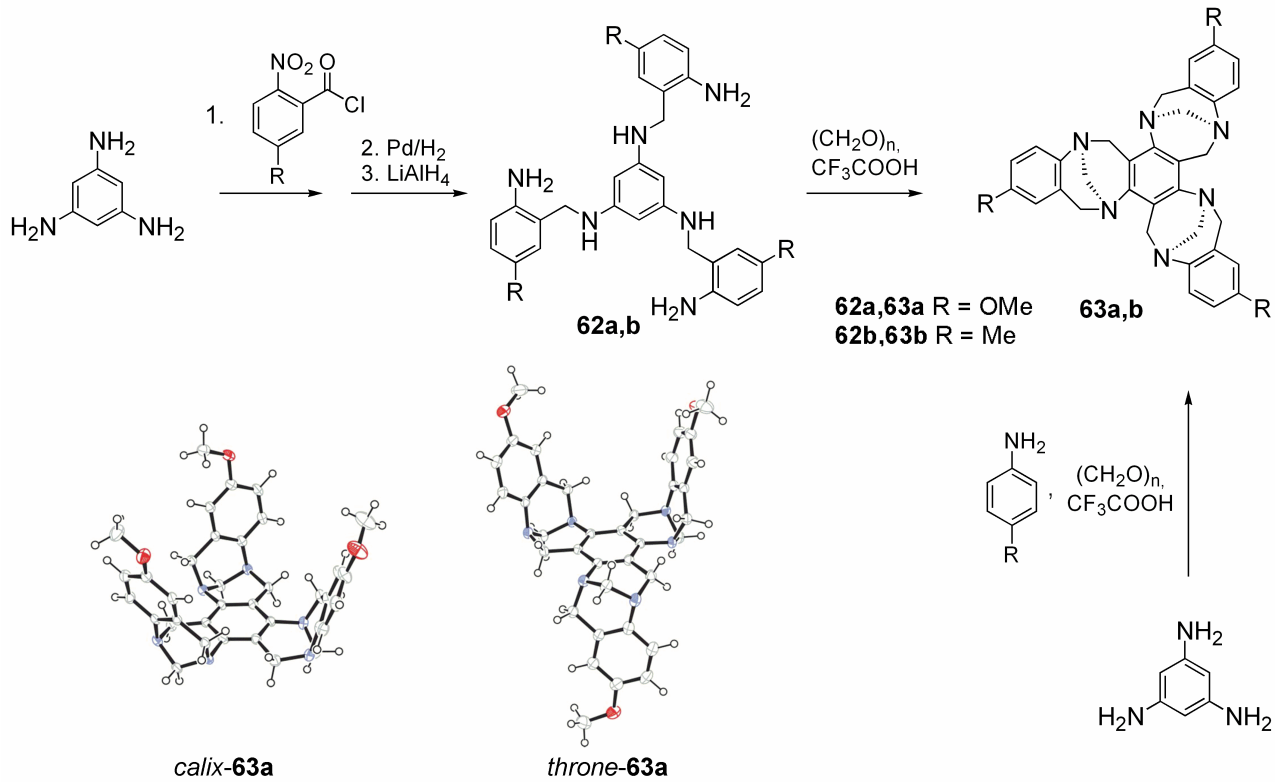
"Tris-Tröger's base" **61** was obtained as a mixture of three diastereoisomers, schematically represented in Scheme 20. All three diastereoisomers of **61** that differ in mutual orientation of methanodiazocine bridges were isolated and two of them (*syn*,*syn* and *anti*,*syn*) were unambiguously identified by X-ray diffraction analysis. A molecule of (±)-*syn*,*syn*-**61** has a cleft-like shape with distances of 8.5–9.0 Å between the planes of aromatic rings A–C and A–D. (±)-*Anti*,*syn*-**61** also features a cleft but its size is smaller. Interestingly, addition of NH_4Cl to the reaction mixture during the synthesis of **61** resulted in the increase of the ratio of cleft-shaped *syn*,*syn* and *anti*,*syn* isomers respective to *anti*,*anti* isomer, suggesting a template effect of the ammonium ion. It is worth mentioning that Cl atoms primarily served to

block one of the *ortho*-positions and therefore to exclude formation of other possible regioisomers. However, it turned out that they also bring stability towards the acid-promoted isomerization: little or no interconversion was observed for all three diastereoisomers upon treatment with 3M HCl at temperatures up to 95 °C for 6 days. This is in striking contrast with general ease of racemization of Tröger's base derivatives, as well as with facile interconversion of diastereoisomers of some other "oligo Tröger's bases" lacking substituents in *ortho* positions relative to the nitrogen (see references cited in[46]). At the same time, stability of **61** is in perfect agreement with the high enantiomerization barrier for the analogue of Tröger's base **14a** bearing methyl substituent in *ortho* positions (see Section 3. above).





Scheme 20



ORTEP style plots reproduced from ref.[69] by permission of the Royal Society of Chemistry

Scheme 21

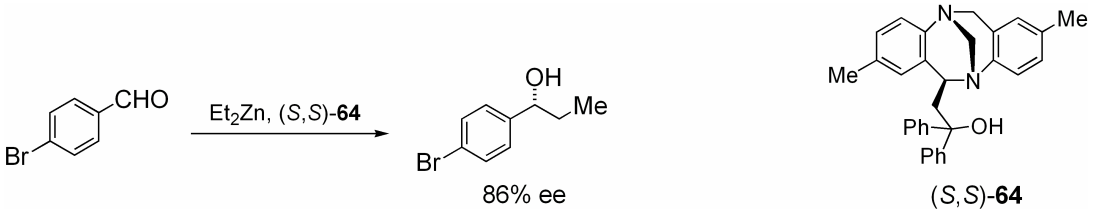
Recently, a unique "tris-Tröger's base" system with all three methanodibenzodiazocine units sharing a single benzene ring was reported. In the crucial synthetic step, the treatment of a precursor **62a,b** (prepared from 1,3,5-triaminobenzene in a three-step synthesis) afforded "tris-Tröger's bases" **63a,b** in 8–18% yield.[69] Rather strikingly, **63b** was also prepared in one-step direct condensation between 1,3,5-triaminobenzene and 4-methylaniline. In spite of low isolated yield (2% of **63b**), this transformation is a spectacular example of a multicomponent reaction with a total of 13 participating molecules and 18 carbon-carbon and carbon-heteroatom bonds formed in a single synthetic step (Scheme 21).

In acidic solution, **63a** exists as an equilibrium mixture of *calix*-**63a** and *throne*-**63a** in a ratio 3 : 97. In neutral conditions both diastereoisomers are stable: they were separated by column chromatography and identified with the aid of single crystal X-ray diffraction analysis. *Calix*-**63a** is particularly attractive since it can be viewed as a cavitand with an estimated cavity volume of ca. 78 $Å^3$ and should be capable to accommodate small guest molecules.

5.2. Applications based on the chirality of Tröger's base scaffold

In this last section, we will focus on applications based on the *chirality* of Tröger's base. Apart from the mentioned above use as a standard probe for the efficiency of chiral sorbents for chromatography, such applications remain rather scarce. Wilen *et al.* have used enantiomerically pure Tröger's base (+)-**1a** as a chiral solvating agent and observed enantiodiscrimination in ^{1}H NMR spectra of a few racemic alcohols.[6] Demeunynck and colleagues reported on a remarkable enantioselective interaction of an acridine analogue of Tröger's base (+)-**41** with calf thymus DNA, presumably, *via* minor groove binding of V-shaped motif rather than by the intercalation of acridine fragment.[28]

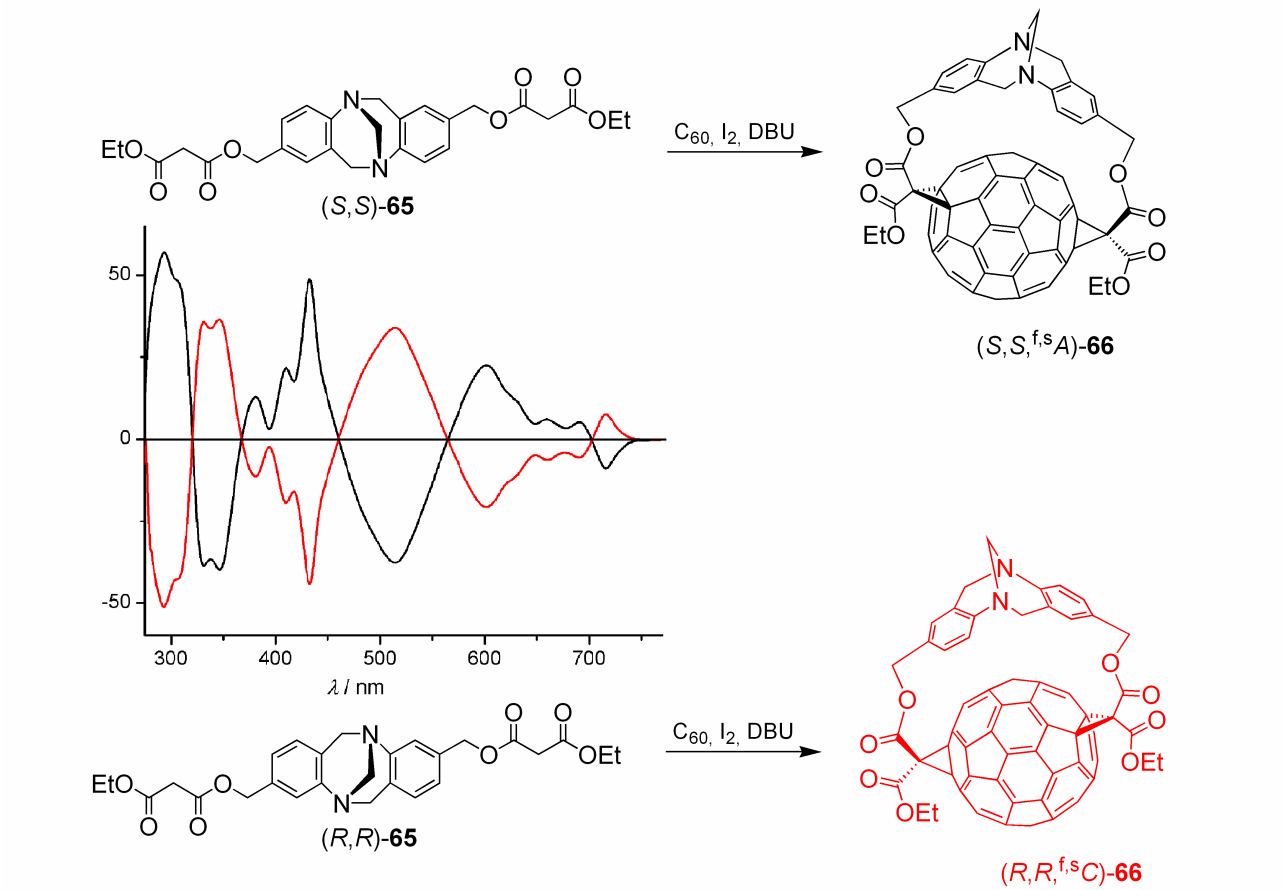
Applications of Tröger's base and its analogues in asymmetric catalysis are very limited. Thus, enantiomerically pure Tröger's base demonstrated moderate asymmetric induction as an additive in the 1,4-addition of aryllithium reagents to α,β-unsaturated esters (57% ee),[70] in heterogeneous hydrogenation of ethyl pyruvate (65% ee)[71] and, more recently, in the aziridination of chalcones.[72] In spite of relatively modest values of asymmetric induction, the results of these scattered studies should be viewed as a promising initial lead, rather than as an ultimate limit. In fact, there is no reason why an arbitrary chosen (apparently, due to its commercial availability in the enantiomerically pure form) derivative of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, lacking any additional functional group, should be the best candidate for applications in asymmetric catalysis. Actually, the only documented attempt to build a rationally designed ligand (*S*,*S*)-**64** for catalytic applications resulted in rather encouraging (up to 86% ee) asymmetric induction in the addition of Et_2Zn to aromatic aldehydes (Scheme 22).[73] On the contrary, when unfunctionalized Tröger's base (*S*,*S*)-**1a** was used as a ligand, ee did not exceed 22%.



Scheme 22

An elegant application of Tröger's base in the functionalization of fullerenes has recently been reported by Sergeyev and Diederich.[15,74] Two reactive malonate groups were installed in different positions

of the rigid Tröger's base scaffold that was acting as a "tether" or "spacer". In a subsequent "tether-directed" double cyclopropanation of C_{60}, regio- and stereoselectivity is governed by the length and the geometry of a tether. Depending on the distance between reactive malonate groups, derivatives of Tröger's base afforded various bisadducts of C_{60}, and each time only one out of multiple, theoretically possible regioisomers was obtained. Even more remarkably, addition of enantiomerically pure bismalonates to C_{60} proceeds with perfect diastereoselectivity and afforded enantiomerically pure fullerene derivatives with inherently chiral *trans*-2 addition patterns: (*R*,*R*)-**65** gave exclusively (*R*,*R*,^{f,s}*C*)-**66** and (*S*,*S*)-**65** gave exclusively (*S*,*S*,^{f,s}*A*)-**66**, respectively (Scheme 23).[75]



Diastereoselective synthesis of fullerene bisadducts with inherently chiral *trans*-2 addition pattern and CD spectra of enantiomeric bisadducts (*R*,*R*,^{f,s}*C*)-**66** and (*S*,*S*,^{f,s}*A*)-**66**

Scheme 23

This very high asymmetric induction is particularly noticeable, given the very large distance between the two reactive centers spanned by a chiral tether. To the best of our knowledge, there are no other examples of asymmetric syntheses using the structural motif of Tröger's base as a chiral auxiliary.

Absolute configuration of fullerene chromophores has been established from the comparison of their CD spectra with those of previously reported optically pure derivatives of C_{60} with the same addition pattern. Absolute configurations of malonates (*R*,*R*)-**65** and (*S*,*S*)-**65** have been assigned on the basis of the sign of the lowest-frequency transition in their CD spectra (see Section 4.). Knowing the absolute configuration of all chiral elements in fullerene adducts **66**, the difference in the enthalpies of formation $\Delta\Delta H$ =

29.4 kcal mol^{-1} in favor of the actually formed (*S*,*S*,^{f,s}*A*)-**66** over the hypothetical diastereoisomer (*S*,*S*,^{f,s}*C*)-**66** has been calculated by semi-empirical PM3 geometry optimization. Assuming that thermodynamic stability of the possible bis-cyclopropanated products is reflected in the energy of the transition state of the second cyclopropanation, this explains very well the experimentally observed high asymmetric induction.

Similar strategy applied to fullerene C_{70} allowed the preparation of bis- and tetrakis-cyclopropanated adducts of C_{70} with well-defined addition pattern and with excellent regioselectivity.[76] An interesting aspect of the described above Bingel additions to fullerenes is an efficient chirality transfer from the C_2-symmetrical framework of Tröger's base to the extended helix-shaped fullerene chromophores that display pronounced Cotton effect over remarkable range of wavelengths (up to 750 nm).

There are only a very limited number of reports on the attempted applications of Tröger's base for chiral separations. Thus, "molecular imprinting" of polymers with enantiopure Tröger's base was successfully attempted. However, the efficiency of the obtained polymer was only demonstrated for the resolution of Tröger's base itself.[60,77] To the best of our knowledge, there were no reports on the use of analogues of Tröger's base as chiral selectors for CSP. This is rather surprising considering the above mentioned enantiorecognition of Tröger's base by variety of chiral phases. A notion of reciprocity plays a considerable role in the design of CSPs: if a single molecule of a chiral selector has various affinities for two enantiomers of another substance, then a single enantiomer of the latter will also have different affinities for the two enantiomers of the selector. Taking into account the extraordinary enantioseparation of Tröger's base on some CSPs, the use of its derivatives in the design of novel chiral selector may prove promising.

6. Conclusions

Review of the recent literature devoted to the chemistry of Tröger's base analogues shows a number of remarkable achievements. New synthetic methods provide access to complex derivatives of Tröger's base, functionalized in a variety of ways. The fact that some of the old paradigms related to the synthesis and chiral separations need to be revisited makes the research in this field even more exciting.

Tröger's base has already become very useful in some areas of chemistry, for instance in the design of V-shaped synthetic receptors and of "molecular torsion balances" for the quantification of weak molecular forces. In the future, we hope to see a growing number of new applications and uses of this fascinating molecule. In particular, the chirality of Tröger's base still has to uncover its true potential. Increasing research efforts in chiral separations of analogues of Tröger's base paves the way to their application in asymmetric catalysis and organocatalysis. Recently pioneered applications of the Tröger's base skeleton in charge-transfer chromophores lay the groundwork for the design of prospective NLO materials. Current interest in "oligo-Tröger's bases" is catalyzed by the possibility to create molecular clips and clefts with expanded concave surfaces. Finally, in view of emerging examples of metallomacrocycles and helicates, self-assembly of more complex supramolecular structures – such as capsules, cages, synthetic nanotubes or three-dimensional organometallic networks – appears as a promising field.

Acknowledgments

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75. Configurational descriptors $^{f,s}C/^{f,s}A$ (f = fullerene, s = systematic (numbering), *C* = clockwise, *A* = anticlockwise) are used to express the chirality sense of fullerenes and their derivatives, similarly to descriptors *R*/*S* for a stereogenic center, or *P*/*M* for a helix. For detailed explanation of descriptors $^{f,s}C/^{f,s}A$, see: Powell, W. H.; Cozzi, F.; Moss, G. P.; Thilgen, C.; Hwu, R. J.-R.; Yerin, A. *Pure Appl. Chem.* **2002**, *74*, 629.
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PHENOLIC OXIDATIVE COUPLING IN THE BIOMIMETIC SYNTHESIS OF HETEROCYCLIC LIGNANS, NEOLIGNANS AND RELATED COMPOUNDS

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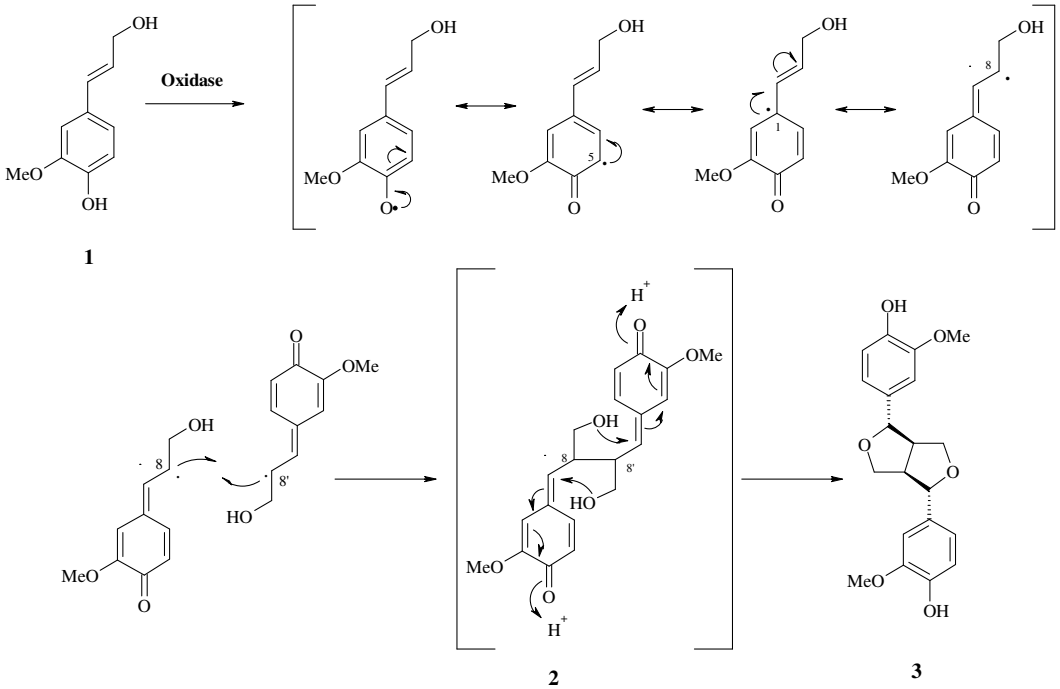
Abstract. *The literature of the period 1994–2007 on phenolic oxidative coupling in the biomimetic synthesis of heterocyclic lignans, neolignans and related compounds has been reviewed. More than 100 dimeric and trimeric compounds have been reported, some of them with unusual structures (for instance, benzo[kl]xanthenes, stilbenolignans, nitrogenated neolignans and others) or displaying promising biological properties (for instance, antioxidative, antitumor, antiangiogenic, antimalarial, MDR inhibitory, neurotrophyc or antifeedant activity). Because of the lack of stereochemical control, radical coupling reactions normally give rise to mixtures of enantiomers: this is true not only for metal-mediated reactions, but also for reactions catalysed by peroxidases (such as horseradish peroxidase, HRP) or laccases. Nothwithstanding this limitation, radical coupling reactions frequently occur with high regio- and diastereoselectivity and, in some cases, high (> 80%) overall yields are reported. Thus, this kind of simple reaction, occurring in mild conditions, may be of preparative utility, in particular when a library of analogues of bioactive lignans has to be prepared. Evidence suggests that the regio- and diastereoselectivity are strongly influenced by the relative stability of the intermediate radicals or quinone methides. Attempts to orient the stereoselectivity of the coupling by means of a chiral auxiliary pendant have been reported only in a few cases. The cross-coupling reactions afforded interesting heterodimers such as those including a 1,4-benzodioxane nucleus or stilbenolignans.*

Contents

1. Introduction

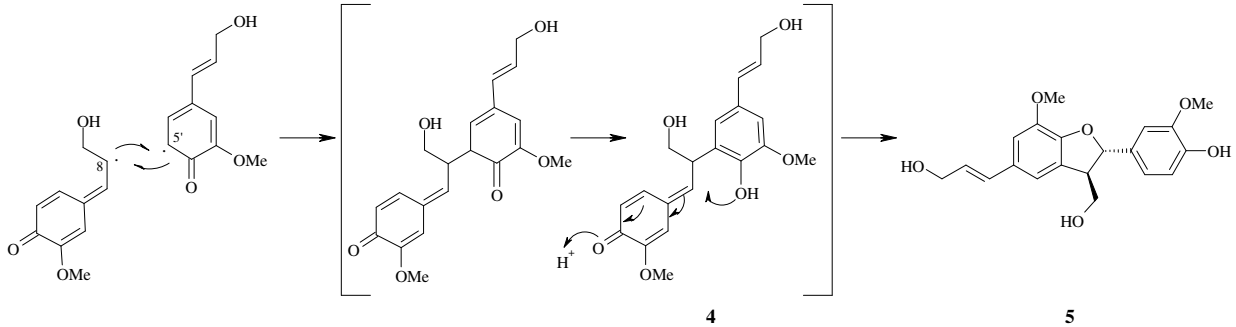
Lignans and related compounds (neolignans, oxyneolignans and others) are widely distributed within the Plant Kingdom. In these secondary metabolites, carbon skeletons are normally constituted by two phenylpropanoid (C_6C_3) units. Their biosynthetic origin is from the shikimate pathway: the term 'lignans', originally introduced by Haworth[1] and related to the woody tissue from which many of the first specimens were obtained, refers to dimers generated by β-β' (8-8') oxidative coupling of two cinnamic acid residues. Many lignans and neolignans include a heterocycle in their structure. This is normally generated through intramolecular cyclization of a reactive intermediate (quinone methide) formed in the oxidative coupling step, as exemplified by the biosynthesis of the lignan (+)-pinoresinol (**3**) (Scheme 1a). This biosynthetic

pathway has been widely studied and it is known that pinoresinol originates from the monolignol coniferyl alcohol (**1**): in the first step an oxidase gives rise to the coniferyl alcohol radical, whose mesomeric forms are reported below. Subsequently, a coupling reaction affords a reactive quinone-methide intermediate (**2**) whose cyclization gives the final product **3**.[2]



Scheme 1a

An important point on lignan and lignin biosynthesis is that the regio- and stereospecificity of bimolecular phenoxy radical coupling is not controlled by peroxidases, laccases or other oxidases, as demonstrated by the formation of racemic mixtures as product of *in vitro* oxidative coupling experiments.[3] An authoritative study by Davin *et al.*, published in *Science*,[4] showed that the stereospecificity of 8-8'-radical coupling is not due to the oxidase but is under control of a 'Dirigent Protein (DP)': two coniferyl radicals are hosted in binding sites '*si*-face to *si*-face' in order to determine the stereochemical asset of the quinone-methide intermediate and consequently the configurations of the stereogenic centres in (+)-pinoresinol (**3**).

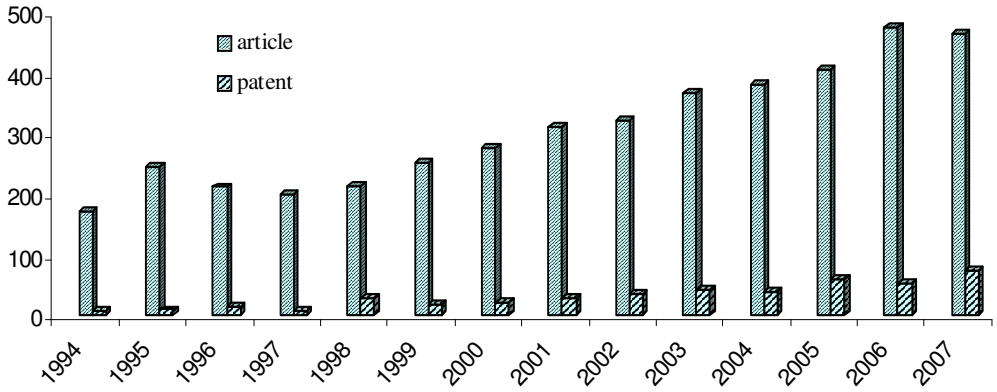


Scheme 1b

According to the IUPAC recommendations 2000,[5,6] 'neolignans' are distinguished in referring to dimers with a carbon linkage between two C_6C_3 units different from 8-8', as for example in

(+)-dehydrodiconiferyl alcohol (**5**), whose biosynthesis, outlined in Scheme 1b, proceeds *via* the quinone-methide intermediate **4** formed through an 8-5' coupling of coniferyl radicals.[2] The term 'oxyneolignans' should be reserved to dimers linked by an ether oxygen atom where there are no direct carbon–carbon bonds between the C_6C_3 units.

As shown by Graph 1, the number of references retrieved through Scifinder Scholar using the term 'lignans' is in constant growth since 1997 to date and a similar trend is observed if the search is restricted to the patents.



Graph 1

This is probably due to the wide range of biological activities reported for many lignans, neolignans and related compounds of synthetic/semisynthetic origin: the most cited example of bioactive lignan is podophyllotoxin (**6**), a dimeric phenylpropanoid known as a constituent of *Podophyllum peltatum* since 1880, and isolated as an antitumor principle around 1950;[7] later work on **6** as lead compound afforded the semisynthetic anticancer drug etoposide (**7**) (Figure 1).[8]

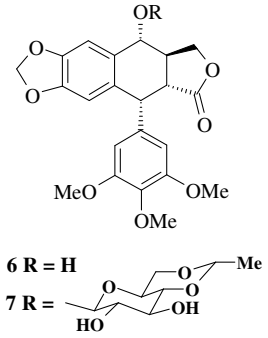


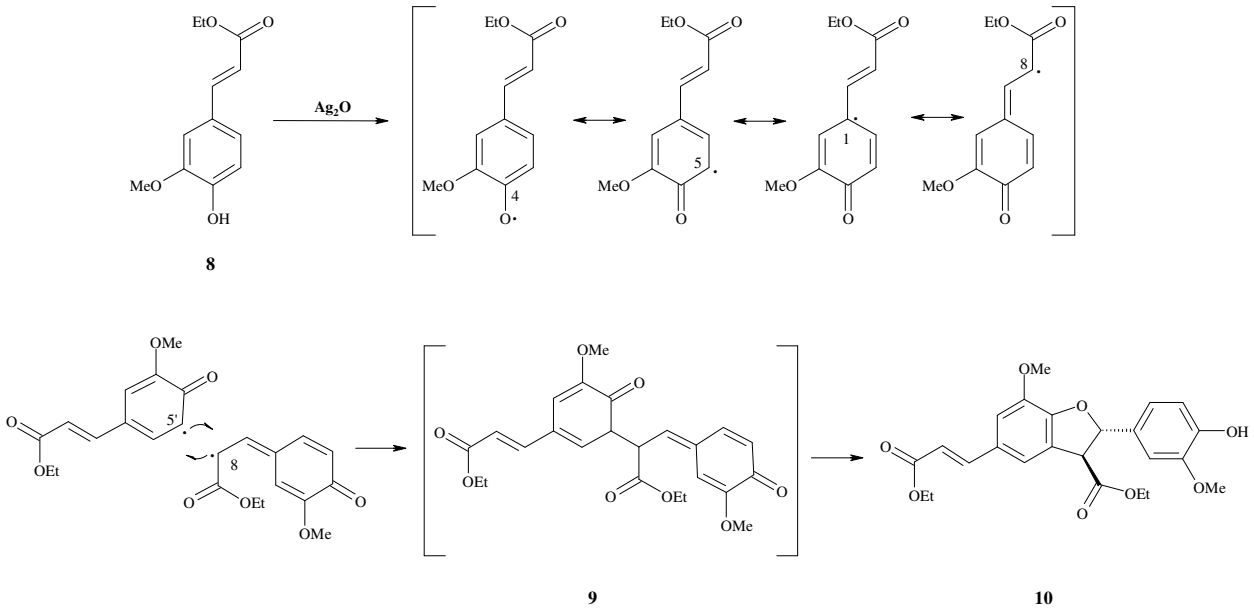
Figure 1

A book on the chemical, biological and clinical properties of lignans, edited by Ayres and Loike, was published in 1990[9] and many other data have been reported in excellent reviews by Whiting,[10–12] Ward[13–15] and other authors.[16] More recently, various biological activities of lignans and neolignans have been reviewed, among them cytotoxic, antimitotic, antileishmanial,[17–19] antiangiogenic,[20] cardiovascular[21] and antiviral activity.[22] Lignans are involved in the chemical defence of plants against insects, acting as regulator of insect feeding and the antifeedant activity of some compounds of this group has been reported.[23] In addition, lignans as constituents of foods and herbs have been studied as chemopreventive agents able to counteract degenerative diseases.[24–26]

Due to their biological properties as well as to their structural variety, lignans, neolignans and related compounds are an attractive target for chemical synthesis/modification. A number of synthetic methods has been reviewed previously, with particular reference to podophyllotoxin and analogues.[9–15,27–30] A review on biotransformation of lignans and neolignans has also been reported.[31] Thus, this chapter will focus on a specific aspect of lignans/neolignans synthesis, namely the biomimetic phenolic oxidative coupling. Due to space constraints, only the literature of the period 1994–2007 has been reviewed. Because of the lack of stereochemical control, the radical coupling reactions normally give rise to mixtures of enantiomers: for the sake of simplicity, only the structural formula of one enantiomer is reported here. The material has been organized in two sections, devoted respectively to metal- and enzyme-mediated phenolic oxidative coupling. Of course, papers dealing with both chemical and enzymatic methods are cited in both sections.

2. Metal-mediated phenolic oxidative coupling

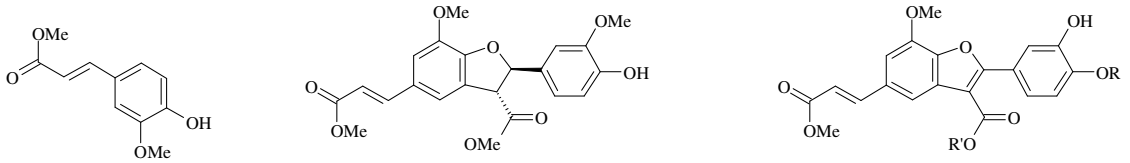
In a interesting work by Ralph *et al.*,[32] the synthesis of seven isomeric ferulic acid dehydrodimers has been carried out in the frame of a study of grass cell walls constituents. These dimeric compounds were synthesized to provide structural authentication of the products identified in extracts of saponified cell wall of cocksfoot, switchgrass and suspension-cultured corn. Various synthetic routes, including metal-mediated oxidative coupling, were employed to obtain the desired products. Employing ethyl ferulate (**8**) as substrate and Ag_2O (in dry acetone) as the oxidative agent, an intermediate quinone-methide (**9**) is formed by 8-5' coupling of the electron-delocalized phenoxy radical and this gives rise to the cyclization product, the racemic *trans* 2,3-dihydrobenzofuran neolignan **10** (only one enantiomer is reported), obtained in ca 30% yield (Scheme 2). After saponification, this and the other dimeric esters afforded the desired products employed for identification of grass cell wall constituents.



Scheme 2

A number of bioactive lignans synthesized by Maeda and co-workers were obtained through a phenolic oxidative coupling key step. Treatment of methyl ferulate (**11**) with Ag_2O in benzene-acetone afforded the racemic dihydrobenzofuran lignan **12** in 50% yield.[33] This was converted by

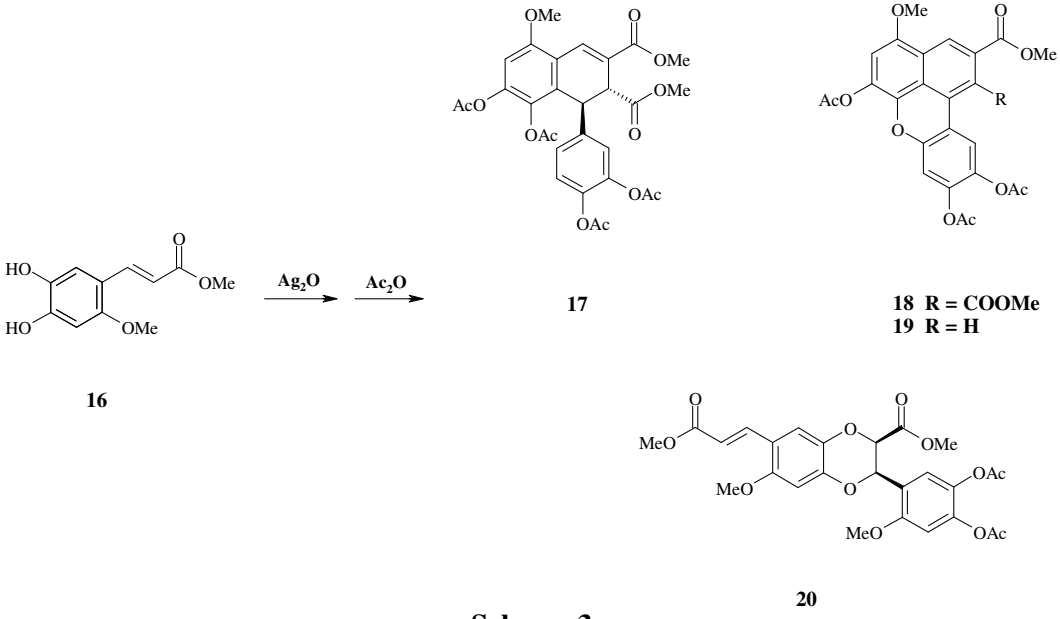
acetylation/dehydrogenation to the benzofuran neolignan **13**, related to the caffeic acid oligomers schizotenuins, inhibitors of 3α-hydroxy steroid deidrogenase (Figure 2).[34]



11 **12** **13 R = Ac, R' = Me**
14 R = H , R' = Me
15 R = H , R' = H

Figure 2

A series of schizotenuin-related lignans were prepared starting from **11** and were tested for lipid peroxidation inhibition in rat brain homogenate: the most promising compounds, **14** and **15** (Figure 2), were submitted to a further test on rat liver microsomes and their lipid peroxidation activity was found to be more potent than that of α-tocopherol. In a subsequent study,[35] the substrate **16**, prepared from the natural coumarin esculetin, was subjected to a coupling reaction in the presence of various oxidative agents. The reaction of **16** with Ag_2O in benzene-acetone (Scheme 3), followed by acetylation of the reaction mixture, afforded the aryldihydronaphtalene (**17**) (28% yield) accompanied by the unusual benzo[*kl*]xanthene (**18**) (10%) as major products. Without acetylation, **17** was obtained in 22% yield. Minor amounts of the benzo[*kl*]xanthene (**19**) and the 1,4-benzodioxane (**20**) were also obtained. Many natural analogs of **17** are known, among them magnoshinin,[36] thomasic acid,[37] thomasidioic acid[38] and rabdosiin.[39] Conversely, natural benzoxanthene lignans are quite rare: although authors did not cite any example, yunnaneic H acid (from *Salvia yunnanensis*)[40] and rufescidride (from *Cordia rufescens*)[41] have a benzoxanthene core structure. Benzoxanthene lignans had never been previously reported as the products of an oxidative coupling reaction. In this study, a mechanism of the formation of the aryldihydronaphtalene lignan **17** is proposed, starting from an 8-8' coupling of the radicals originated by **16**.

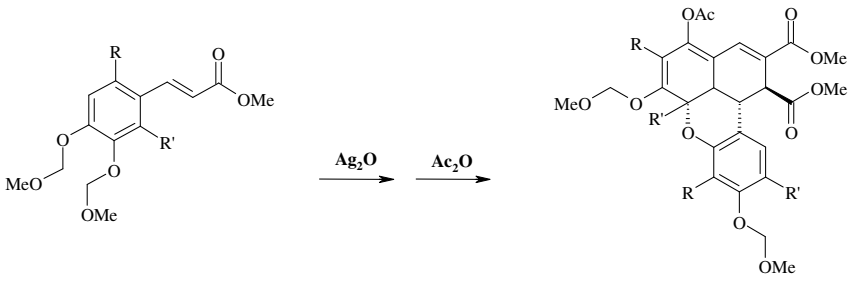


16 **17** **18 R = COOMe**
19 R = H
20

Scheme 3

The formation of dihydrobenzofurans neolignans (8-5' coupling) is blocked by the presence of the methoxy group at C-2 position. A hypothetical mechanism for the formation of the benzoxanthenes, through biradical intermediates, is also proposed. Compounds **17**, **18** and **20** resulted much more effective inhibitors of lipid peroxidation in rat liver microsomes than α-tocopherol.

In a further work of the same group[42] the oxidative coupling of 2-hydroxycinnamates was examined: the substrate **21** afforded, through the usual Ag_2O oxidation followed by acetylation, the oxotetraidro-benzoxanthene **22** in 65% yield. When the substrate **23** was subjected to the same treatment, **24** was obtained in low yield (Scheme 4). A mechanism based on a hetero Diels-Alder key step was proposed. Compounds **22** and **24** exhibited moderate inhibitory activity on lipid peroxidation in rat liver microsomes.

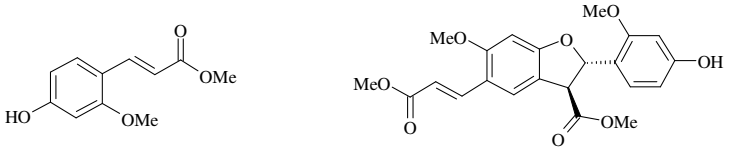


21 R = OH, R' = H
23 R = H, R' = OH

22 R = H, R' = OCH_2OMe
24 R = OCH_2OMe, R' = H

Scheme 4

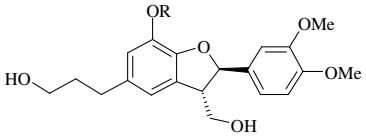
These authors studied also the oxidative coupling of **25**, prepared from umbelliferone.[43] The major product, both with $K_3Fe(CN)_6$ or Ag_2O, was by far the neolignan **26** (Figure 3); this was converted into its acetate, schizotenuin D analogs and a coumestan derivative. A further study[44] on hydroxycinnamates bearing a methyl group α to the aromatic ring, led to the conclusion that these substrates are not suitable for the preparation of dimers by oxidative coupling.



25 **26**

Figure 3

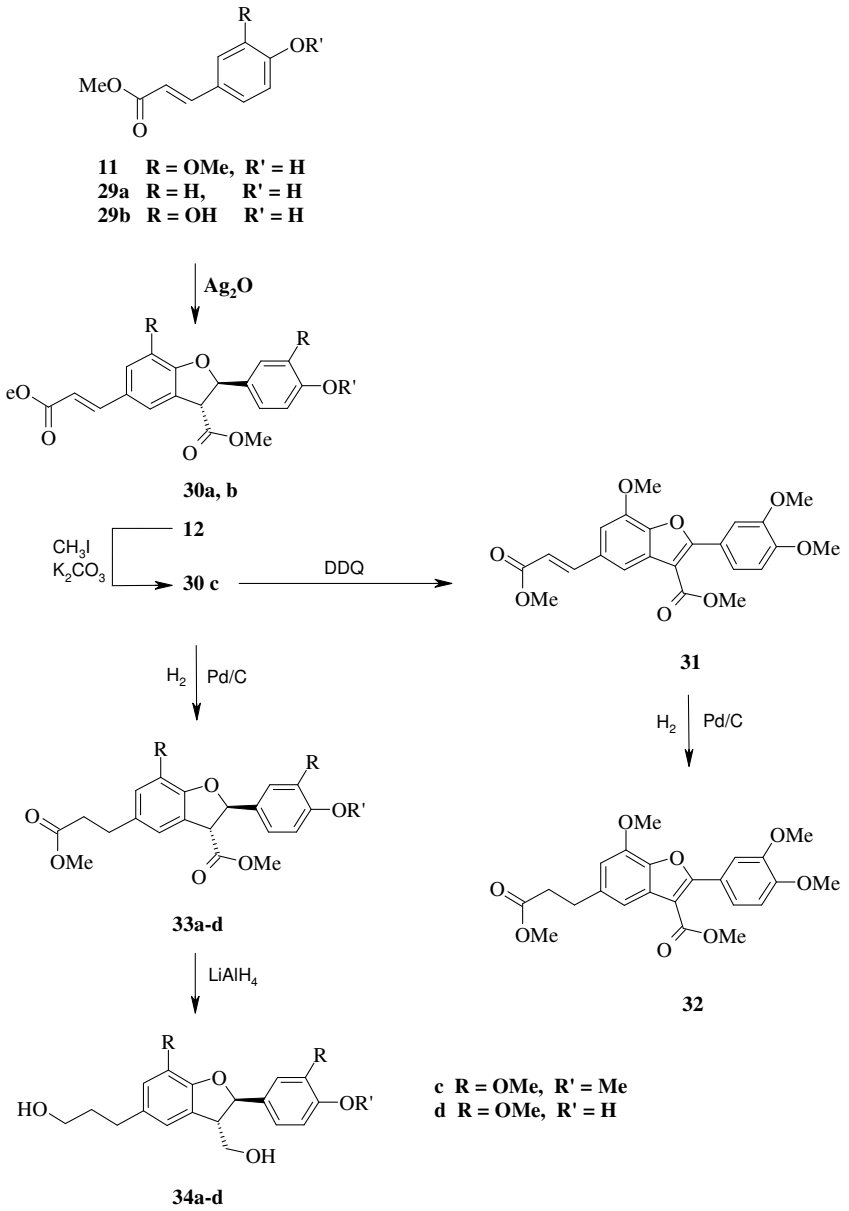
The dihydrobenzofuran lignan 3',4-di-*O*-methylcedrusin (**27**) (Figure 4) was isolated as one of the active principles of 'dragon's blood', the blood-red latex produced by some *Croton* spp. growing in South America and employed in traditional medicine for its wound-healing and anti-cancer properties.



27 R = Me
28 R = H

Figure 4

This lignan proved to be a wound healing agent and an inhibitor of thymidine incorporation in endothelial cells.[45] A biomimetic synthesis of racemic **27** has been carried out by Lemière *et al.*,[46] through the Ag_2O-mediated oxidative coupling of methyl ferulate (**11**), which afforded the racemic neolignan **12** (40% yield), whose *trans* configuration was unequivocally established on the basis by X-ray crystallography. This product was permethylated to **13** and subsequently subjected to catalytic hydrogenation of the double bond followed by $LiAlH_4$ reduction of the methylester groups to obtain **27**. Attempts to resolve the racemic mixtures by chiral HPLC gave satisfactory results with racemic **13**: on the basis of CD spectra and comparison with CD data of related natural products of known configuration, a tentative assignment of the absolute configuration for the synthetic enantiomers and consequently the 2*R*,3*S*-configuration to natural **27** was proposed. In a later work of Wong *et al.*,[47] a conventional Ag_2O oxidative coupling was employed to obtain *trans* racemic mixtures, subsequently resolved. On the basis of X-ray and CD results, the absolute configurations of optically active dihydrobenzofuran lignans, including **27**, were determined, thus confirming the 2*R*,3*S* configuration for **27**.



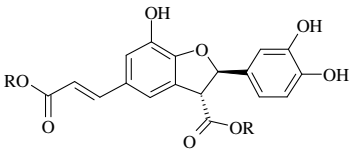
Scheme 5

More recently, a synthesis of 4-*O*-methylcedrusin (**28**) (Figure 4), a minor constituent of 'dragon's blood', has been reported.[48] The basic Ag_2O-coupling step afforded the dihydrobenzofuran skeleton; the key step of the synthesis is a selective protection of a cathecol group as a cyclic carbonate. An extensive study on dihydrobenzofuran lignans and related compounds, including SAR considerations, was carried out by Pieters, Lemière and others[49] with the aim of identifying potential antitumor agents acting through inhibition of tubulin polymerization. A biomimetic reaction sequence involving oxidative dimerization of methyl ferulate (**11**), *p*-coumarate (**29a**) and caffeate (**29b**), followed by derivatization reactions, was employed to synthesize a series of compounds, according to Scheme 5. The oxidative coupling step was carried out in the usual conditions (Ag_2O in benzene-acetone) and afforded racemic mixtures **30a–b** and **12** of dihydrobenzofurans with 2,3-*trans* configuration (only the 2*R*,3*R*-enantiomer is reported). The above cited sequence methylation/hydrogenation/$LiAlH_4$ reduction afforded a series of related compounds: in particular, methylation of **12** afforded its permethylated analogue **30c**; dehydrogenation of this latter with DDQ gave **31**, which by hydrogenation of the side chain afforded **32**. A similar hydrogenation carried out on **12** and **30a–c** yielded the corresponding products **33a–d**; $LiAlH_4$ reduction of both ester groups afforded the alcohols **34a–d**, the racemic mixture **34d** including the natural enantiomer 3',4-di-*O*-methylcedrusin **27**. The racemic products **30b** and **30c** were resolved by preparative chiral HPLC, thus allowing the synthesis of both enantiomers of **33c** and **34c** and their enantiomers. The absolute configuration of the enantiopure of **30c**, **33c** and **34c** was established through CD spectroscopy, by comparison with a compound of known configuration (ephedradin A). Thus, the 2*R*,3*S*-configuration for **27** was again confirmed.

All the compounds synthesized were evaluated in an *in vitro* cytotoxicity screening panel at the NCI and proved significantly active towards the leukaemia and breast cancer cell lines. The dimerization product of methyl caffeate **30b** showed promising antitumor properties (average GI_{50}=0.3 μM; GI_{50}<10nM towards breast cancer cell lines) and resulted 10 times more active than the ferulic acid derivative **12**. The 2*R*,3*R*-enantiomer of **30b** proved far more active than the 2*S*,3*S*-enantiomer as inhibitor of tubulin polymerization. In a further work,[20] the dihydrobenzofuran lignans, obtained by biomimetic oxidative coupling of methyl caffeate and methyl ferulate, were tested for antiangiogenic activity in the CAM (chorioallantoic membrane assay). Also in this assay, the 2*R*,3*R*-dimer of **30b** proved to be more active than its enantiomer showing pronounced angiogenesis-inhibitory activity. Very recently, a further series of dihydrobenzofuran neolignans was synthesized by the same authors, employing the standard Ag_2O-mediated oxidative coupling protocol.[18] In addition to previously reported dihydrobenzofuran dimers, caffeic acid esters with various alcoholic portions were used for coupling to obtain the sterically hindered dimers **35a–d**. A series of related benzofuran lignans was obtained by dehydrogenation followed by further simple chemical conversions. The new bulky esters were addressed to NCI cytotoxicity assay, but the observed activity was much lower than that of the methyl ester **30b**. A series of 19 neolignans were tested for their antiprotozoal activity and cytotoxicity against L6 cells;[18] compound **35b** (Figure 5) resulted highly active against chloroquine-resistant *Plasmodium falciparum* and *Leishmania donovani*. QSAR models for cytotoxic and antileishmanial activity were generated using *Quasar* receptor surface modelling.

An unusual method for the biometic oxidative coupling of coniferyl alcohol (**1**) has been reported by Sipilä *et al.*[50] These authors employed a series of Salen complexes as catalytic oxidative agents in aqueous water-dioxane solutions (pH 3–10). The results showed the formation of an open-bridge 8-*O*-4' oxyneolignan (here not reported), pinoresinol (**3**) and dehydrodiconiferyl alcohol (**5**), or oligomeric lignans.

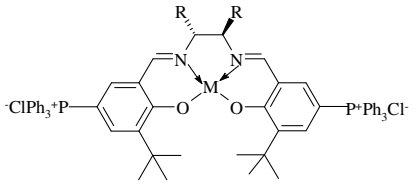
Mn complexes **36** and **37**, bearing bulky substituents, gave an approximate ratio of the dimers 1:1:1, whereas **38** afforded a ratio 1:2:3 (the main products being respectively **5** and **3**) (Figure 6).

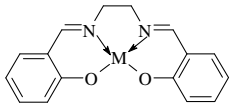


35 a R = Et,
35 b R = *n*-Bu,
35 c R = *i*-Pr,
35 d R = *t*-Bu

Figure 5

The higher amounts of dimers **3** and **5** were obtained with catalysts **39**, **40** or **41** (O_2 as the oxidant) and **38** (H_2O_2 as oxidant) (Figure 6). Mn catalysts were found to oxidize coniferyl alcohol in a same reaction time as horseradish peroxidase (HRP) enzyme. Interestingly, the oxidations of **1** catalyzed by bulky Mn, Cu and Fe complexes show the same regiochemistry obtained with HRP. By using the chiral manganese complex **37**, the dimeric 8-5' product **5** was checked by chiral HPLC and resulted racemic. In conclusion, the results indicated that the complexes catalyze one- and two-electron oxidations depending on the bulk of the substrate.





36 R = H, M = Mn(OAc)
37 R = (R, R)-cyclohexyl, Mn(OAc)
39 R = H, M = Co
40 R = (R, R)-cyclohexyl, M = Co

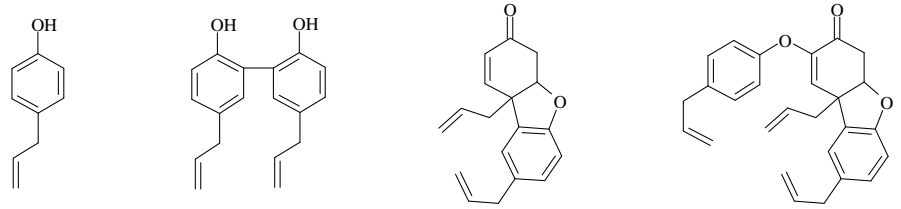
38 M = MnCl
41 M = Co

Figure 6

The 4-allylphenol **42** was selected, by Brown and Sy,[51] as a putative biogenetic precursor of the oligomeric neolignans isolated from *Illicium* spp., linked through the aromatic rings and exemplified by magnolol (**43**), a dimeric *o,o*-coupled product displaying interesting biological properties (Figure 7).[52–54] Treatment of **42** with $FeCl_3$ in 95% EtOH at rt afforded **43** (15% yield), its isomer isomagnolol (not reported) and the minor product dunnianol. Employing $K_3Fe(CN)_6$ in place of $FeCl_3$, a more complex mixture of dimeric, trimeric and tetrameric products was obtained, among them the heterocyclic neolignans **44** (11%) and **45** (12%) (Figure 7).

An efficient method for the synthesis of various families of lignans was developed by Hou *et al.*[55] and was also applied to the preparation of substituted tetrahydrofurans. By means of the insertion of a *t*-butyl group at position 5 of the phenyl ring in ethyl ferulate the reaction was oriented to an 8-8' coupling instead of the more favoured 5-8' coupling. The *t*-butyl group was later removed as reported by Tashiro *et al.*[56] The key step was the coupling of the substrate **46** (prepared *ad hoc* starting from a commercially available

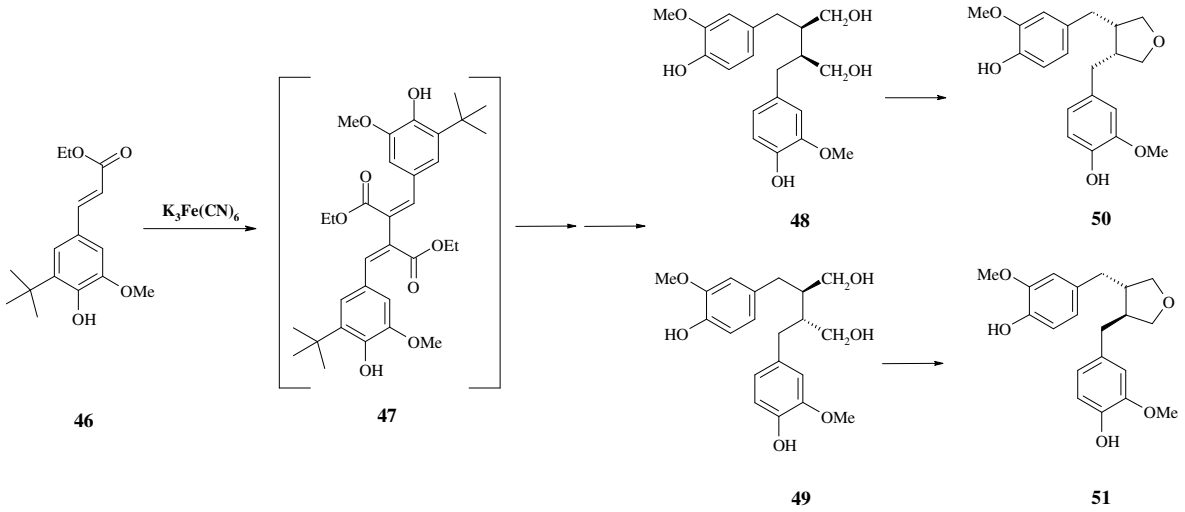
aldehyde) in a benzene-water two-phase system and in the presence of $K_3Fe(CN)_6$ (Scheme 6). This afforded in excellent yield (92%) the dimeric product **47**, in turn submitted to a sequence of chemical conversions (hydrogenation, removal of *t*-butyl group, $LiAlH_4$ reduction) to obtain secoisolariciresinol [meso-**48** + (±)-**49**], which, under reflux in MeOH/HCl, afforded the divanillyltetrahydrofurans meso-**50** and (±)-**51**.



42 **43** **44** **45**

Figure 7

Some syntheses by oxidative coupling were carried out in the frame of studies on lignin biosynthesis. Among these, K. Syrjiänen and G. Brunow[57] examined the oxidative coupling of structurally different phenols (cross-coupling) and in particular between phenols of unequal redox potentials. Different reaction conditions and various oxidants were tested (see Section 3 for HRP-mediated oxidation). In dimerization reaction of coniferyl alcohol (**1**), the heterocyclic coniferyl dimers **3** (8-8' coupling) and **5** (8-5') were obtained with a slight prevalence over the formation of 8-*O*-4' open-bridge oxyneolignans (not reported here).



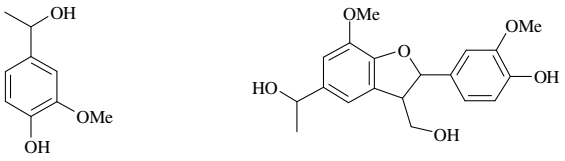
46 **47** **48** **49** **50** **51**

Scheme 6

The coupling of coniferyl alcohol (**1**) and apocynol (**52**) (Figure 8), employing MnO_2 in acetone 20% and buffer (pH 3.5) or $FeCl_3$ in acetone-water, afforded as main products only coniferyl dimers, among them **3** and **5**. When $Mn(OAc)_3$ was added to an equimolar mixture **1** and **52** in glacial acetic acid, the main product (18% yield) was an 8-*O*-4' oxyneolignan and only minor amounts of the heterodimer **53** (Figure 8) were obtained.

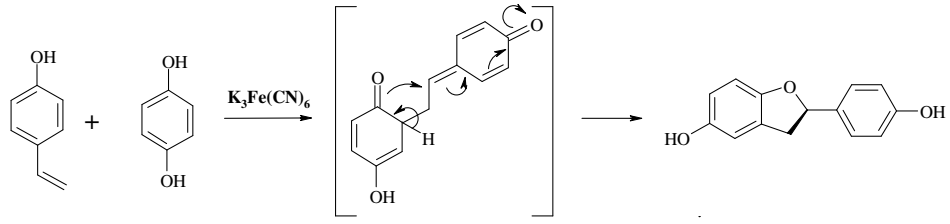
In a work by Torres and Rosazza[58] on biotrasformations of *p*-coumaric acid (**54**) by cell cultures of *Bacillus megaterium* (see Section 3), the biomimetic cross-coupling of 4-vinylphenol (**55**) and hydroquinone (**56**) was carried out with $K_3Fe(CN)_6$ in chloroform-water, affording the racemic neolignan **57** (only the 2*R*-

enantiomer is reported), also obtained by microbial conversion of **54**; the proposed mechanism is reported in Scheme 7.



52 **53**

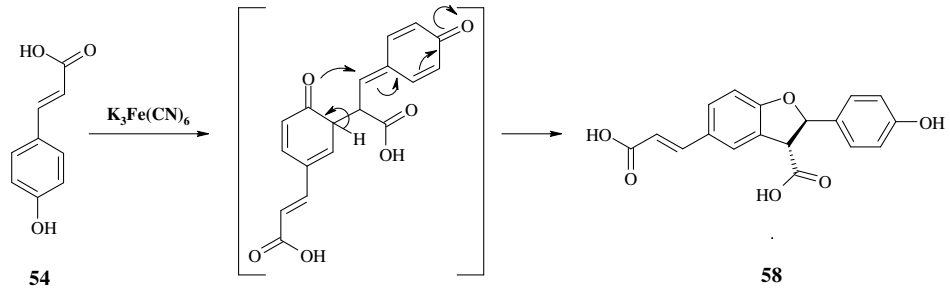
Figure 8



55 **56** **57**

Scheme 7

Analogously, to mime the formation of the neolignan dicarboxylic acid (**58**) in the *Curvularia lunata* biotrasformation of **54**, a $K_3Fe(CN)_6$ mediated dimerization of *p*-coumaric acid was carried out and gave the racemic *trans* **58** (only the 2*R*,3*R*-enantiomer is reported), according to the mechanism proposed in Scheme 8.

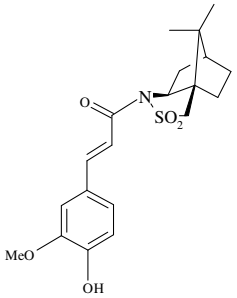


54 **58**

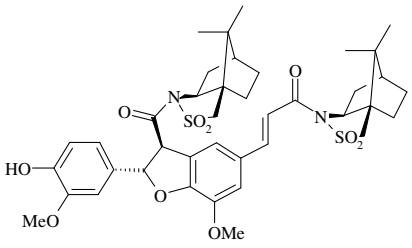
Scheme 8

In recent times, several attempts to obtain lignans through metal-mediated stereoselective coupling of phenols have been reported; actually, already in 1997 a biomimetic route to the aryltetralin lignan (+)-rabdosiin was reported by Bogucki and Charlton,[59] which employed $FeCl_3$ as oxidant and as substrate a protected form of (*S*)-rosmarinic acid, an ester of caffeic acid with 3-(3, 4-dihydroxyphenyl)-(*S*)-lactic acid. The chiral pendant was used to influence the oxidation-cyclization reaction and this allowed to obtain the two diastereoisomers of rabdosiin with a 1:1.6 ratio. Rummakko *et al.* reported later a preliminary study[60] on the asymmetric biomimetic oxidation of phenol substrates containing a chiral auxiliary moiety. Enantiopure analogues of ferulic acid were coupled stereoselectively employing Ag_2O in CH_2Cl_2 or HRP/H_2O_2 in the preparation of dimeric benzofuran lignans. Oppolzer's sultam and Evans's 2-oxazolidinone were used to induce asymmetry in phenol oxidations. The results were reported in details in more recent papers. In particular, Orlandi *et al.*[61] reported that the ferulic amide (**59**), bearing the Oppolzer's sultam as chiral

auxiliary, afforded with 40% overall yield a mixture of two *trans*-stereisomers, namely **60** (as major product) and its diastereoisomer at C-2, C-3 (Figure 9). After RP-HPLC separation, $LiAlH_4$/THF reduction of **60** removed the camphor sultam auxiliary, affording dehydrodiconiferyl alcohol. This latter was compared with authentic specimens through chiral HPLC, thus establishing the absolute configuration as 2*S,*3*R*, as reported for **5**. Diastereomeric ratios were determined by ^1H NMR from the reaction mixtures. The *trans*-2*S,*3*R* dimer **60** was obtained with 80–84% of diastereomeric excess. The observed stereoselectivity is consistent with the conformational analysis of the quinone methide intermediates.



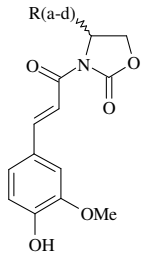
59



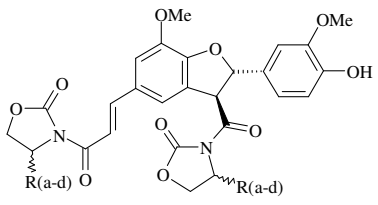
60

Figure 9

More recently, Rindone *et al.*[62] reported the use of Evans's 2-oxazolidinones derivatives of ferulic acid to obtain diastereomeric mixtures of benzofuran neolignans in 40–50% overall yields. The chiral substrates **61a–d** were oxidized with Ag_2O/CH_2Cl_2 or HRP/H_2O_2 (see Section 3) to give two series of dehydrodimers: **62a–d** and their diastereoisomers at C-2, C-3 (Figure 10). When the sterically smaller chiral auxiliary 2-phenyloxazolidinone was used, considerably higher selectivities (e.e. 53% for 2*R*,3*S* enantiomer) were obtained, with respect to the 2-benzyloxazolidinone chiral auxiliary (e.e. 18% for 2*R*,3*S* enantiomer). After dimerization, $LiBH_4$ reduction afforded the mixture of the enantiomers of dehydrodiconiferyl alcohol, **5** and its 2*R*,3*S* enantiomer (not reported). The conformational analysis and the calculated activation energies of the intermediate quinonemethides are in agreement with the observed stereoselectivity. In conclusion, these results show that chiral auxiliaries can afford significant diastereoselectivity in phenolic oxidative coupling, thus providing satisfactory enantioselection in the final product.



61a R = CH_2Ph (*S*)
61b R = CH_2Ph (*R*)
61c R = Ph (*S*)
61d R = Ph (*R*)

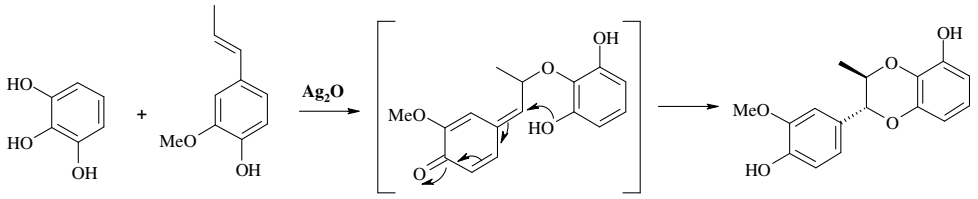


62a -d

Figure 10

Some interesting cross-coupling reactions have been employed to obtain heterocyclic neolignans with a 1,4-benzodioxane portion. This ring system is found in several neolignans and other bioactive natural products. Among them, eusiderins are benzodioxane neolignans isolated from *Eusideroxylon* spp.[63] and other

species. Lariucci *et al.*[64] employed an Ag_2O-promoted cross-coupling between pyrogallol (**63**) and isoeugenol (**64**) to obtain eusiderin analogues (Scheme 9). The reaction proceeds with high regio- and diastereoselectivity, affording as major product the racemic *trans* neolignan **66**. The proposed mechanism is an *O*-β coupling between the pyrogallol phenoxy radical (where the hydrogen atom on the central hydroxyl group is removed preferentially) and the isoeugenil radical (where the unpaired electron is located preferentially in β-position).

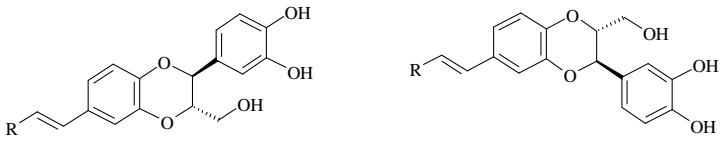


63 **64** **65** **66**

Scheme 9

The intermediate **65** undergoes cyclization through a preferential nucleophilic attack of the hydroxyl group on the *re* face of the quinone methide system, thus affording mainly the 2,3-*trans*-fused benzodioxane neolignan **66** (only one of the two *trans* enantiomers is reported here), with an approximate ratio *trans*:*cis* 21:1. Methylation of (**66**) afforded a derivative used for a complete NMR study; acetylation gave a diacetate submitted to single-crystal X-ray diffraction analysis, thus allowing a definitive confirmation of the stereochemical asset of the molecule.

A unique group of benzodioxane neolignans is constituted by americanol A (**67**), isoamericanol A (**68**), americanin A (**69**) and isoamericanin A (**70**) (Figure 11) occurring exclusively in the seeds of *Phytolacca dodecandra* and displaying significant biological activities; in particular, **68** is a neurotrophic principle[65] and **69** can increase the release of endogenous prostaglandin I_2 from the rat aorta.[66]



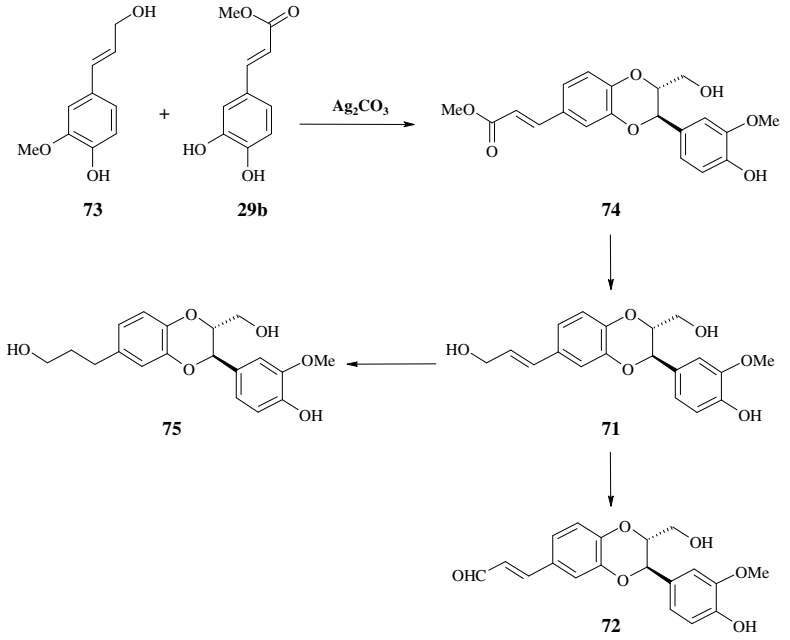
67 R = CH_2OH **68 R = CH_2OH**
69 R = CHO **70 R = CHO**

Figure 11

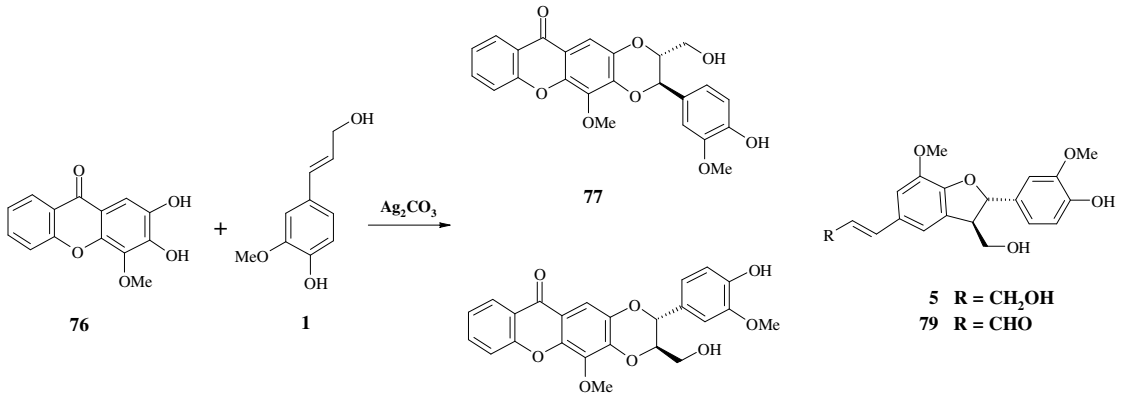
Pan *et al.*[67] reported a convenient synthesis of methyl ethers of isoamericanol A (**71**) and isoamericanin A (**72**) based on a cross-coupling key step. Substrates **73** and **29b** (prepared from caffeic acid) were coupled in the presence of Ag_2CO_3/acetone-benzene at rt (Scheme 10) to give with high regioselectivity and 40% yield the racemic neolignan **74**. This latter was further converted by $LiAlH_4/AlCl_3$ reduction to **71**; this in turn was hydrogenated (H_2, Pd/C) to **75** or oxidated (MnO_2-SiO_2) to **72**.

The 1,4-benzodioxane moiety is also included in xantholignonoids, fused with a xanthone nucleus. Fernandes *et al.*[68] carried out a cross-coupling of the xanthone **76** with coniferyl alcohol (**1**) in the presence of Ag_2CO_3 (in benzene/acetone, rt, 3 days) to synthesize *trans*-(±)-kielcorin B (**77**), previously isolated from

Kielmeyera coriacea.[69] The reaction also afforded the isomer **78** and dehydrodiconiferyl alcohol **5**, coming from the dimerization of **1**, together with the related aldehyde **79** (Scheme 11).



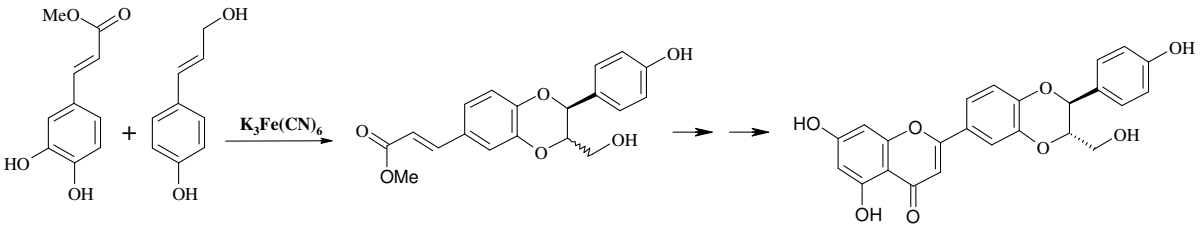
Scheme 10



Scheme 11

Also flavonolignans, mixed dimers including a flavonoid portion, have a 1,4 benzodioxane nucleus. Silybin, the first natural flavonolignan, was isolated in 1968 from fruits of the medicinal plant *Silybum marianum*,[70–72] and in 1980 it was synthesized by oxidative phenol coupling.[73] More recently, the flavonolignan sinaticin (**80**), isolated from leaves of a *Sinaticum* sp. with anti-leukaemia properties, was obtained by Pan *et al*.[74] as racemate by total synthesis based on a cross-coupling key step: methyl caffeate (**29b**) was coupled with coniferyl alcohol (**1**) in the presence of $K_3Fe(CN)_6$/NaOAc to give a 1:5 *cis*/*trans* mixture of the benzodioxane dimer **81** (Scheme 12). This was converted to (±)-sinaticin in four steps.

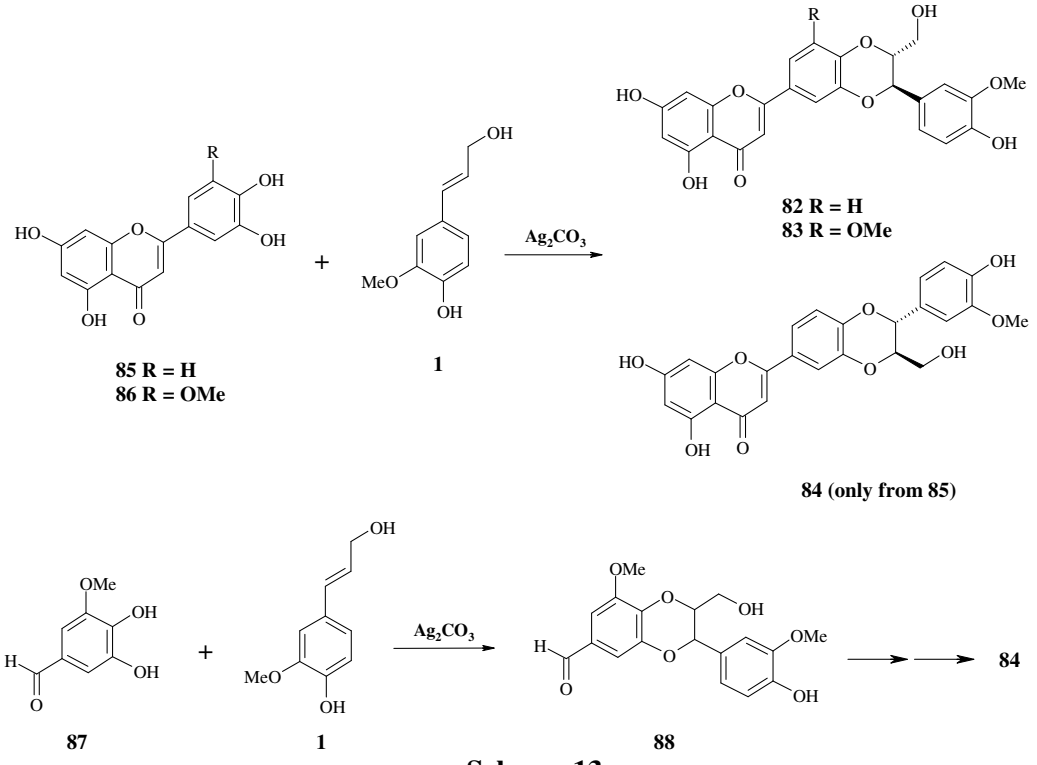
Stermitz *et al.* isolated a flavonolignan related to hydnocarpin (**82**), subsequently established as 5'-methoxyhydnocarpin-D (**83**), which proved to be a potent inhibitor of a *Staphylococcus aureus* multidrug resistance (MDR) efflux pump.[75]



29b **1** **81** **80**

Scheme 12

Guz and Stermitz[76] carried out the synthesis of **82**, its regioisomer **84** and related flavonolignans by a cross-coupling reaction between coniferyl alcohol (**1**) and the flavonoid luteolin (**85**), employing Ag_2CO_3 in benzene-acetone (Scheme 13). This coupling was also carried out with horseradish peroxidase: hydnocarpin (bearing the coniferyl-derived ring in the 'down' position) was the major product (9:1, 21% yield) in the metal-mediated reaction, whereas **82** (bearing the ring 'up') resulted the major product when HRP/H_2O_2 was employed (see Section 3). To obtain the desired 5'-methoxyhydnocarpin-D, further Ag_2CO_3-mediated syntheses were carried out: coupling between **1** and the flavone selgin (**86**), prepared *ad hoc*, gave only the (±)-5'-methoxyhydnocarpin-D (**83**). Analogously, when **1** was coupled with the aldehyde **87** only the dimer **88** (whose regiochemistry was confirmed by X-ray diffraction) was obtained; this was converted to **84** through a series of chemical conversions. The authors suggest that the high regioselectivity observed in the syntheses of **83** is due to the stability of the intermediate phenoxide radical, enhanced by the presence of a methoxy group in *ortho*.



85 R = H
86 R = OMe

1

82 R = H
83 R = OMe

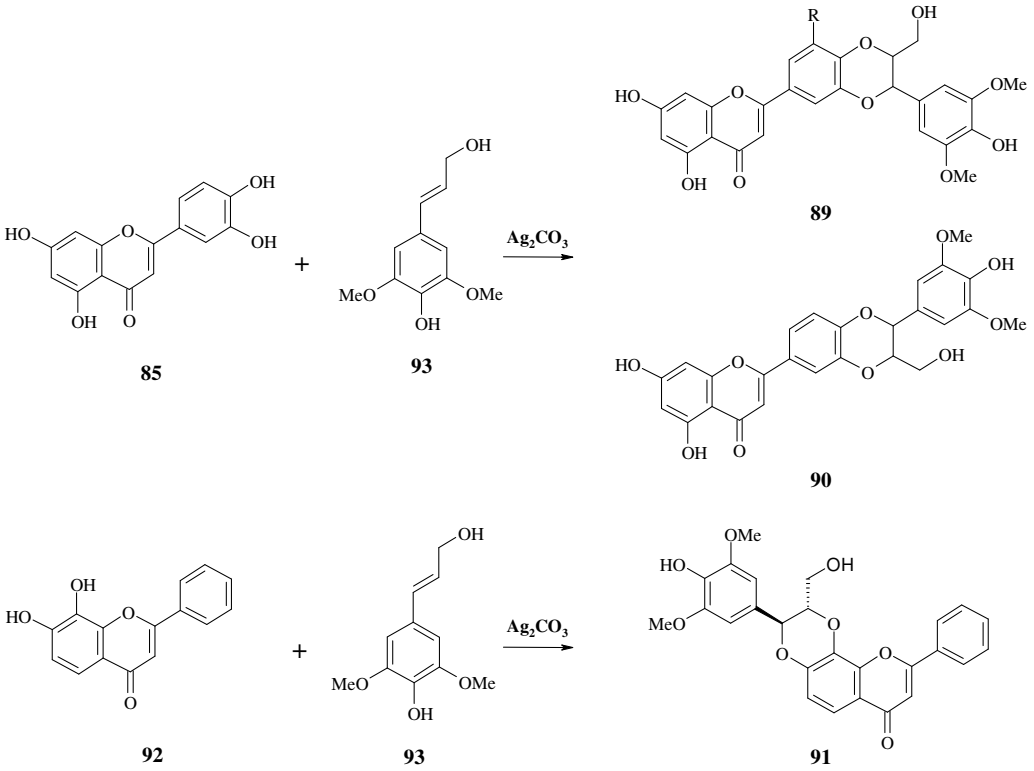
84 (only from 85)

87 **1** **88**

Scheme 13

As a continuation of this study,[77] Stermitz *et al*. evaluated a series of synthetic flavonolignans and flavones as inhibitors of a *S. aureus* multidrug resistance efflux pump. As exemplified by Scheme 14, the flavonolignans (**89–91**) were prepared by oxidative coupling of a flavone (exemplified by **85** or **92**) with **1** or

related alcohols (exemplified by sinapyl alcohol, **93**) promoted by Ag_2CO_3 or HRP/H_2O_2. Again, the former method afforded as major product the regioisomer with coniferyl ring 'down' (exemplified by **89**), whereas HRP-catalysed coupling afforded preferentially the regioisomer (exemplified by **90**). Several synthetic flavonolignans were more potent MDR pump inhibitors than the natural 5'-methoxyhydnocarpin-D (**83**).

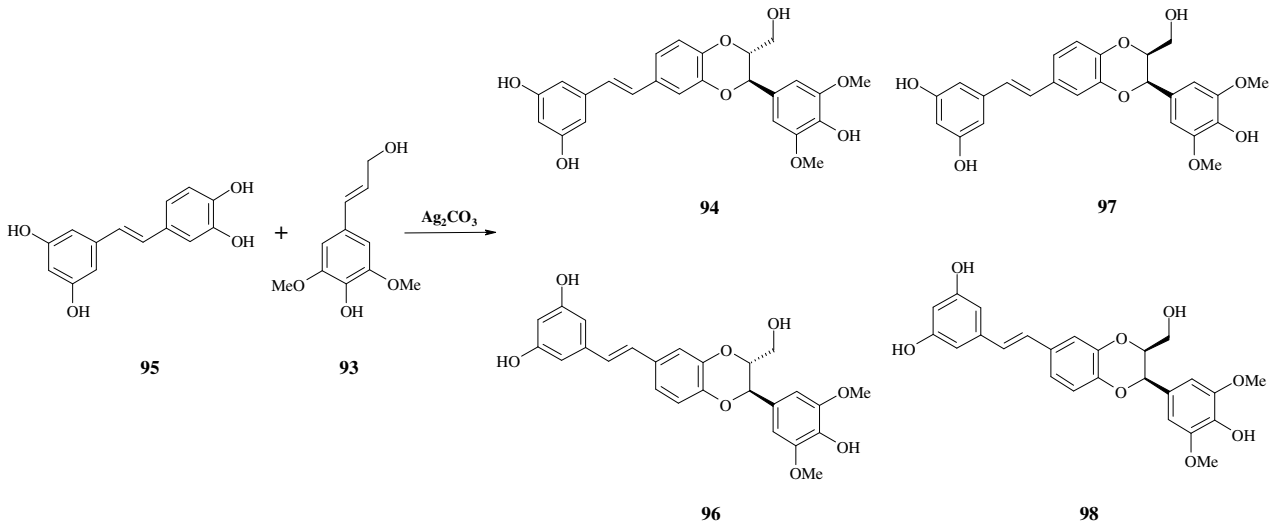


85 **93** **89** **90** **92** **93** **91**

Scheme 14

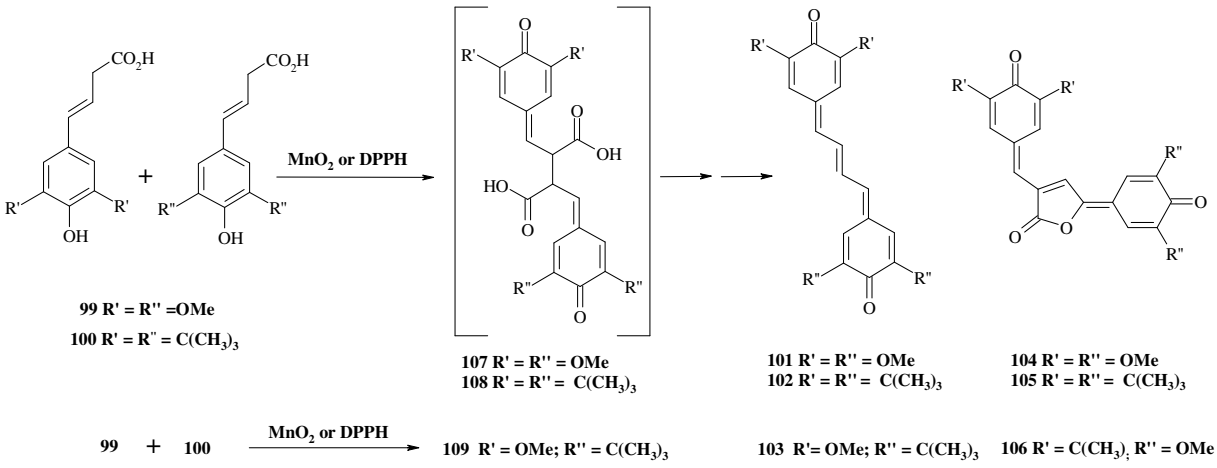
Among the dimeric compounds with an 1,4-benzodioxane ring, (-)-aiphanol (**94**) is an unprecedented natural dimer where the dioxane bridge connects a phenylpropane unit with a stilbene unit. This stilbenelignan was recently obtained through bioassay-guided isolation from the seeds of *Aiphanes aculeata*[78] and resulted a potent inhibitor of both COX-1 (IC_{50} = 1.9 μM) and COX-2 (IC_{50} = 9.9 μM). A simple and convergent (but non-selective) synthesis of **94** as a racemic mixture has been carried out by Banwell *et al.*[79] through a cross-coupling between stilbenoid and phenylpropanoid substrates. In this synthesis (Scheme 15), the natural stilbenoid piceatannol (**95**), prepared by condensation of a suitable ylide and an aromatic aldehyde (followed by deprotection of the primary product) undergoes an Ag_2CO_3-promoted oxidative coupling with sinapyl alcohol **93** affording (±)-aiphanol (only the levorotatory 2*R*,3*R*-enantiomer is reported here) and a mixture of related dimers (**96–98**) (yields from 12% to 19%; 67% overall yield).

All these compounds inhibited both COX-1 and COX-2 (IC_{50} in the range 0.17–9.5 μM). Interestingly, (±)-aiphanol proved to be a potent anti-angiogenic agent, completely inhibiting blood vessels growth at 100 μg/mL. Also compounds **96** and **97** were comparable angiogenesis inhibitors, whereas **98** resulted less active. Compounds **94–96** proved more active than PI-88, an anti-angiogenic polysulphated oligosaccharide now in clinical development as anti-cancer agent.[80] In the frame of this work, the stilbenoid **95** was tested as anti-angiogenic inhibitor and resulted almost active as (±)-aiphanol.



Scheme 15

An interesting addition to the above cited series of metal-mediated phenolic oxidative coupling reaction has recently been reported by Daquino and Foti.[81] Employing 4-hydrocinnamic acids (**99**, **100**) as substrates and DPPH or MnO_2 in acetone as oxidative agents, the unusual *p*-quinomethanes **101–103** (yields 22–40%) were obtained and, as minor products, the quinones **104–106** (10–20%) (Scheme 16) containing an unsaturated γ-lactone ring.

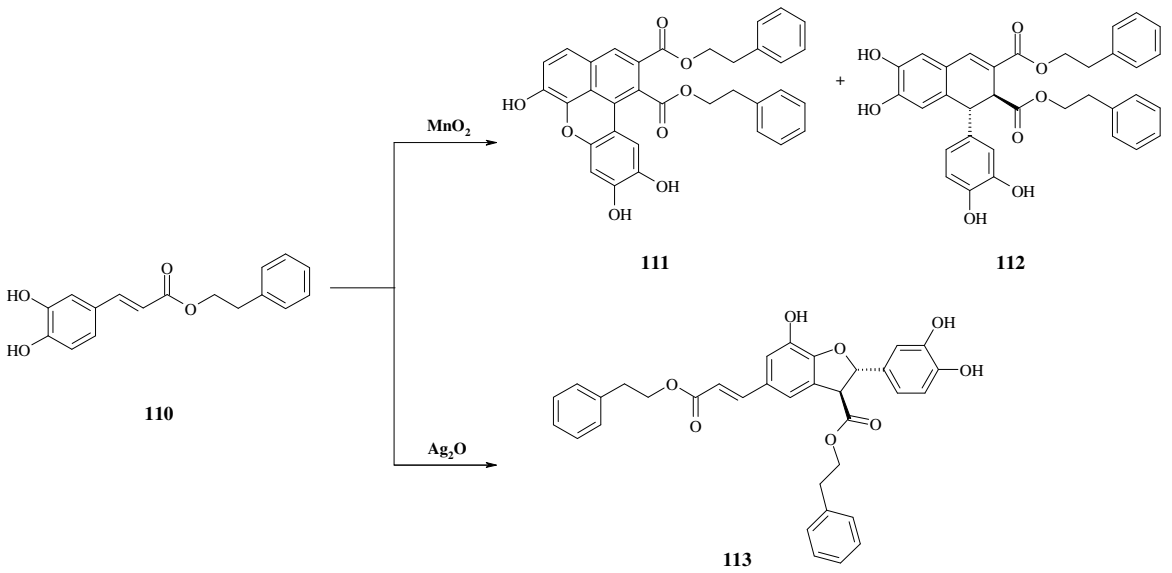


Scheme 16

A mechanistic study allowed to establish that the originally formed 8-8' dimers **107–109** undergo a fast didecarboxylation to give the *p*-quinomethanes or an intramolecular cyclization followed by monodecarboxylation to afford the unsaturated heterocyclic quinones.

Very recently, we have employed MnO_2 as oxidative agent in a biomimetic coupling reaction of caffeic acid phenetyl ester (CAPE, **110**). This natural product is a component of propolis and it is reported as anti-inflammatory, antioxidant and antitumoral agent.[82–85] According to Scheme 17, the manganese-mediated reaction afforded with good yield the benzo[*kl*]xanthene lignan (**111**) as major product, accompanied by minor amounts of the aryldihydronaftalene lignan (**112**).[86]

Interestingly, when Ag_2O was employed as oxidative agent, the neolignan **113** was obtained as major product.[87] The dimers **111–113** have not previously been reported and are currently under investigation for their biological properties.



Scheme 17

A rare example of biomimetic synthesis of lignanamides has been reported by Lajide *et al.*[88] in a study on constituents of *Xylopia aethiopica* displaying termite antifeedant activity. Lignanamides are less common than lignans and their biological activity has not been extensively evaluated. To authenticate the structures of some *X. aethiopica* lignanamides, the antifeedant amide **114**, occurring in the same plant, was submitted to oxidative coupling both with metal- and enzyme-mediated reactions. Employing a chiral Cu(II)-α (-)-phenylethylamine complex (degassed EtOH, rt, 20 hr), grossamide (**115**, 14% yield) was obtained as racemate and cannabisin (**116**, 7%) was obtained predominantly as the levorotatory enantiomer (Figure 12). The same products were obtained with the HRP-H_2O_2 method. Both lignanamides (and **116** in particular) resulted active termite feeding deterrents at 5000 ppm. It is worth of note here that in recent times further lignanamides have been synthesized by enzymatic coupling, as detailed in Section 3.

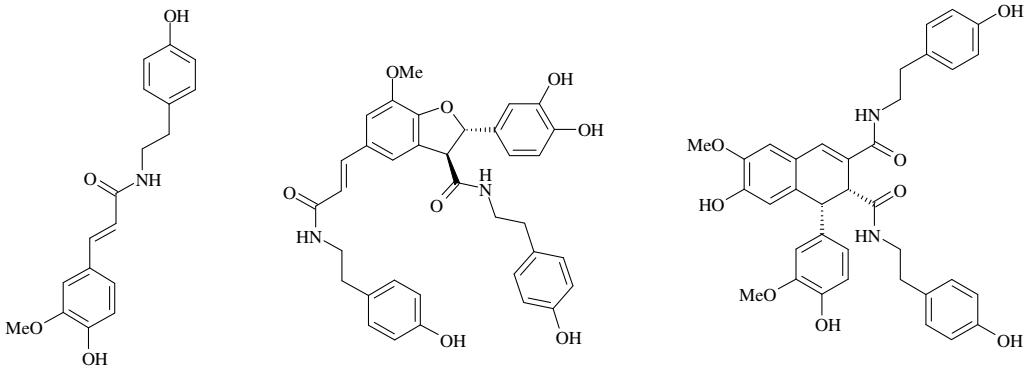


Figure 12

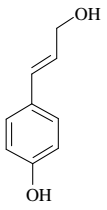
3. Enzyme-mediated phenolic oxidative coupling

In the last decade, metal-mediated biomimetic syntheses based on phenolic oxidative coupling have been frequently paralleled by coupling methods mediated by enzymes, mainly peroxidases or laccases. Peroxidases oxide phenols by H_2O_2-dependent one-electron oxidation. Laccases are copper oxidases capable to oxide phenols through the reduction of molecular O_2 to H_2O by single electron transfer reactions. As

reported in the introduction, the products of coupling reactions catalyzed by these enzymes are optically inactive and the involvement of 'dirigent' proteins has been suggested in the enantiospecific formation of the radical coupling products. This has been demonstrated for (+)-pinoresinol (**3**) by Davin *et al.*[4] who carried out the stereoselective synthesis of **3** from coniferyl alcohol (**1**) in the presence of a laccase and a 'dirigent protein' from *Forsythia suspensa*; this was a 78-kilodalton protein without catalytic activity. Other one-electron oxidants were employed with and without the 'dirigent' protein, thus confirming its role in the stereocontrol of the coupling reaction.

Horseradish Peroxidase (HRP) in the presence of H_2O_2 is one of the most frequently used enzymes for phenolic oxidative coupling. A variety of diferulates were obtained by Ralph *et al.*[31,89] employing both metal- and enzyme-mediated coupling reactions. In particular, a simple preparation of the neolignan **10** (8-5' coupled diethyl diferulate) with HRP/H_2O_2 at pH 4 gave a better yield (~50%) than the previously used Ag_2O-promoted reaction (~30%).

As reported in Section 2, some oxidative coupling reactions were carried out in the frame of studies on lignin biosynthesis, also employing the HRP/H_2O_2 system. In particular, K. Syrjiänen and G. Brunow[90] examined an array of substrates in HRP-catalysed coupling reactions with the aim to mime some steps of the lignification processes. Three lignin precursors, coniferyl (**1**), sinapyl (**93**) and *p*-coumaryl alcohol (**117**) and three β-*O*-4 dimers (here not reported) were used for cross-coupling reactions, which appeared to be restricted to phenols of similar oxidation potential (Figure13). The products included various open-bridge dimers, trimers, tetramers and pentamers, and the heterocyclic lignans **3**, **5** and **118** (Figure 13).



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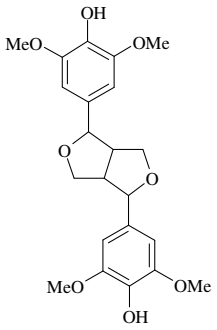
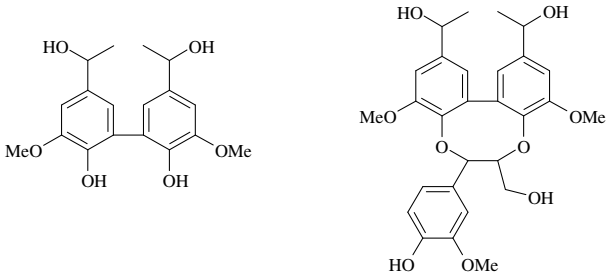


118

Figure 13

The same authors subsequently studied[56] the cross-coupling between **1** and apocynol (**52**) with HRP/H_2O_2, obtaining the same products of the reactions with MnO_2 or $FeCl_3$, namely **3**, **5** and open-bridge oxyneolignans. The dihydrobenzofuran **53** was obtained as a minor product in cross-coupling reactions. In a more recent paper,[91] these authors further refined their studies on regioselectivity in HRP-catalysed oxidative cross-coupling reactions, also performing dialysis experiments. When **1** and dehydrodiapocynol (**119**) were employed as substrates and treated with HRP-H_2O_2 in acetone/buffer (pH=6), the *trans*-dibenzodioxocin **120** was obtained in 25% yield (Figure 14). The authors observed that in the homocoupling of **1**, the 8-*O*-4' and 8-5' dimers are formed in comparable amounts; conversely, when **1** is coupled with a phenol lacking of the conjugated bond in the side chain, dimers are formed with a 10:1 ratio of the 8-*O*-4' to 8-5' coupling. This remarkable difference in regioselectivity may be due to different configurations of intermediate π-complexes. In conclusion, it was observed that regioselectivity of cross-coupling differs

significantly from that of dimerization; a careful administration of the reactants can promote the cross-coupling between phenols with different rates of oxidation.



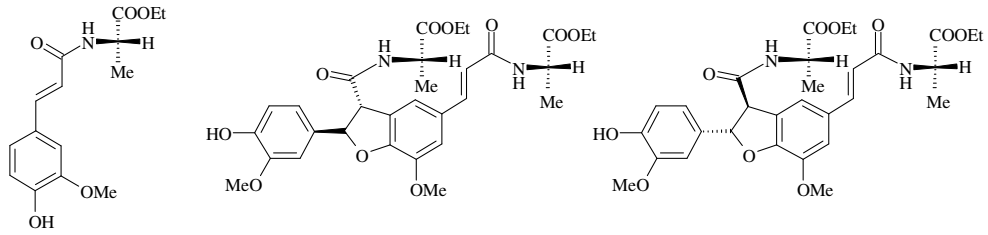
119 **120**

Figure 14

A further biomimetic study of lignin biosynthesis, carried out by De Angelis *et al.*,[92] allowed to identify by ESI-MS the dimers **3** and **5** among the products of a *in vitro* coupling of **1** with HRP/H_2O_2.

Sipilä *et al.*[50] compared a series of Salen metal complexes (see Section 2) with HRP/H_2O_2 as oxidative catalysts in the oxidative coupling of coniferyl alcohol (**1**). Results showed that Mn catalysts were found to oxidize **1** in a same reaction time as HRP, affording the same products **3**, **5** and an 8-*O*-4' oxyneolignan.

The first HRP-catalysed enantioselective phenol oxidative coupling has been reported by Orlandi *et al.*[93] in 1998. They employed a ferulic amide (**121**), bearing the ethyl *S*-alaninate group as chiral auxiliary. The reaction was performed in dioxane-aqueous buffer (pH = 3) and afforded a mixture of two *trans*-diastereoisomers (**122** and its 2*R*,3*S*-isomer **123**) with 70% overall yield (Figure 15). The diastereoisomeric excess in this reaction was determined to be 65% by RP-HPLC analysis of the mixture. Conventional chromatography, crystallization and preparative RP-HPLC allowed to obtain the individual diastereoisomers. The subsequent hydrolysis (LiOOH in THF), diazomethane methylation and $LiBH_4$ reduction give optically pure (2*S*,3*R*) dehydrodiconiferyl alcohol (**5**).

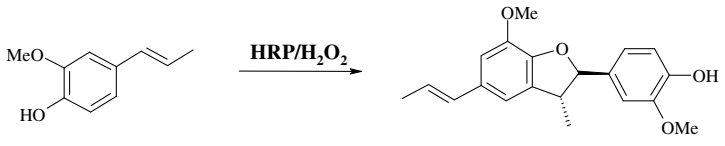


121 **122** **123**

Figure 15

As cited in Section 2, the same group published some papers[60–62] on the enantioselective synthesis of dimeric benzofuran lignans, also employing the HRP/H_2O_2 system. When the chiral ferulic amide **59** was used as substrate, the products (**60** and its 2*R*,3*S*-diastereoisomer) were identical to those obtained with the Ag_2O-promoted reaction. The major product **60** (d.e. 81%) was then separated and converted into *trans*-2*S*,3*R*-(+)-dehydrodiconiferyl alcohol (**5**). Analogously, the HRP/H_2O_2 oxidation of the chiral amides **61a–d** gave the dehydrodimers **62a–d** and their 2,3-diastereoisomers. The smaller chiral auxiliary gave higher selectivities (e.e. 62%). Subsequent reduction afforded a mixture of enantiomeric dehydrodiconiferyl alcohols: **5** and its 2*R*,3*S* enantiomer.

(+)-Licarin A (**124**) and the related 8,9-licarinediols are neolignans isolated from *Aristolochia pubescens*.[94] In a study reported by Lewis *et al.*[95] a stereoselective synthesis of licarinediols was carried out from (±)-licarin A (Scheme 18), obtained by HRP/H_2O_2 oxidative coupling (MeOH, citrate-phosphate buffer, pH = 3) of isoeugenol (**64**), which in turn was prepared by the stepwise reduction of coniferyl aldehyde.



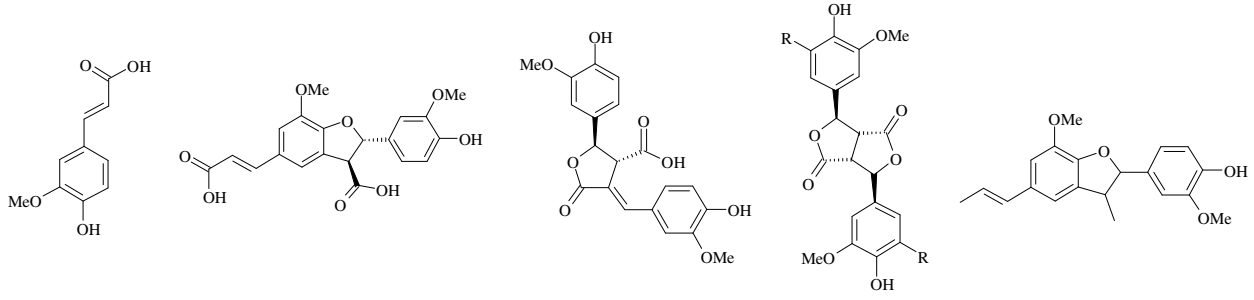
64 **124**

Scheme 18

The racemic mixture of **124** and its enantiomer (not reported) was submitted to asymmetric Sharpless oxidation to afford the analogous diastereoisomers of licarinediols.

As reported by Christensen *et al.*,[96] ferulic acid dehydrodimers can be obtained in one step from ferulic acid using the biomimetic HRP/H_2O_2 system in a micellar solution generated by long aliphatic chain quaternary ammonium ions. The coupling reaction of ferulic acid (**125**) in acetate buffer solution gave primarily (38% yield) the benzofuran neolignan (**126**) and the 8-8'-γ-dilactone (**127**) and other open-bridge dimers, (8-*O*-4', 5-5' coupled, here not reported) as minor products. No reaction was observed in a phosphate buffer solution. When the *n*-hexadecyltrimethylammonium hydroxide was used as surfactant, **126**, **127** and a magnolol analogue (5-5'-coupled) were obtained in comparable amounts (respectively 14, 25 and 21% yields); employing *n*-tetradecyltrimethylammonium bromide, the 8-8-bis-lactone **128** was obtained as main product (18% yield) (Figure16).

The oxidation of coniferyl alcohol (**1**) and isoeugenol (**63**) has been carried out by Chen *et al.*[97] employing laccases isolated from *Rhus vernicifera* and *Pycnoporus coccineus* in acetone-water. The effect of pH and methanol-water was examined. Various dimeric and tetrameric products were obtained; in particular, the *Rhus* laccase slowly catalysed the coupling of **1** to give dehydrodiconiferyl alcohol (**5**) as main product (31 mol%) and pinoresinol (**3**) as further heterocyclic product (18 mol%); *Pycnoporous* laccase catalysed more readily the conversion, affording **3** as main product.



125 **126** **127** **128 R = H** **130 R = OMe** **129**

Figure 16

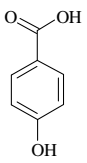
When **63** was used as substrate, the dehydrodiisoeugenol (**129**) (Figure 16) was obtained in 43 mol% yield, employing the *Rhus* laccase. Very recently, Wan *et al.*[98] employed laccases from Chinese *Rhus*

vernicifera in water miscible organic solvents to carry out one-step oxidative coupling reactions of phenylpropanoids, obtaining a variety of dimers and oligomers, among them **3**, **5** and related lignans and neolignans.

The action of laccase from *Pyricularia oryzae* on ferulic acid (**125**) was reported by Carunchio *et al.*:[99] the products obtained were identified as the neolignan dicarboxylic acid (**126**) and a β-O-4 oxyneolignan (here not reported).

A very recent work of Iacazio *et al.*[100] focused on the use of laccase in a biphasic system to promote the phenolic oxidative coupling of sinapic (**99**) and ferulic (**125**) acids. The *Trametes versicolor* laccase was used for the oxidation of sinapic acid in phosphate buffer at pH 5; HPLC analysis of mixture revealed a rapid formation of the racemic bis-lactone lignan **130**, which disappeared gradually from the reaction medium. To circumvent this problem, four organic co-solvents were added; the highest yield (85%, 2 h) was obtained with either ethyl acetate or toluene. *Agaricus bisporus, Trametes* C30 Lac 1, *Trametes* C30 Lac 3 and *Melanocarpus albomyces* laccases were used in the same conditions: quasi-quantitative yields were obtained with all laccase. When *Trametes versicolor* laccase was used for the oxidation of **125** in buffer alone (at pH 4 or 5) and/or added co-solvent, the racemic bis-lactone **128** was found to be the main product.

In an interesting study by Torres and Rosazza,[58] the use of the enzymatic systems (peroxidase and laccase) of microbial cultures to carry out oxidative biomimetic syntheses was reported. In particular, this work was focused on biotrasformations of *p*-coumaric acid (**54**) and includes the first screening of bacteria, yeasts, and filamentous fungi for their abilities to convert **54** in an array of products, including heterocyclic neolignans. 4-Vinylphenol **55** was the most frequently observed metabolite of **54**. The preparative biotransformation of **54** by whole cell cultures of *Bacillus megaterium* afforded a series of phenolic metabolites, among them the **55**, which, on the basis of a D_2O incorporation study, is supposed to be formed by decarboxylation of a vinilogous β-chetoacid tautomer of **54**. A further product, formed in 5% yield, was isolated from the culture supernatants and characterized as the racemic neolignan **57**. This was proposed as derived from cross-coupling between **55** and the hydroquinone (**56**) as reported in Scheme 7 (Section 2). Authors suggest that **56** may be derived by vinylgroup elimination from **55**, or it may be a biosynthetic product of *B. megaterium*. When **54** was used as substrate for *Curvularia lunata*, the formation of 4-hydroxybenzoic acid (**131**) (Figure 17) and the neolignan dicarboxylic acid (**58**) (17% yield) was observed. As already cited in Section 2, the biomimetic cross-coupling of **55** and **56** mediated by $K_3Fe(CN)_6$ afforded racemic **57**; in analogous conditions, methyl *p*-coumarate (**29a**) gave the racemic *trans* dimethyl ester **132** (Figure 17). It is worth noting that the synthetic ester **132** showed, as expected, a specific optical rotation of 0°, whereas **132** isolated from *C. lunata* gave a specific rotation of +3.8°, indicating a degree of stereospecificity in the biotransformation reaction.



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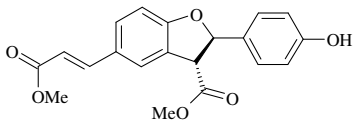


132

Figure 17

The metal-mediated syntheses of various flavonolignans, such as hydnocarpin (**82**) and its regioisomer **84** have been reported with some detail in Section 2. Some of these reactions were carried out by Guz and

Stermitz[76] with the HRP/H_2O_2 system, and it was observed that in all the peroxidase-catalyzed reactions, the regioisomer bearing the coniferyl-derived ring in the 'up' position was the major product.

We have already cited in Section 2, the 1,4-benzodioxane neolignans found in seeds of *Phytolacca dodecandra*.[65] Among them, americanol A (**67**) and isoamericanol A (**68**), which exhibit neurotrophic properties, have been synthesized by Fukuyama *et al.*[101] employing a peroxidase-mediated oxidative coupling as key step. Caffeic acid was treated with HRP/H_2O_2 (dioxane/phosphate buffer, pH = 6) to obtain the dimers **133** and **134** (Figure 18), which were submitted to a sequence of methylation, DIBAL-H reduction and $LiAlH_4$ reduction to afford **67** and **68**. The authors showed that HRP has a preference for the C-O coupling leading to 1,4-benzodioxane ring formation, not readily accessible from caffeic acid with other methods. In a subsequent paper,[102] these authors reported in detail all the products of this coupling, including also the trimer **135**, the lignan **136** and the neolignan **137** (Figure 18), as well as an aryldihydronaftalene lignan, here not reported. In addition, the HRP-catalysed coupling of 3,4-dihydroxycinnamyl alcohol was carried out, and allowed to obtain directly **67** and **68** in 22% and 60% yield, respectively.

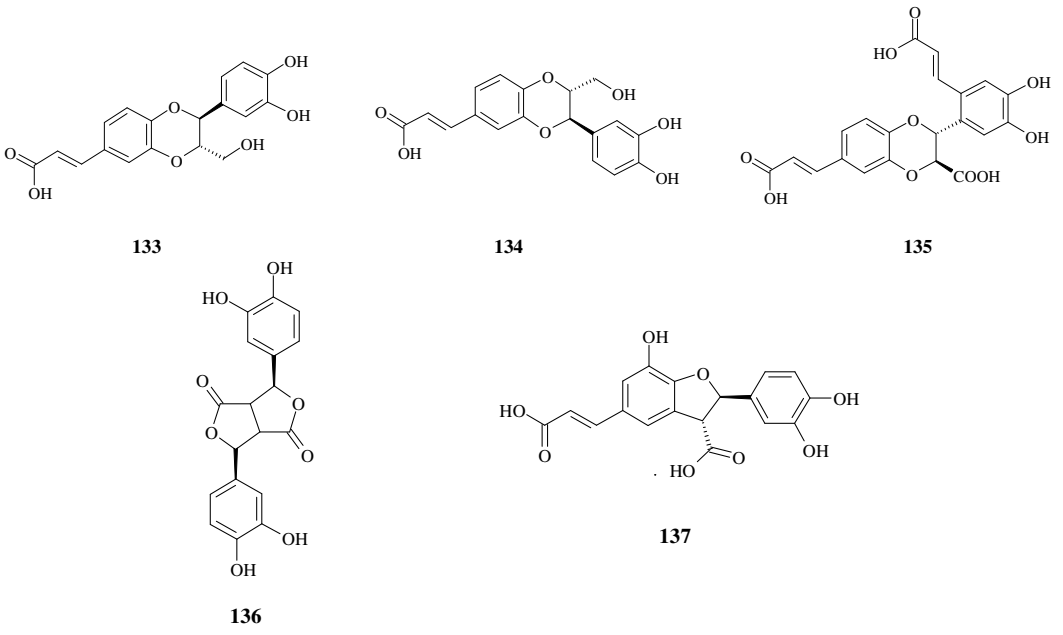
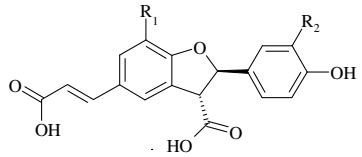


Figure 18

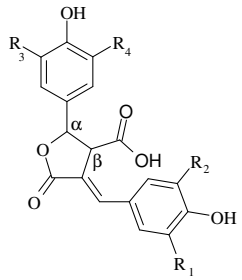
In Section 2, the biomimetic synthesis of magnolol (**43**) and other lignans starting from the allylphenol **42** and employing $K_3Fe(CN)_6$ or $FeCl_3$ has been reported[51]. More recently, Liu *et al.*[103] used the same substrate **42** to carry out the oxidase-catalysed synthesis of **43** as well as of dunnianol, isomagnolol and the Pummerer's ketone derivative **44**. In this work, the effects of various enzymes, co-solvents, pH, addition rate of H_2O_2 and the ratio enzyme/substrate were compared. The HRP type I (methanol, buffer pH 6.0) afforded a yield of **43** (40%) significantly higher than that of the chemical methods.

The hydroxycinnammic acids (*p*-coumaric, caffeic, ferulic and sinapic acid) are known to accumulate in potato tubers during wound healing and have been identified as monomers in the suberin structure. An anionic potato peroxidase (APP) is thought to be involved in plant tissues suberization after wounding. On this basis, Arrieta-Baez and Stark[104] carried out parallel enzymatic conversions using HRP and APP in the presence of H_2O_2 to elucidate the first steps of dehydrogenative polymerization between pairs of different

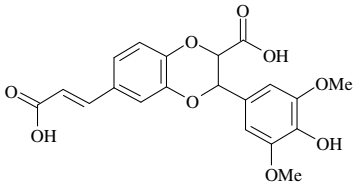
hydroxycinnamic acids. When a single hydroxycinnamic acid and H_2O_2 were employed in the presence of HRP or APP peroxidases, a complex mixture was obtained, from which the major products were isolated and resulted open-bridge dimers derived from 8-5', 8-8' or 8-*O*-4' coupling. When mixtures of two different hydroxycinnamic acids were employed in equimolar mixture, using the peroxidase-H_2O_2 system, only caffeic acid reacted with ferulic acid and sinapic acid to form heterodimers; in particular the reaction of caffeic and ferulic acid gave the dicaffeoyl dimer **126** and three cross-coupling products (**137–139**). From caffeic and sinapic acids, two cross-coupling products **140** and **141** and three homodimers **142–144** were obtained (Figure 19). For the other mixtures of hydroxycinnamic acid, only dimers derived from a single monomer were formed. The same lignans were obtained as major products with either APP or HRP: thus, commercial HRP may be employed as a suitable model enzyme for studies on the APP role and activity.



126 $R_1 = OCH_3$, $R_2 = OH$
137 $R_1 = OH$, $R_2 = OH$
138 $R_1 = OH$, $R_2 = OCH_3$



139 $R_1 = OCH_3$, $R_2 = H$, $R_3 = OH$, $R_4 = H$
140 $R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = OH$, $R_4 = H$
142 $R_1 = OH$, $R_2 = H$, $R_3 = OH$, $R_4 = H$
143 $R_1 = R_2 = R_3 = R_4 = OCH_3$ (α, β *trans*)
144 $R_1 = R_2 = R_3 = R4 = OCH_3$ (α, β *gauche*)



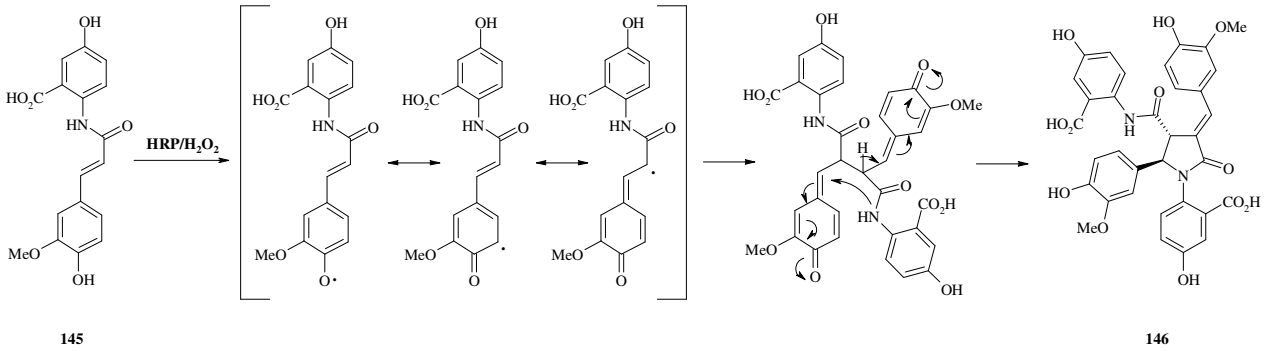
141

Figure 19

The results of this work suggest that the final step in the formation of the main dehydrodimers may not be enzymatically controlled, rather being governed by the oxidation potential and reactivity of the radical. Radicals at C-8 are the most reactive and coupling models producing a covalent bond at this position are expected to predominate in the reaction mixture.

As reported in Section 2, biomimetic synthesis of lignanamides are quite rare. Two antifeedant lignanamides isolated from *Xylopia aethiopica*[88] were authenticated by chemical or enzymatic synthesis. This latter was carried out treating the phenolic amide **112** with HRP/H_2O_2 (EtOH, buffer pH = 7.4) and afforded the same products of the chemical synthesis (see Section 2) in better yields, namely (±)-**113** (18%) and (-)-**114** (10%). More recently, Ishihara *et al.*[105] reported the identification of a lignanamide phytoalexin in oat (*Avena sativa*) leaves, which was corroborated by the synthesis through oxidative coupling of aventhramide B (**145**), affording the dehydrodimer bisaventhramide B (**146**). The proposed mechanism was analogous to those reported for dehydrodimer neolignans formation (Scheme 19). An extensive NMR study established the reported structure; chiral HPLC confirmed that **146** was obtained as a racemate. The same authors (Okazaki *et al.*[106]) reported very recently a further study on phytoalexin lignanamides in elicited oat leaves. In addition to **146**, they reported five new aventramide B dimers. These dimers were synthesized in a peroxidase-catalysed reaction in the presence of H_2O_2 and their structures were established as **147–151** (Figure 20) (only one enantiomer for each racemic couple is reported), on the basis of an extensive spectroscopic study, chemical derivatization and ^{15}N labelling. A mechanism for the formation of these

unusual products is proposed, where the first step is an 8'-8' coupling reaction between two avenanthramide B units (Scheme 19).



Scheme 19

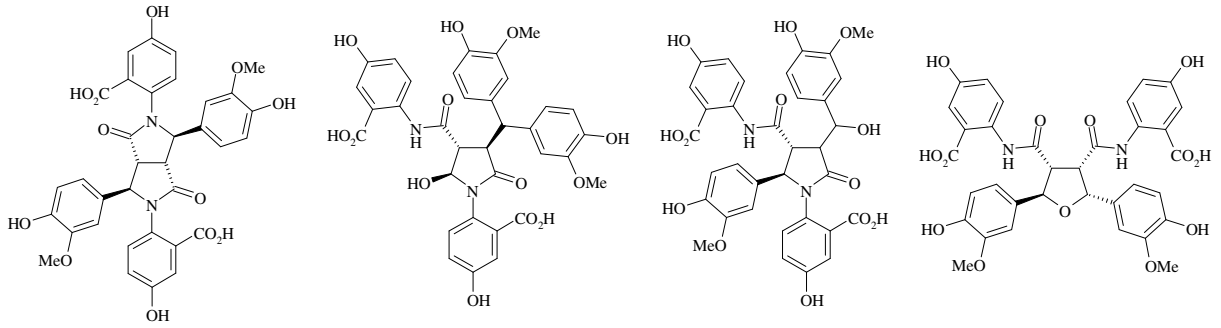


Figure 20

4. Conclusions

The literature of the period 1994–2007 on phenolic oxidative coupling in the biomimetic synthesis of heterocyclic lignans, neolignans and related compounds has been reviewed. The material has been organized in two sections, devoted respectively to metal- and enzyme-mediated phenolic oxidative coupling. More than 100 dimeric and trimeric compounds have been reported, some of them with unusual structures (for instance, benzo[*kl*]xanthenes, stilbenolignans, nitrogenated neolignans, and others) or displaying promising biological properties (for instance, antioxidative, antitumor, antiangiogenic, antimalarial, MDR inhibitory, neurotrophic or antifeedant activity). Because of the lack of stereochemical control, the radical coupling reactions normally give rise to mixtures of enantiomers: this is true not only for metal-mediated reactions, but also for reactions catalysed by peroxidases (such as horseradish peroxidase, HRP) or laccases. In fact, the stereocontrol of biosynthetic coupling reactions is due to a 'dirigent' protein, lacking catalytic activity. Nothwithstanding this limitation, radical coupling reactions frequently occur with high regio- and diasteroselectivity and, in some cases, high (> 80%) overall yields are reported. Thus, this kind of simple reaction, occurring in mild conditions, may be of preparative utility, in particular when a library of analogues of bioactive lignans has to be prepared. The most frequently employed oxidative agents in chemically promoted reactions are Ag_2O and Ag_2CO_3, but also less common reagents, such as MnO_2 or Salen complexes have been employed. The enzymatic coupling has largely been carried out with the HRP/H_2O_2 system, but also laccases or other enzymatic systems, including cell cultures, have been used. These 'environmental friendly' methods have the important advantage of avoiding the use of heavy metals.

Only a limited number of papers includes a study of the reaction mechanism supported by experimental data or calculations. Evidence suggests that the regio- and diastereoselectivity are strongly influenced by the relative stability of the intermediate radicals or quinone methides. Many of the reported examples are homocoupling reactions, frequently affording *trans* dihydrobenzofuran neolignans as the main product: these are exemplified by dihydrodiconiferyl alcohol **5**. Attempts to orient the stereoselectivity of the coupling by means of a chiral auxiliary pendant have been reported only in few cases and it is worth noting that a diastereomeric excess higher than 80% was obtained. The cross-coupling reactions can be used with phenols of comparable reactivity and this methodology allowed obtaining interesting heterodimers such as those including a 1,4-benzodioxane nucleus (for instance racemic **91**, obtained in 40% yield) or stilbenolignans (for instance the racemic antiangiogenic agent **96**). In conclusion, we think that the use of phenolic oxidative coupling as key step in biomimetic synthesis of heterocyclic dimers (lignans, neolignans and related compounds) may be very useful in many cases and future work may afford new bioactive 'lead compounds' obtainable with easy and mild synthetic methods.

Acknowledgements

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NEW SYNTHETIC APPROACHES TO BIOLOGICALLY RELEVANT HETEROCYCLIC QUINONES AND QUINONEIMINES

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Abstract. *Synthetic work aimed at the preparation of compounds related to antitumour natural heterocyclic quinones or quinoneimines is discussed. The natural products used as leads in this research were diazaquinomycin A, calothrixin B, mitomycin C, ascididemin and meridine. Besides yielding some of the natural products and their analogues for biological and structure-activity relationship studies, this research prompted the development of new synthetic methodologies, which are also discussed.*

Contents

1. Introduction

Heterocyclic quinones[1] are very interesting compounds from the point of view of medicinal chemistry, specially in the field of anticancer drug design.[2] In some cases, these compounds are designed as isosters of bioactive non-heterocyclic compounds. For instance, natural and unnatural products containing a 9,10-anthracenedione substructure are an important class of antitumour compounds that include the anthracyclines,[3] mitoxantrone,[4] the pluramycins[5] and some of the enediyne antibiotics. Their planar structures allow these compounds to act as DNA intercalating agents,[6] causing topoisomerase II inhibition,[7] and one-electron reduction of their quinone unit leads to the generation of DNA-damaging oxygen radicals.[3,8] Isosteric substitution of one or more carbons of the benzene rings by nitrogen atoms affords compounds with geometries similar to those of the parent compounds, but with increased affinity for DNA due to the presence of sites suitable for hydrogen bonding or ionic interactions.[9] Thus, pixantrone has shown an antitumour activity similar to that of its deaza analogue mitoxantrone, but with less toxicity, and is undergoing phase III trials for the treatment of non-Hodgkin's lymphoma.[10] One example of a natural 1,8-diazaanthracene is diazaquinomycin A, an inhibitor of thymidylate synthase from *Streptococcus faecium.*[11] The closely related compound Sch-538415, isolated from an unidentified bacterial microorganism, has been characterized as an inhibitor of acyl-carrier protein synthase (AcpS), an interesting antibacterial target.[12] Carbazolequinones are also very interesting from the point of view of the design of chemotherapeutic agents. For instance, the natural product calothrixin B, which has been shown to induce the intracellular formation of oxygen reactive species,[13] displays a very high (nanomolar) *in vitro*

cytotoxicity against HeLa cancer cells and it is also very interesting as a potential antimalarial agent because it inhibits the growth of a chloroquine-resistant strain of *Plasmodium falciparum.*[14] The presence of a quinone moiety is also the basis for a mechanism of DNA alkylation involving the generation of cytotoxic species through *in situ* bioreductive activation.[15] The natural product mitomycin A is the prime example of these type of compounds, and has served as a lead for the design of a large number of analogues. Heterocyclic quinoneimines are also biologically very relevant. One important example can be found in a group of marine alkaloids collectively known as the pyridoacridines,[16] which are exemplified by meridine and ascididemin. These compounds exhibit a wide range of biological activities,[17] and are particularly promising as anticancer leads.[18]

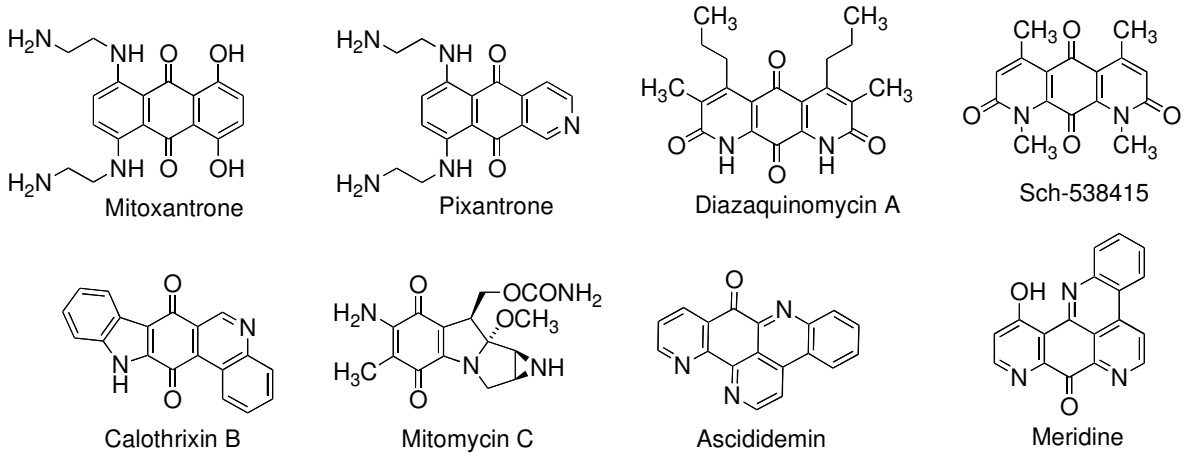
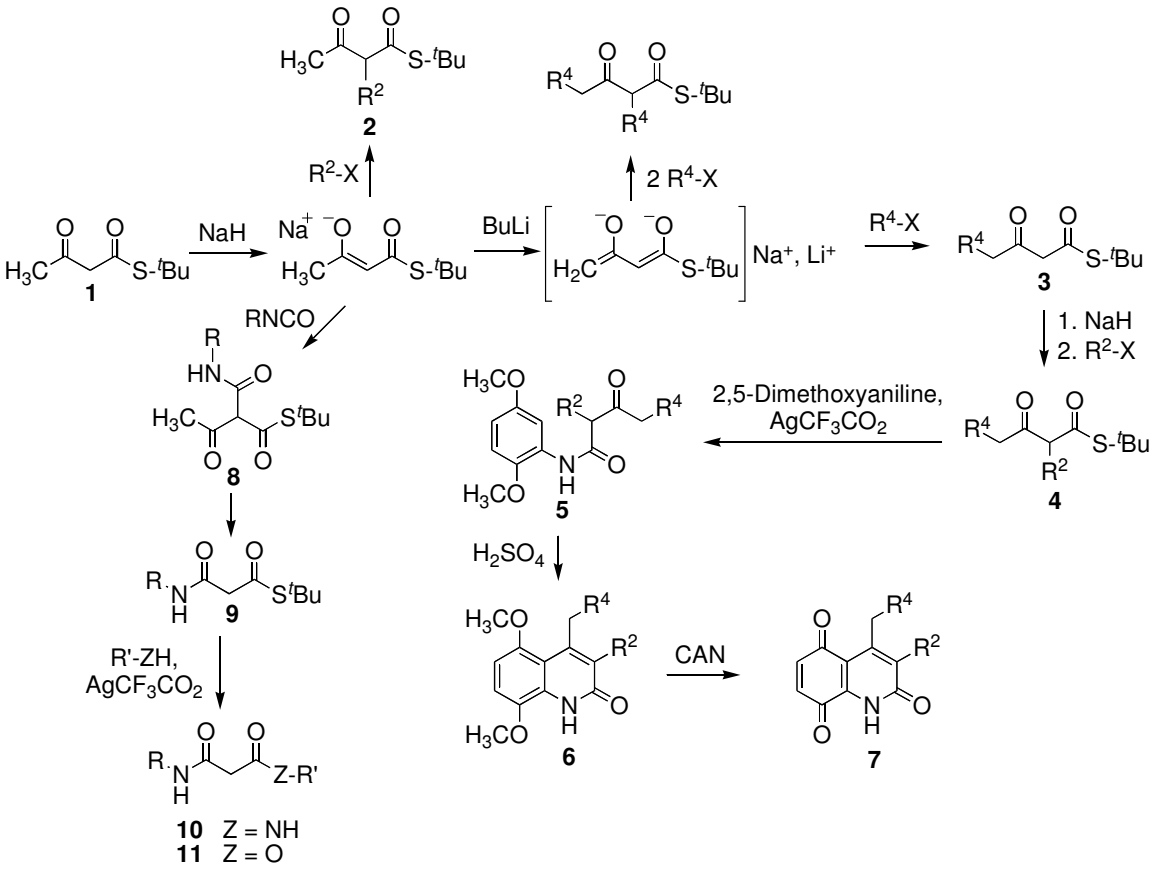


Figure 1

2. Diazaanthraquinones

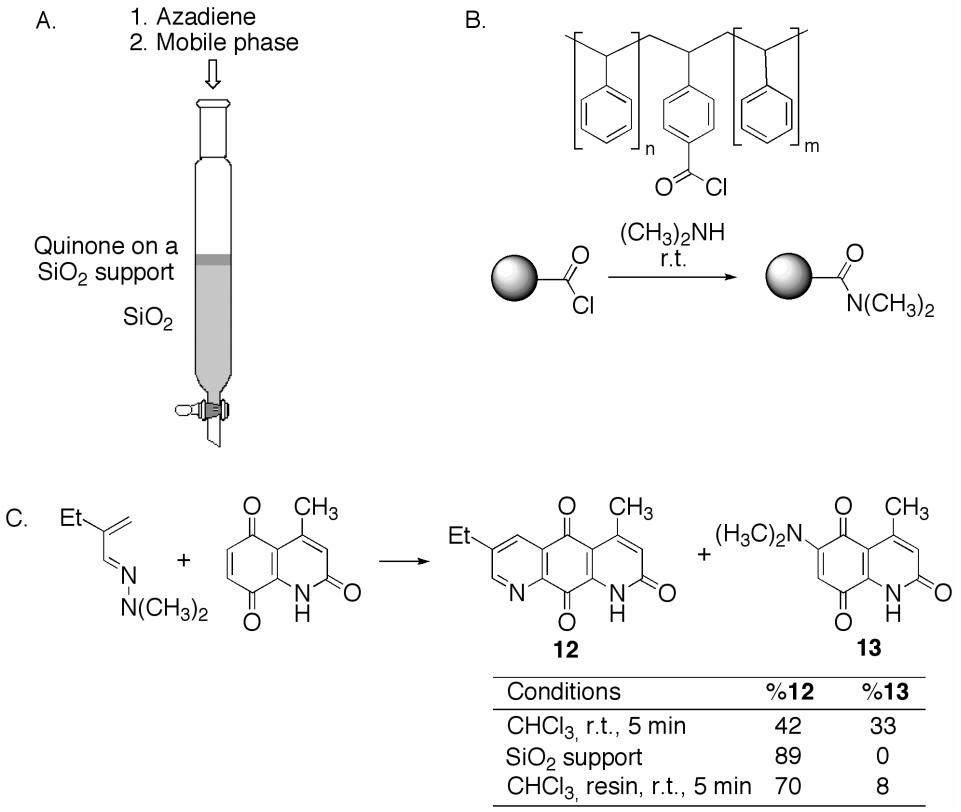
The cytotoxic activity of diazaquinomycin A and its interesting mechanism of action, coupled with the poor pharmacokinetic properties of the natural product,[19] prompted us to investigate the preparation of a large number of analogues. When we began our work, only one total synthesis of the natural product had been reported, involving as the key step a double Knorr cyclization of 3,5-bis-(2-methyl-3-oxohexanoylamino)hydroquinone.[20] We felt, however, that an alternative approach based on the use of normal electron demand hetero Diels-Alder reactions between 1-dimethylamino-1-azadienes and 2,5,8(1*H*)-quinolinetriones (**7**) would be more versatile for the preparation of structurally varied analogues.[21] The application of this strategy to the total synthesis of diazaquinomycin A required the development of a general approach to 2,5,8(1*H*)-quinolinetriones, since previously known methods[22] were not suitable for the preparation of 3,4-disubstituted systems. To achieve this goal, we resorted to the relatively little studied chemistry of β-ketothioester anions. Thus, *S-tert*-butylacetothioacetate **1**[23] was transformed into its C-2 mono-, C-4-mono- and C-2,4-dialkylated derivatives **2–4** by regioselective alkylation of its mono- or dianions, as shown in Scheme 1. These thioesters were then used as acylating reagents for 2,5-dimethoxyaniline in the presence of silver trifluoroacetate, affording anilides **5**, which were then cyclized to the corresponding carbostyrils **6** under Knorr conditions, usually by exposure to sulfuric acid. Finally, the desired quinones **7** were prepared from **6** by oxidative demethylation in the presence of cerium(IV) ammonium nitrate (CAN).[24] The chemistry of β-ketothioester anions was also

used to develop a new synthetic approach to malonamic esters **10** and malonamides **11**. This process was based on the treatment of the C-2 monoanion with isocyanates to give tricarbonyl compounds **8**, which could be detected in the crude reaction products but were deacetylated during workup and purification to give **9**, specially in the presence of silica gel. Compounds **9** were treated with several amines at room temperature in the presence of silver trifluoroacetate, yielding diamides **10**. Similar treatment of **9** with alcohols or phenols afforded malonamic acid esters **11**, also in excellent yields.[25]



Scheme 1

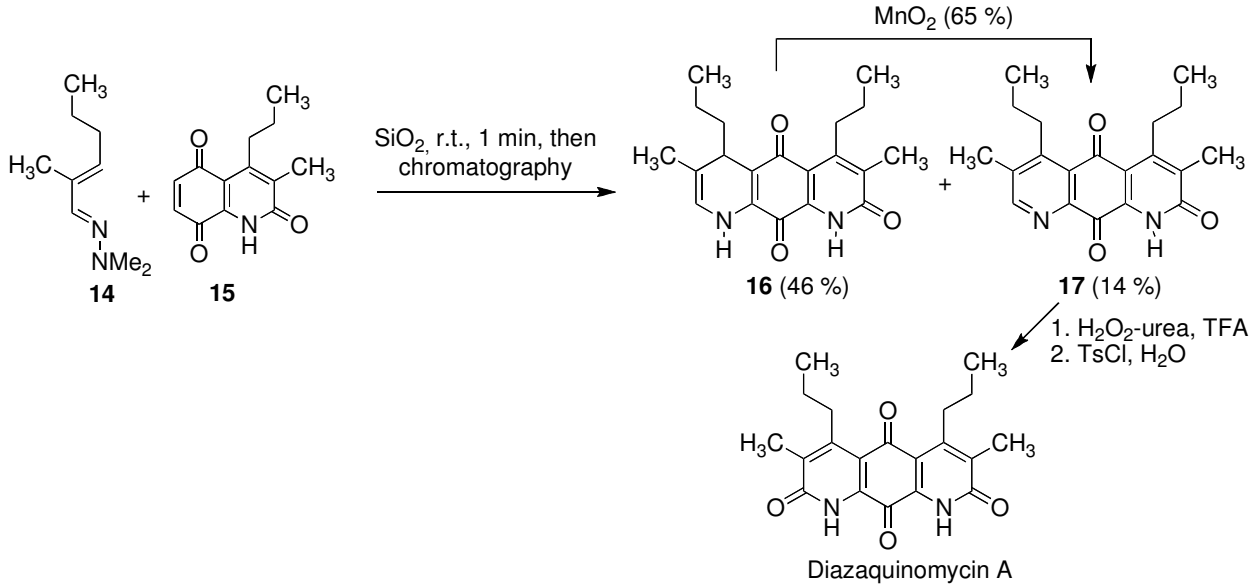
Our previous experience with the reactions between 1-dimetylamino-1-azadienes and 2,5,8-quinolinetriones[26] had revealed one major problem associated to the very fast liberation of dimethylamine from the primary Diels-Alder adduct. This amine reacted with the starting quinone, affording a 6-dimethylamino derivative **13** that was in some cases the major product isolated from the reaction. In an effort to alleviate this problem, we developed a new type of normal electron-demand 1-azadienes, namely 1-acetylamino-1-azadienes, but they proved to be relatively unreactive towards our quinones.[26b] In an alternative approach, which worked well for fast cycloadditions, we found that addition of the azadiene to the silica gel-supported quinone placed on top of a silica gel column, followed by fast elution, allowed to suppress the side product (Figure 2.A).[27] Alternatively, dimethylamine could also be trapped by addition of a modified Merrifield resin containing chloroformyl groups, prepared in two steps from the commercially available parent polymer (Figure 2.B).[28] A comparison of the yields obtained with these two methods and the conventional conditions in the preparation of compound **12** is given in Figure 2.C.



Conditions	%**12**	%**13**
$CHCl_3$, r.t., 5 min	42	33
SiO_2 support	89	0
$CHCl_3$, resin, r.t., 5 min	70	8

Figure 2

With these developments in hand, we could finally undertake the total synthesis of diazaquinomycin A (Scheme 2) and also use the methodology developed for this purpose to prepare new diazaquinomycin analogues. Our first route started by treatment of dimethylhydrazone **14** with carbostyrilquinone **15**, using the previously developed silica gel support protocol.

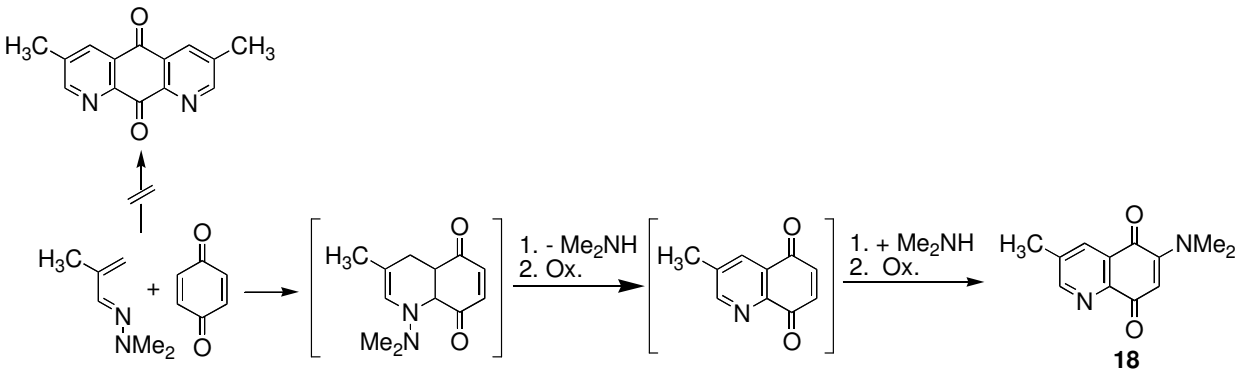


Scheme 2

This reaction afforded a mixture of the 5,8-dihydro-1,8-diazaanthracene derivative **16** and its aromatization derivative **17**, which could also be prepared by manganese dioxide-promoted dehydrogenation of **16**. Treatment of **17** with the urea-hydrogen peroxide adduct (percarbamide, UHP)[29]

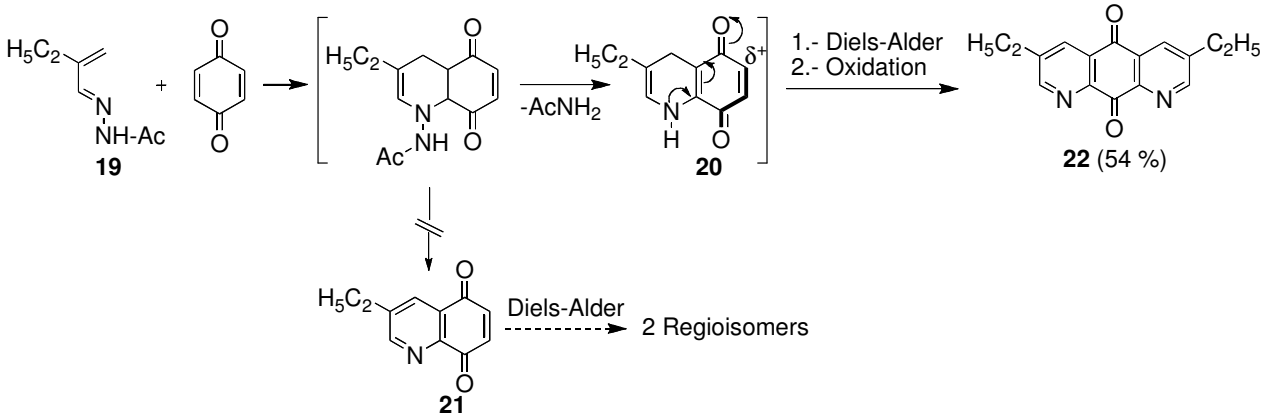
afforded the corresponding *N*-oxide, which was rearranged to diazaquinomycin A by treatment with tosyl chloride in the presence of water.[30]

We envisioned that a simpler approach should be possible that took advantage of the symmetry present in the diazaquinomycin molecule. In principle, double hetero Diels-Alder reactions of benzoquinone derivatives and 1-azadienes should provide a very simple synthesis of symmetrically substituted 1,8-diazaanthraquinones. Unfortunately, the only literature precedent of this reaction was discouraging, since treatment of benzoquinone with excess methacrolein dimethylhydrazone was known to afford 6-dimethylaminoquinolinequinone **18** as the only reaction product rather than 3,6-dimethyl-1,8-diazaanthraquinone.[31] This result can be rationalized in terms of a single hetero Diels-Alder cycloaddition, followed by a two-step aromatization to quinolinequinone with concomitant elimination of dimethylamine, addition of the latter to quinolinequinone and a new oxidation (Scheme 3).



Scheme 3

We initially addressed the problem of dimethylamine addition by use of the previously mentioned 1-acetylamino-1-azadienes, which, although less reactive, have the advantage of not delivering nucleophilic species into the reaction medium. Indeed, treatment of benzoquinone with two equivalents of 1-acetylamino-3-ethyl-1-azadiene **19** in refluxing toluene for 28 h afforded a 54% yield of 3,6-diethyl-1,8-diazaanthraquinone **22** (Scheme 4).

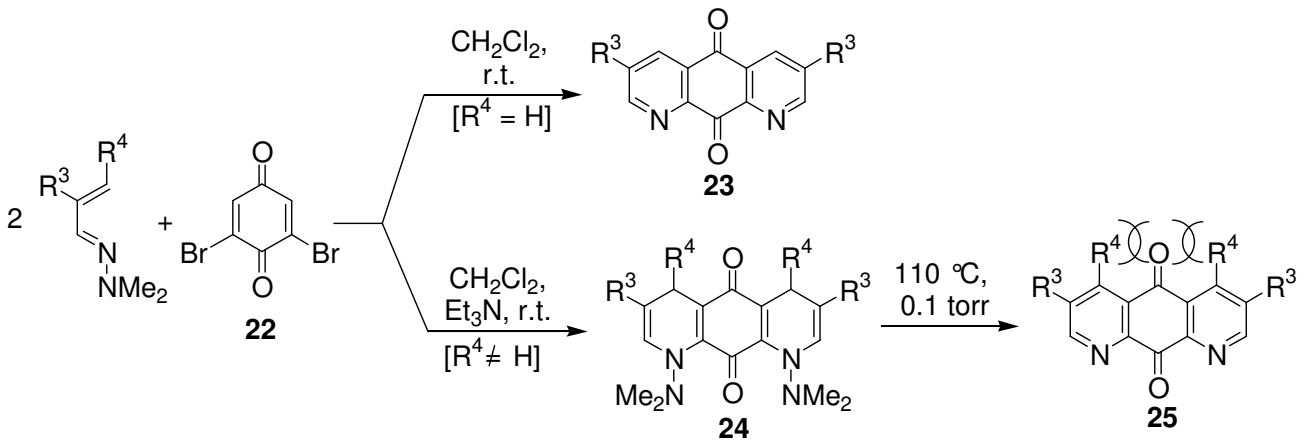


Scheme 4

The fact that **22** was the only isolated reaction product indicates that 3-ethylquinolinequinone **21** was not an intermediate of the reaction, because in that case a mixture of both possible regioisomers should

have been obtained. This suggests that the second Diels-Alder reaction takes place on the non-isolated 1,4-dihydroquinoline intermediate **20**, in which conjugation between the nitrogen and the C-5 carbonyl leaves the C_6=C_7-C_8=O portion of the molecule as a relatively isolated conjugated system with its electrophilic end at C-6, leading to the observed regioselectivity.[32]

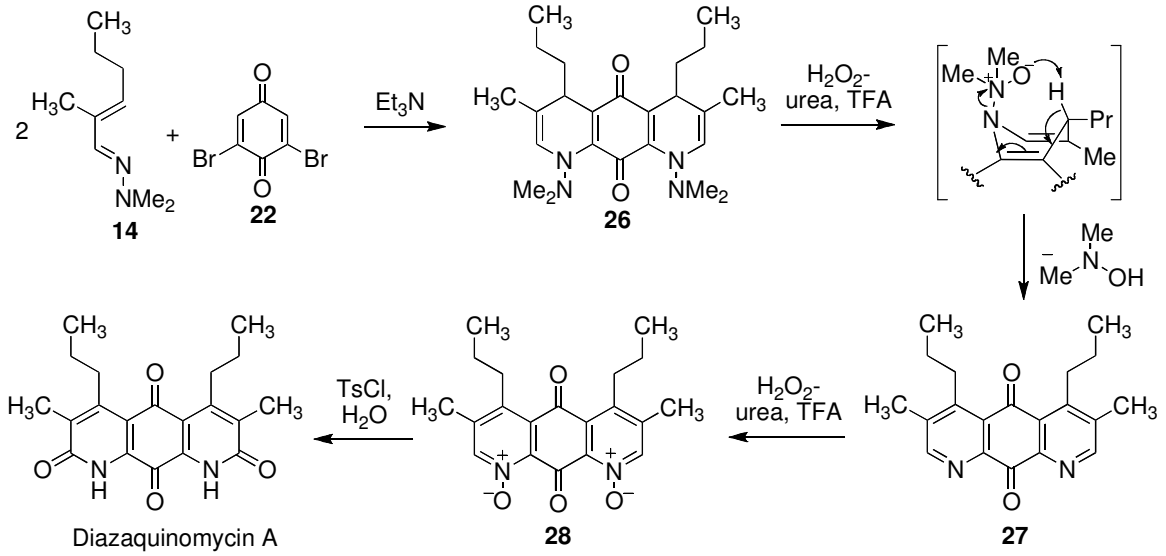
In an effort to achieve the same transformation under milder conditions, we decided to study the reactions between 1-dimethylamino-1-azadienes and halogenated benzoquinones, since we hoped that, besides the higher reactivity expected for these quinones, the hydrogen halide liberated from the primary Diels-Alder adduct would trap dimethylamine and prevent its undesired addition to intermediate quinolinequinones. In the event, treatment of 2,6-dibromobenzoquinone **22** with several 3-substituted 1-dimethylamino-1-azadienes afforded good to excellent yields of symmetrical 1,8-diazaanthraquinone derivatives, which were isolated as the fully aromatic derivatives **23**. By tuning the reaction conditions, it was also possible to isolate the product of the first cycloaddition, a 7-haloquinolinequinone derivative, and this finding gave access to the preparation of non-symmetrical 1,8-diazaanthraquinones. The reactions starting from 4-substituted azadienes gave the 1,8-bis-(dimethylamino)-1,4,5,8-tetrahydro derivatives **24**, arising from double elimination of hydrobromic acid from the primary Diels-Alder adduct. Compounds **24** were unstable to acid and their isolation required the addition of triethylamine to the reaction medium in order to trap hydrobromic acid. Steric compression between the C_4- and C_5- alkyl groups and the C_{10} carbonyl presumably prevented their spontaneous aromatization through double elimination of dimethylamine, as observed during the preparation of compounds **23**. Indeed, aromatization of **24** proved more difficult than expected, but, after several unsuccessful attempts under varied literature conditions, we found that heating the neat compounds **24** under vacuum afforded excellent yields of their aromatic derivatives **25** (Scheme 5).[33]



Scheme 5

Unfortunately, the diazaquinomycin precursor **27** was not available by this route because the aromatization step failed, probably due to the increased steric compression between the C_4- and C_5- alkyl groups and the C_{10} carbonyl in the desired product. Fortunately, we discovered that brief exposure of the bis(dimethylamino) intermediate **26** to UHP in trifluoroacetic acid at room temperature afforded **27** in 73% overall yield. This aromatization can be explained through the *N*-oxidation of the dimethylamino group of compound **26** followed by an aza-Cope elimination; the *N*-oxidation step is probably very fast, which prevents decomposition of the acid-sensitive starting material under the conditions employed (in

fact, addition of neat trifluoroacetic acid to **26** in the absence of UHP led to its rapid decomposition). According to the literature, *N*-oxidations of very deactivated nitrogens are difficult and double *N*-oxidations like the one we required were unprecedented. However, after assaying some other reagents, we were gratified to find that use of UHP, employing a modified workup procedure, allowed the transformation of compound **27** into the bis-*N*-oxide **28**, which was treated without purification with tosyl chloride in acetonitrile-water, yielding diazaquinomycin A in 30% overall yield (Scheme 6).[30,34]

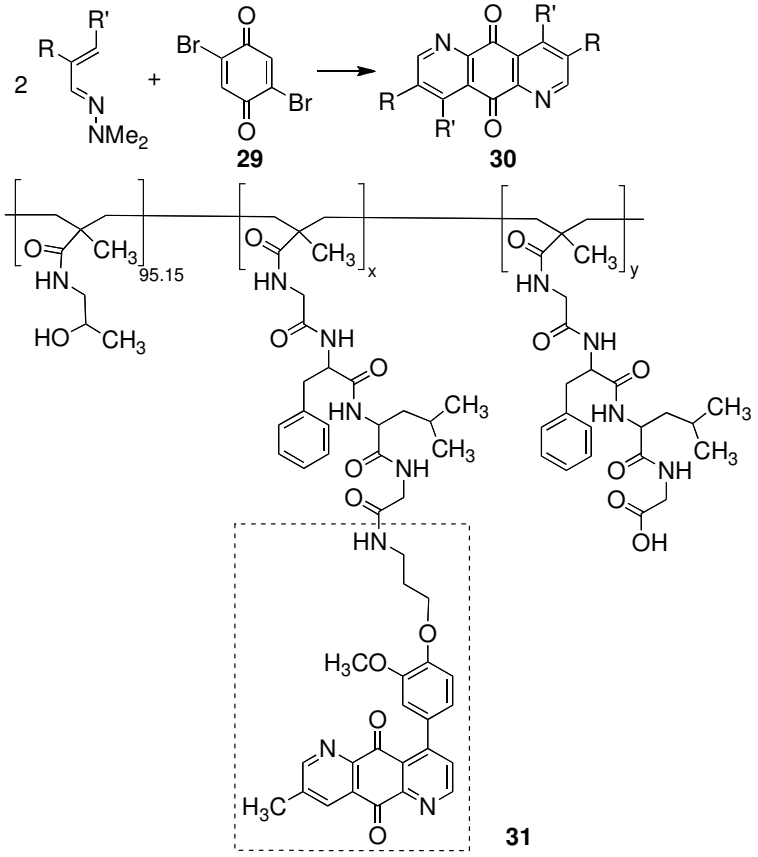


Scheme 6

Some diazaquinomycin analogues prepared using this chemistry were found to inhibit the growth of a panel of several human tumor cell lines, specially lung and colon carcinoma, with IC_{50} values much better than those of the natural product and in many cases comparable with those of doxorubicin. They also have the advantage of being unsensitive to the multidrug resistance mechanism mediated by glycoprotein P-170. Their mechanism of action has not been clearly established, although they have been found not to inhibit purified murine thymidylate synthase, in contrast with Omura's initial report.[11] A more detailed study was undertaken with some 1,8-diaza-2,7,9,10-anthracenetetraones closely related to diazaquinomycin, which showed that the growth inhibitory action of these compounds was unrelated to the p53 status of the cells. At micromolar concentrations, all compounds induced apoptosis, inhibited the activation of c-Jun NH_2-terminal kinase by various stimuli and prevented growth factor-induced extracellular signal-regulated kinase (ERK)-5 activation. At least, one of the compounds also inhibited p38, which was surprising because proapoptotic antitumour drugs activate stress signaling pathways. Activation of ERK1/2 by growth factors or phorbol esters was unaffected by preincubation of cells with these compounds. *In vitro*, they inhibited the NQO1 quinone reductase but not c-Jun NH_2-terminal kinase or ERK-5. Because doxorubicin also inhibits quinone reductase, it was concluded that the inhibitory effect of diazaquinomycin analogues on stress signaling kinases is not due to a direct effect on the kinases and is attributable to upstream elements of the activation cascades.[35]

The availability of 1,8-diazaanthraquinones **25** and **27** prompted us to study their *in vitro* antitumour activity, which turned out to be quite promising.[36] We therefore decided to investigate the preparation of their 1,5-diaza isomers using a double Diels-Alder approach similar to the one previously described.

Treatment of 2,5-dibromobenzoquinone **29** with several 1-dimethylamino-1-azadienes afforded the target compounds **30** without the need for additional aromatization steps, which was ascribed to lower steric compression than in the case of **25** (Scheme 7). Some compounds **30** showed very interesting *in vitro* activities against solid tumours,[37] but their clinical potential was considered poor because of their low solubilities. This observation stimulated the preparation of conjugates such as **31** with copolymers of *N*-(2-hydroxypropyl)-methacrylamide (HPMA) and a Gly-Phe-Leu-Gly (GPLG) linker designed to facilitate the intralysosomal liberation of the drug by cysteine proteases. Although these compounds showed decreased *in vitro* cytotoxicity, their lysosomal activation was observed and this suggested that *in vivo* evaluation of their antitumour potential was warranted.[38]

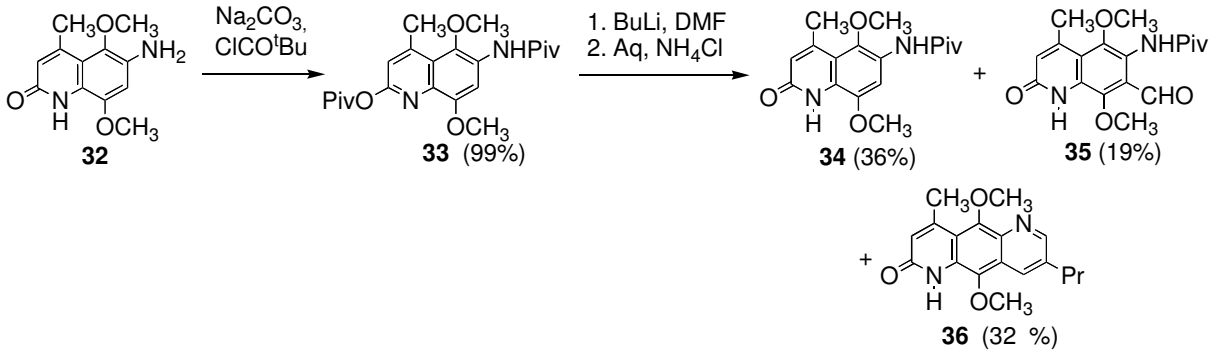


Scheme 7

In view of these data, we considered of interest the preparation of 1,5-diazaanthracene-2,9,10-triones, which are related to compounds **30** and also bear an isomeric relationship to previously studied diazaquinomycin analogues such as **12**. To this end, we studied the application of a modification[39] of the Friedländer quinoline synthesis to the preparation of precursor **35** by formylation of the *N*,*O*-dipivaloyl derivative **33**, which was obtained by reaction of the known carbostyryl **32** with pivaloyl chloride under phase-transfer conditions. Treatment of **33** with excess *n*-BuLi and DMF using conditions employed for other pivaloyl-assisted lithiations,[39] followed by acid hydrolysis, afforded a mixture of the *O*-deprotected compound **34**, the expected formyl derivative **35** and, most importantly, the 1,5-diazaanthracene derivative **36** (Scheme 8).

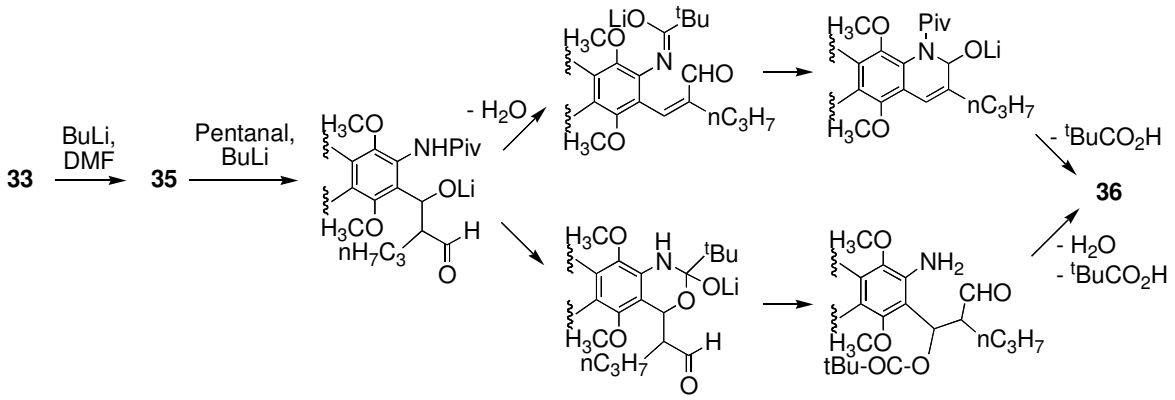
The isolation in one pot of **36**, albeit in modest yield, was very interesting, as it had the structure of our target compounds. Its formation can be explained by *in situ* formylation of *n*-BuLi to give *n*-pentanal,

which would react with **35** to give an aldol adduct. Intramolecular lithium exchange accompanied by loss of a molecule of water would be followed by cyclization, intramolecular pivaloyl transfer and final elimination of pivalic acid.[39a]



Scheme 8

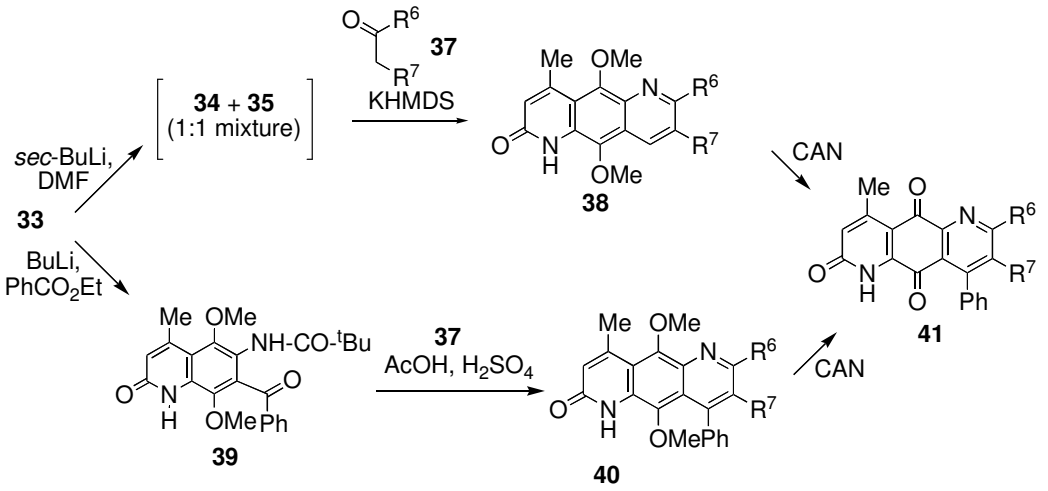
An alternative mechanism[40] could involve a series of equilibria from the aldol adduct to a benzoxazine derivative followed by ring opening, cyclization and final irreversible elimination of water and pivalic acid (Scheme 9).



Scheme 9

The use of *sec*-BuLi (instead of *n*-BuLi) and DMF prevented the formation of **36** and led to the isolation of an inseparable 1:1 mixture of compounds **34** and **35**. Treatment of this mixture with potassium hexamethyldisilazide and a carbonyl reagent containing at least one α-methylene group (**37**) gave the 9,10-dimethoxy-1,5-diaza-2(1*H*)-anthracenones **38** (Scheme 10). Subsequent experimentation proved that the preparation of **38** could be performed as a one-pot procedure, without isolation of the formyl intermediate. The spontaneous loss of the pivaloylamino group is particularly interesting because it avoids the need for an independent deprotection step, which normally requires harsh reaction conditions. In order to take further advantage of this self-deprotection and because of the excellent activities found in many 4-aryl-1,8-diaza-2,5,8-anthracenetriones, we sought to extend our method to the synthesis of regioisomers of this type of compounds containing the 1,5-diazaanthraquinone framework. After some experimentation, we found that the lithiated species generated from our starting material **33** and BuLi reacted cleanly with ethyl benzoate to give the benzoyl derivative **39**, which was transformed into the fused quinolines **40** by acid-catalyzed Friedländer reaction. This transformation was again accompanied by loss of the pivaloyl protection, presumably through a mechanism similar to the one proposed in Scheme 9. In this case, all

attempts to carry out the reaction in the presence of base were unsuccessful, in agreement with literature examples of Friedländer chemistry of *o*-aminobenzophenones, which also explains the absence of side products similar to **36** in the acylation step. Finally, compounds **38** and **40** were easily oxidized with cerium(IV) ammonium nitrate to give the target quinones **41** in quantitative yields.[41] Unfortunately, these compounds showed poor antitumour properties.



Scheme 10

3. Carbazolequinones

In view of the excellent antitumour activities found in many 1,8-diazaanthracene-2,9,10-triones, we decided to extend the aromatic system in an effort to achieve efficient DNA intercalation, which is the prime mechanism of action of many anticancer quinones, including the anthracyclines. To this end, and in view of the excellent DNA intercalation properties described in the literature for carbazoles, exemplified by the antitumour alkaloid ellipticine,[42] we chose to prepare compounds **42–44**, containing carbazole subunits and a carbostyrilquinone core (Figure 3).

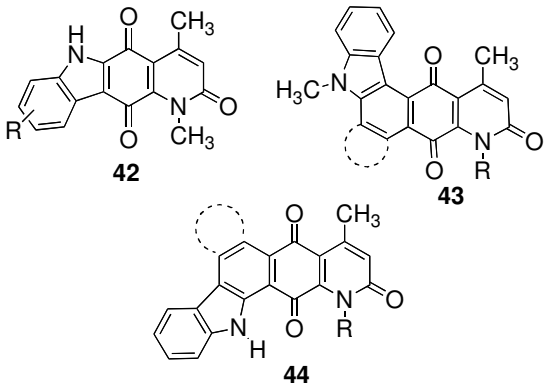
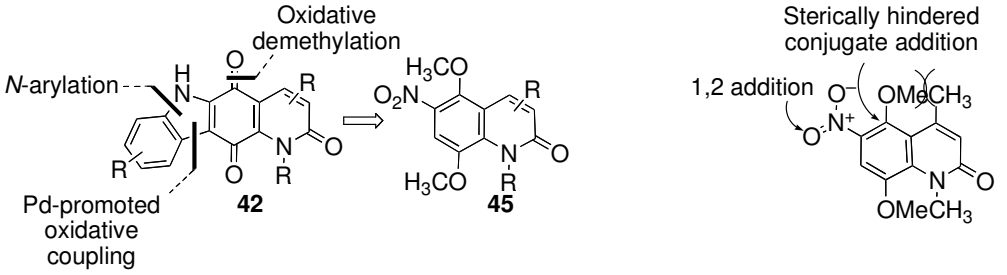


Figure 3

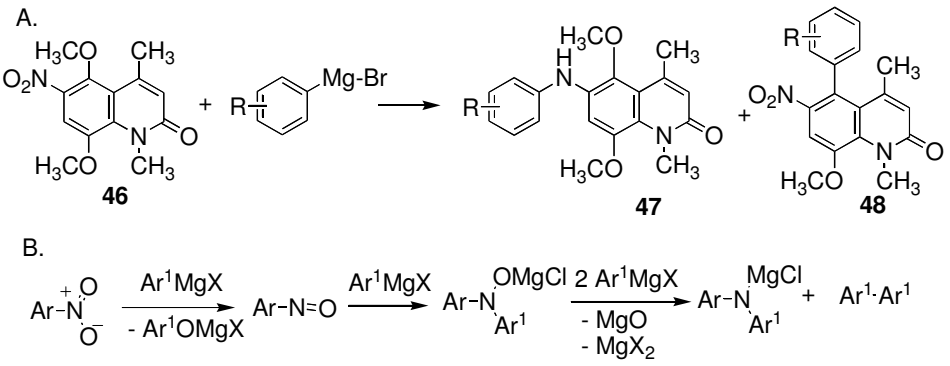
Our plan for the synthesis of **42** involved disconnection of the target structure at the C-N and C-C bonds, followed by oxidative demethylation. The *N*-arylation step would normally be carried out by treatment of a 6-aminocarbostyril derivative with an electrophilic arylation reagent, but we reasoned that use of the corresponding nitro compound, the most likely amino precursor, would save a step in the

sequence. This led to proposing nitrocarbostyril derivatives as the starting materials for a reaction involving a nucleophilic *N*-arylation reagent. The presence in these compounds of an *ortho* methoxy group, which is important for the subsequent oxidative demethylation step, poses an interesting problem because this substituent facilitates a competing conjugate addition to the aromatic carbon β to the nitro followed by elimination of the methoxy leaving group. In fact, this is the only pathway described in the literature for the reaction of 1-methoxy-2-nitronaphthalenes with aryl Grignard reagents, leading to 1-aryl-2-nitronaphthalenes as the sole products. Although this precedent went against the viability of our planned strategy, we reasoned that it should be possible to hamper the undesired reaction by introducing steric hindrance at the C-5 position. Therefore, we decided to employ as the substrate a starting material bearing a methyl substituent *peri* to the methoxy group (Scheme 11).



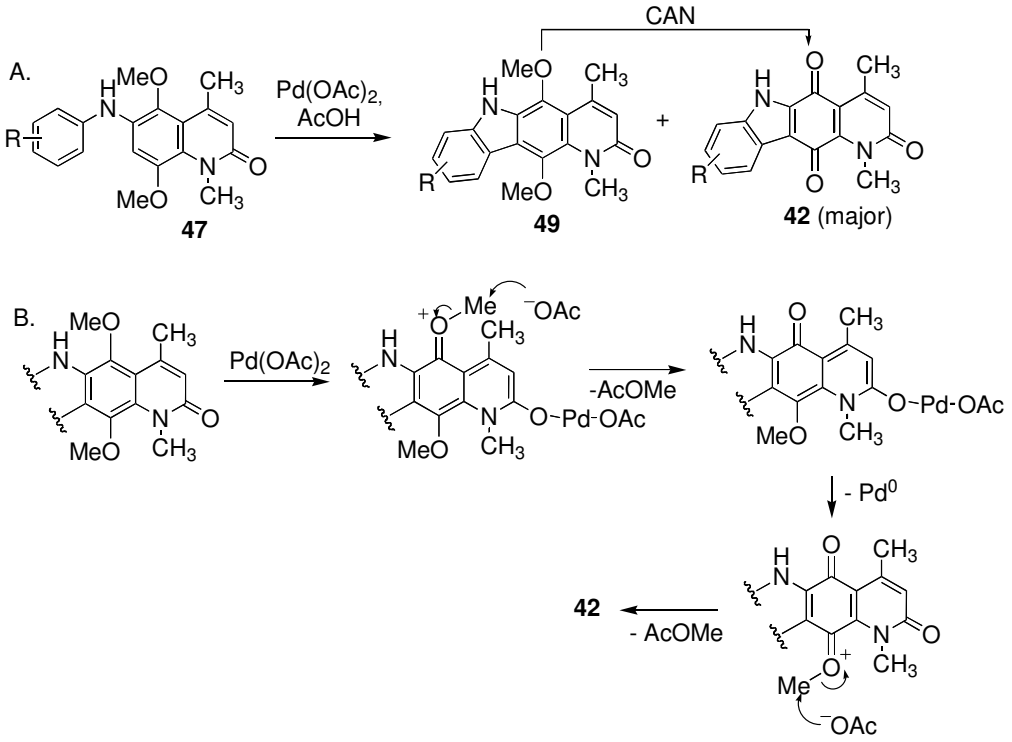
Scheme 11

As expected from our hypothesis summarized above, when compound **46** was treated with 4.5 equivalents of several substituted phenylmagnesium bromides, the diarylamines **47** were isolated as the major reaction products, together with varying amounts of biaryls **48**. In agreement with the expected steric effects, the highest chemoselectivity corresponded to the more hindered *o*-tolylmagnesium bromide, which gave exclusively the corresponding diarylamine, while the other reactions were less selective (Scheme 12A). Although the use of aryl Grignard reagents for the synthesis of diarylamines by 1,2-nucleophilic attack onto a nitro group has been recently described, using 2.5 equivalents of Grignard reagent, the initial reaction leads to an unstable hydroxylamine derivative that requires an additional *in situ* reduction step.[43] We propose that the reason for the direct isolation of diarylamines under our conditions is the use of a larger excess of the starting arylmagnesium compound, which would transform the intermediate hydroxylamine species into the observed diarylamine according to the mechanism shown in Scheme 12B.[44] The biaryls arising as side products in this mechanism were detected in all cases.



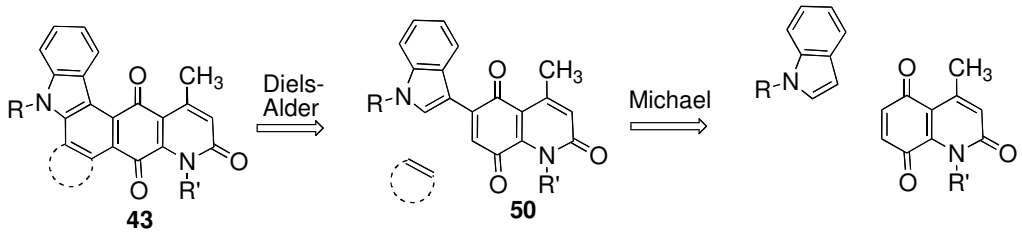
Scheme 12

We next examined the palladium-catalyzed oxidative cyclization of compounds **47** and we found that their treatment with palladium acetate in refluxing acetic acid afforded directly the desired quinones **42** as the major products, the expected fused dimethoxycarbazoles **49** being isolated normally in low yields or not at all (Scheme 13A). Isolated compounds **49** could be transformed into **42** using the traditional cerium(IV) ammonium nitrate-promoted oxidative demethylation. The observed *in situ* oxidative demethylation was unprecedented and we propose for this reaction the mechanism outlined in Scheme 13B, which is based on the observation that simple diarylamines, lacking the carbostyril moiety, do not undergo the oxidative demethylation. The reaction would start by palladation of the carbonyl oxygen, favoured by conjugation with one of the methoxy substituents and the liberated acetate anion would then be responsible for the first demethylation. Subsequent elimination of acetate and Pd (0) would set the stage for the demethylation of the second methoxy group through a similar mechanism.[45]



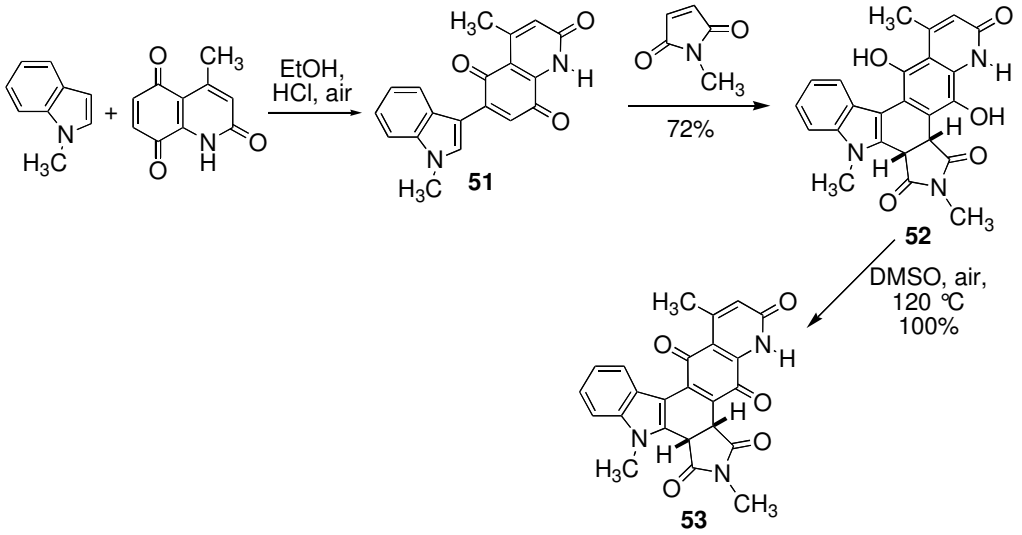
Scheme 13

The preparation of compounds **43** was planned according to the retrosynthetic analysis summarized in Scheme 14, which is based on the use of Diels-Alder reactions on compounds **50**, arising from oxidation of the Michael adducts between indoles and carbostyrilquinones.



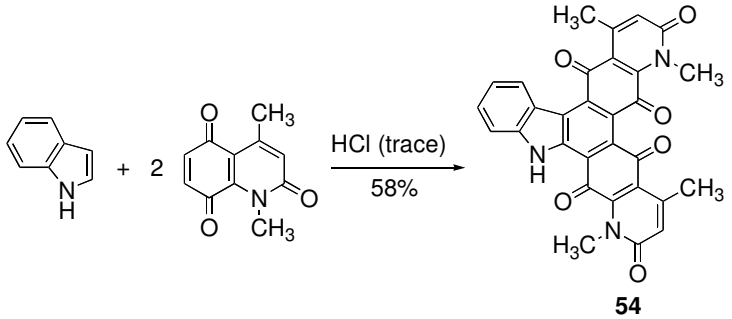
Scheme 14

Addition of 1-methylindole to 4-methylcarbostyrilquinone in ethanol containing a small amount of HCl, in the presence of air to ensure oxidation of the initial adduct, afforded compound **51**. The Michael addition took place in a regioselective fashion at the C-6 position, as confirmed by the study of long-range C-H couplings. This was expected because electron donation of N-1 to the C-5 carbonyl renders its conjugated C-7 position less electrophilic than C-6. Although indolylquinones have received very little attention in their role of Diels-Alder dienes, we found that compound **50** reacted smoothly with a range of dienophiles. As an example, its reaction with *N*-methylmaleimide to give **52** or **53** is summarized in Scheme 15.



Scheme 15

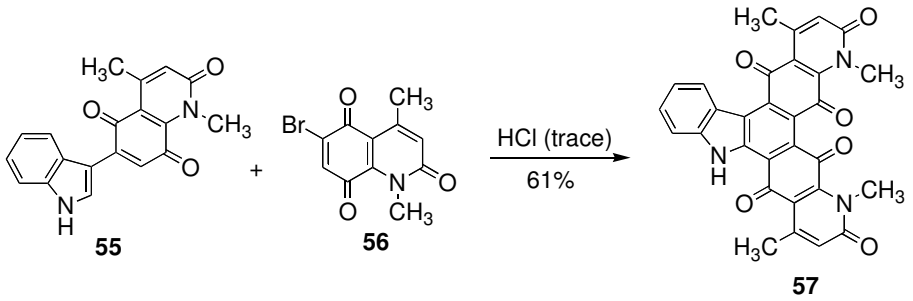
Because carbostyrilquinones can also behave as dienophiles, we envisioned the possibility of carrying out a one-pot, three-component process involving one molecule of indole and two of the quinone. As shown in Scheme 16, this expectation was borne out by experience and treatment of indoles with two equivalents of carbostyrilquinones in refluxing ethanol containing a trace of hydrochloric acid afforded heptacyclic systems in good yields, as exemplified in Scheme 16 for the case of compound **54**.[46] The mechanism of this reaction can be viewed as a sequence of up to five individual steps, namely an initial Michael addition followed by oxidation to give **50**, the Diels-Alder reaction between **50** and a second molecule of quinone, isomerization of the primary cycloadduct and final oxidation.



Scheme 16

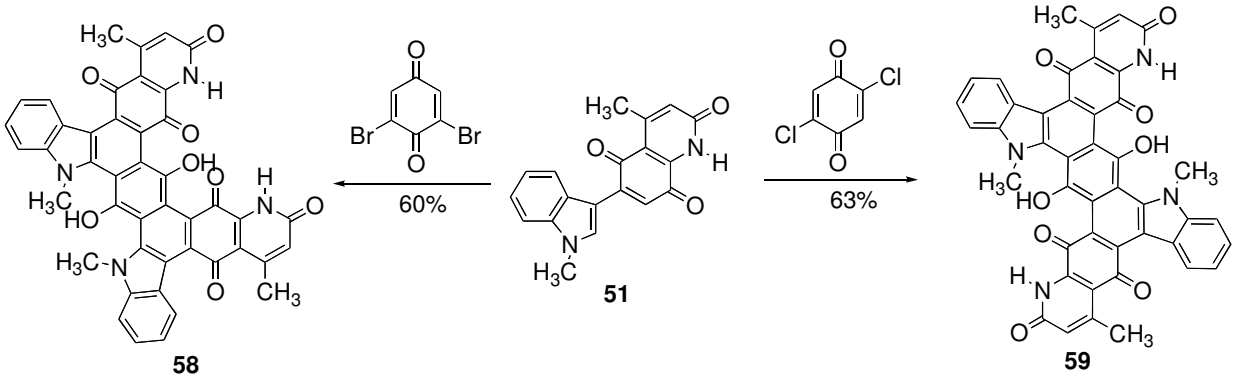
The regiochemistry of the Diels-Alder reaction was very difficult to confirm by spectroscopic evidence due to its extremely low solubility and also to the presence of a large number of quaternary

carbons, which makes spectra very uninformative and prevents the study of long-distance correlations. Therefore, we sought to confirm the structure of compound **54** and its analogues by preparing the other possible regioisomer through a route based on the well-established directing effect of the bromine atom in the Diels-Alder reactions of bromoquinones. In our case, preparation of the desired regioisomer required the presence of a bromine atom at C-6 of the quinone, which would direct the attack of the more electron-rich end of the diene to its neighboring C-7 position. As shown in Scheme 17, when a mixture of compounds **55** and **56** was refluxed in ethanol, compound **57**, the desired regioisomer of **54**, precipitated in 61% yield. The regiochemical assignments were supported by the fact that the ^{1}H-NMR spectrum of compound **57** showed two clearly differentiated signals for some of the protons, which were equivalent in the more symmetrical compound **54**.



Scheme 17

To complete our study of the reactivity of indolylquinones **20**, we examined the possibility of using them as starting materials for double Diels-Alder reactions, which would provide a very concise access to complex and unusual polyheterocyclic quinone systems. As shown in Scheme 18, treatment of compound **51** with a large excess of 2,6-dibromobenzoquinone[47] gave a 60% yield of compound **58**, arising from a double cycloaddition, with no trace of the alternative regioisomer being observed. This regioisomer **59** was prepared by a similar treatment of **51** with a large excess of 2,5-dichloro-benzoquinone, again in a completely regioselective fashion.

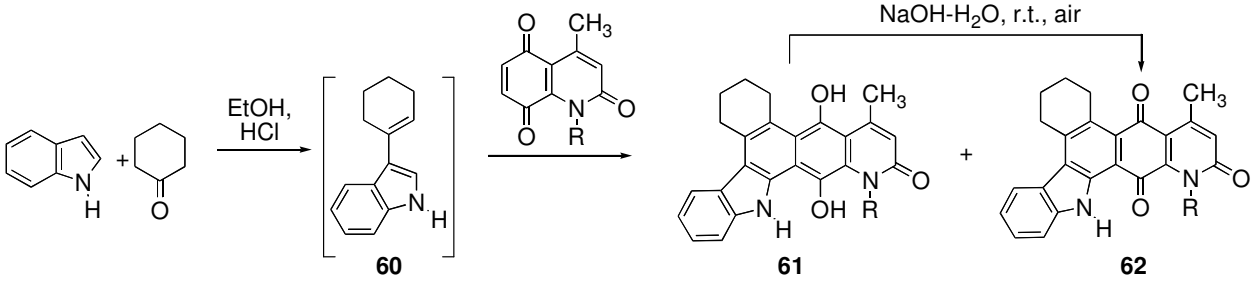


Scheme 18

Although the NMR data of compounds **58** and **59** are almost identical, the fact that **58** has an axis of symmetry (causing its OH groups to be non-equivalent) while **59** has a center of symmetry, potentially allows to establish a difference between them. Indeed, the ^{1}H-NMR spectrum of **58** shows two broad

singlets centered at 10.91 and 9.82 ppm, assigned to the C_{11} and C_{23} hydroxyls, while that of **59** has only one such signal, at 9.87 ppm, in agreement with the proposed regiochemistries. The hydroquinone structure at the central ring is in agreement with the molecular peak at 739 (M^+ + 1) in the ESI mass spectrum of both compounds and was confirmed by the observation of only three carbonyl signals at 211.3, 206.1 and 192.1 ppm in the solid-state ^{13}C-NMR spectrum of **59**. To our knowledge, these were the first double Diels-Alder reactions of an indolylquinone.[48]

Finally, some examples of structures **44** were obtained through reactions involving the use of 3-vinylindoles as Diels-Alder dienes and carbostyrilquinones as dienophiles. These dienes were very unstable and had to be generated *in situ*. Thus, when indole was treated with cyclohexanone and a carbostyrilquinone derivative in the presence of acid, quinones **62** precipitated from the reaction mixtures in moderate yields, and evaporation of the reaction media afforded mixtures of **61** and the hydroquinone derived from reduction of the starting quinones. Although compounds **61** could not be purified from these mixtures, their air oxidation in the presence of base afforded additional amounts of quinones **60**.[49]

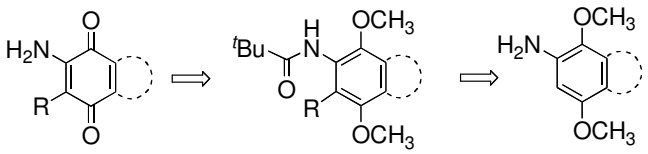


Scheme 19

The *in vitro* antitumour activities of the fused carbazoles described in this section were generally low. The poor solubility of many of these compounds may explain, at least partly, these disappointing results.

4. A new approach to 2-amino-3-alkylquinones

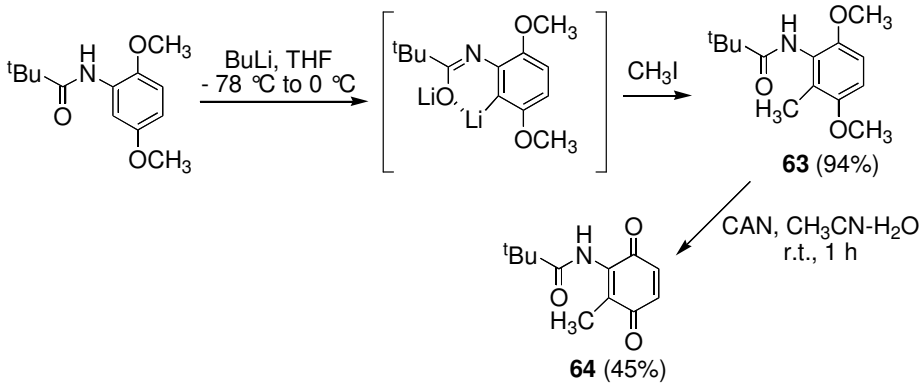
As mentioned in the Introduction, a number of natural heterocyclic quinones with antitumour properties, most notably some members of the mitomycin family, contain a 2-amino-3-alkyl-1,4-benzoquinone fragment. Compounds with this structure can also be considered as useful potential synthons for the preparation of other biologically active natural products. Previous work related to the synthesis of this type of structures has normally involved the construction of 2-methoxy-3-aminobenzoquinone moieties, followed by the displacement of the methoxy group by ammonia, but the preparation of the starting materials involves lengthy routes. For this reason, we became interested in the development of the directed metallation-based strategy summarized in Scheme 20.



Scheme 20

This strategy is simpler and, therefore, potentially more efficient than the previous ones in that it avoids the difficulties associated to the preparation of 1,2,3,4-tetrasubstituted benzene derivatives as starting materials. It also avoids issues of regioselectivity found in other strategies at the oxidation stage due to the generation of *ortho*-quinones, facilitated by the presence of a 2-methoxy group.

Our initial studies were aimed at the preparation of a derivative of the simplest possible 2-amino-3-alkyl-1,4-benzoquinone system, namely the 3-methyl-5,6-unsubstituted derivative **64**. As shown in Scheme 21, directed *ortho*-lithiation of 2,5-dimethoxy-*N*-pivaloylaniline proceeded very efficiently by its treatment with 2.5 equivalents of BuLi to give a non-isolated dilithio species, which was trapped with methyl iodide to afford compound **63** in 94% yield. Oxidative demethylation to **64** was carried out in 45% yield under standard conditions, by treatment with ceric ammonium nitrate.



Scheme 21

Having proved the feasibility of the *ortho*-metallation strategy, we decided to test its scope by applying it to the carbostyril system. In order to facilitate the generation of quinone functionality at a later stage, the presence of methoxy groups at C-5 and C-8 was considered as a requisite and, for this reason, we chose 6-pivaloylamino-4-methyl-5,8-dimethoxycarbostiryl as a suitable substrate for our study. This was a particularly challenging case and hence a good test for the robustness of our method, because, as shown in Figure 4, the 4-methylcarbostyril system contains directing groups that allow two modes of lithiation additional to the one necessary for the generation of the 2-amino-3-alkylbenzoquinone motif, namely lithiation at C-3 assisted by the neighbouring carbonyl group[50] and lithiation of the C-4 methyl substituent, assisted by the neighbouring C-5 methoxy group.[51]

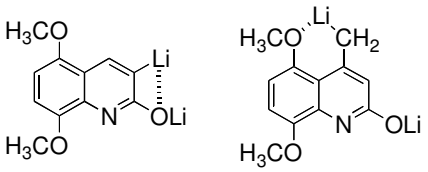
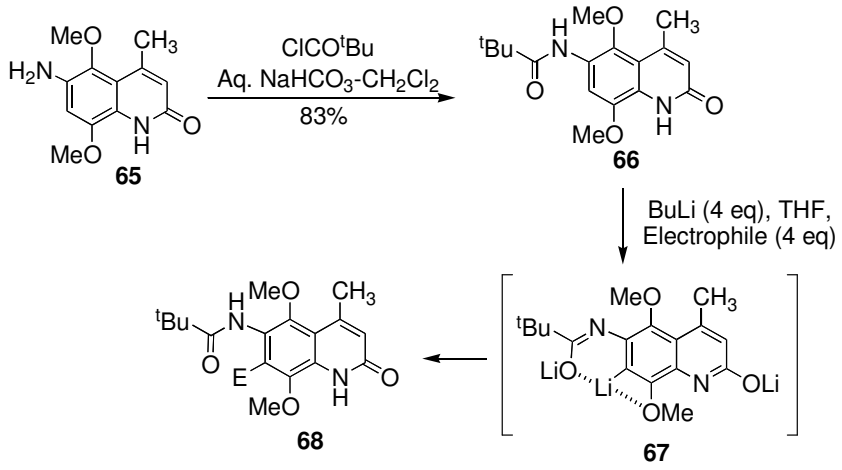


Figure 4

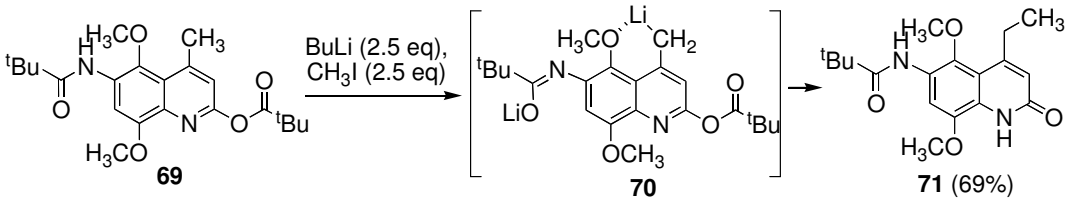
The starting material for our study was compound **66**, which was obtained from the known amine **65** and one equivalent of pivaloyl chloride. As shown in Scheme 22, treatment of **66** with four equivalents of BuLi was followed by the same excess of several electrophiles including alkyl iodides, cyanogen iodide, bis(dimethylamino)methane, dimethyl disulfide and triethyl boronate. All these reactions proceeded

regioselectively and gave the expected C-7 alkylated or functionalized products in good to excellent yields, presumably through the trilithio species **67** as an intermediate.[52]



Scheme 22

We were also able to devise a method leading to the regioselective alkylation of the C-4 methyl group in the presence of the pivaloylamino moiety. This procedure relied on the initial protection of the lactam function in order to prevent its lithiation, which was expected to hamper the generation of an anion at the relatively close methyl group. In the event, treatment of the bis-pivaloyl derivative **69** with 2.5 equivalents of BuLi followed by the same excess of methyl iodide gave compound **71** in 69% yield, presumably through the intermediacy of the dilithiated species **70** (Scheme 23). Interestingly, compound **69** had previously afforded its 7-benzoyl derivative after treatment with five equivalents of *sec*-BuLi and ethyl benzoate.[41] Under the latter conditions, the formation of an intermediate lithiated at both C_4-CH_3 and C-7 can be expected and coordination of the lithio pivaloylamide and C-7 lithio with the carbonyl group of the electrophile prior to nucleophilic attack can explain the reaction at the more hindered C-7.



Scheme 23

5. Heterocyclic quinoneimines

We will finally describe our work on the synthesis and biological evaluation of some polyheterocyclic compounds related to the pyridoacridine family of marine alkaloids, which followed the strategies summarized in Figure 5. As mentioned in the Introduction, these natural products exhibit a broad range of biological activities, including potent cytotoxicities, but they suffer from a number of drawbacks. One of them is their very low concentrations in their natural sources,[53] which, to further complicate the problem, are very often deep-sea sponges or tunicates that are normally quite difficult to reach. For this reason, in many cases, sufficient amounts for biological testing can only be accessed through total

synthesis. On the other hand, these compounds often exhibit very poor solubilities that limit their potential as drug candidates. Owing to these characteristics of the pyridoacridine family, synthetic work aimed at the total synthesis of the natural products and at the preparation of improved analogues appears as particularly relevant.

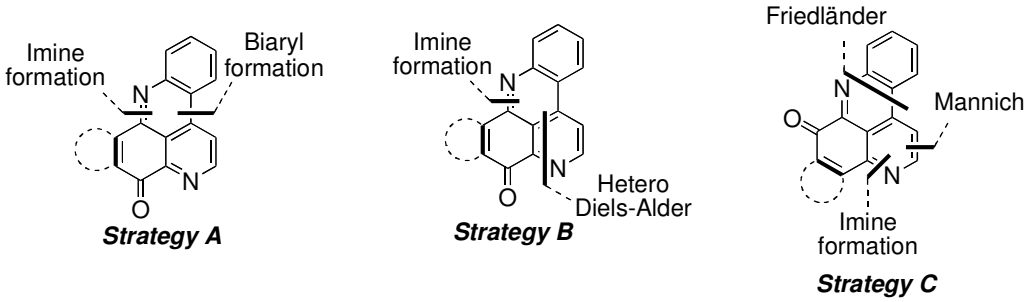
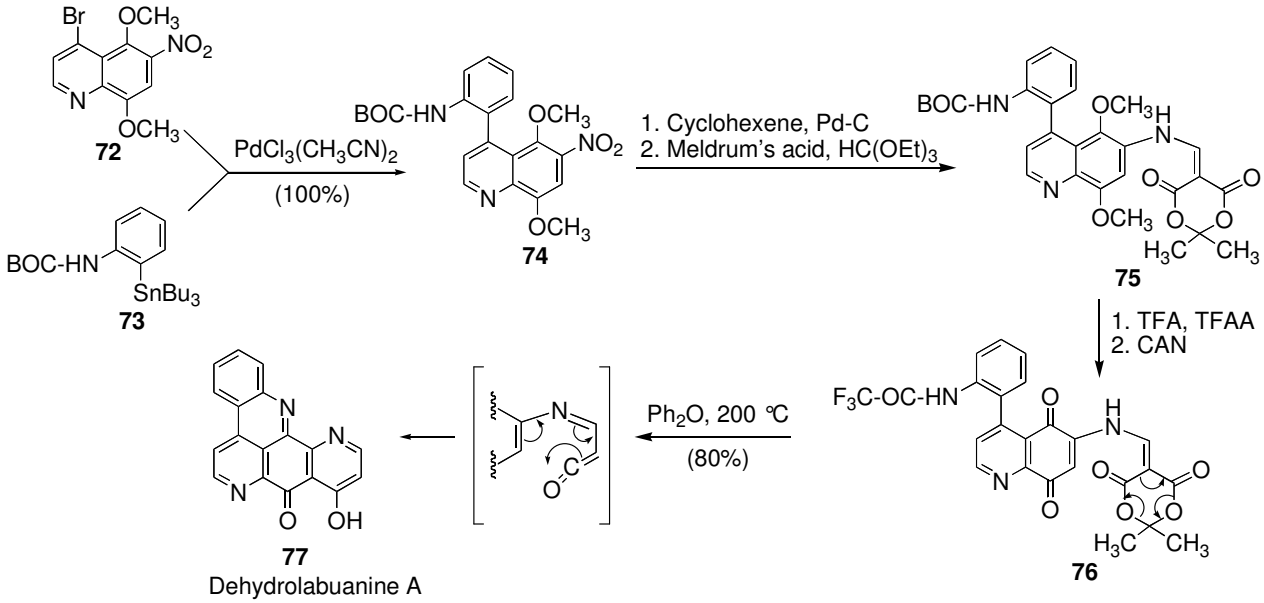


Figure 5

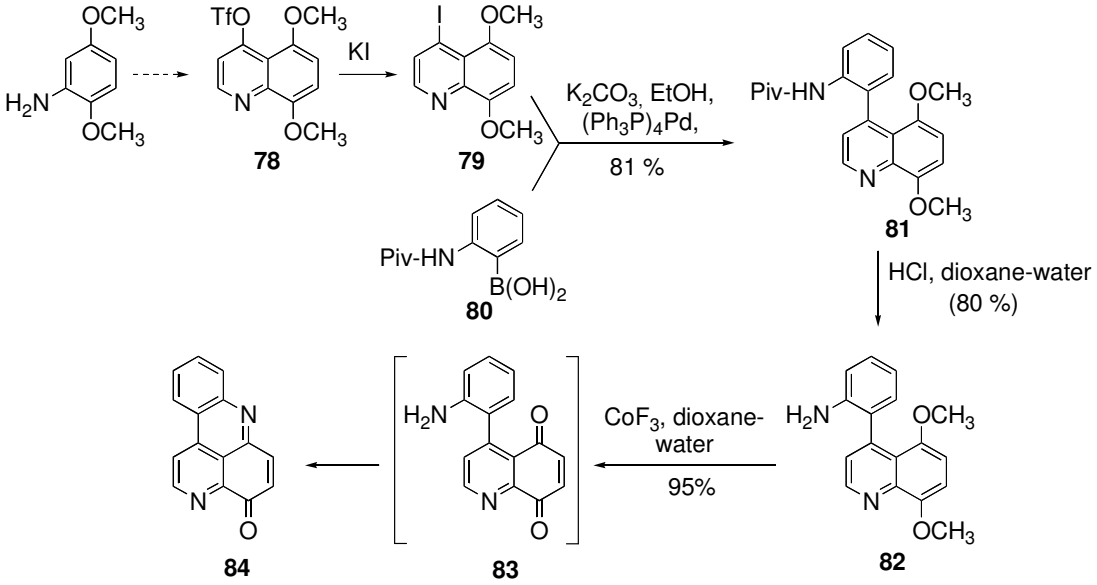
The key step in the first strategy is the formation of a biaryl system by generation of a carbon-carbon bond between pyridine and benzene subunits. We employed a route having as the key step a palladium-catalyzed cross-coupling reaction for this purpose in one of our syntheses of compound **77**, a regioisomer of meridine that was subsequently identified as a natural product (dehydrolabuanine A) with neuronal differentiation inducing properties against a murine neuroblastoma cell line.[54] In this case, following a literature precedent, we employed a Stille coupling for the generation of the required 4-phenylquinoline system. Thus, as shown in Scheme 24, treatment of bromide **72** with tributyl (2-*tert*-butoxycarbonylamino-phenyl) stannane **73** afforded a quantitative yield of compound **74**, which was hydrogenated with cyclohexene in the presence of palladium to give the corresponding amine. This intermediate was transformed into compound **75** by treatment with Meldrum's acid and triethyl orthoformate. All attempts to oxidize **75** to a quinone led to complex mixtures, a result that was attributed to competing oxidation of the relatively electron-rich aniline ring.



Scheme 24

Fortunately, a simple change in the *N*-protecting group from BOC to trifluoroacetyl, as proposed by other authors in a related situation,[55] allowed the oxidative demethylation and afforded the unstable quinone **76**, which by thermolysis gave **77** in 42% yield from **75**. This one-pot double cyclization from **75** to **77** is remarkable and we assume that cyclization of the trifluoroacetamido group onto the quinone carbonyl must involve its prior hydrolysis under the harsh reaction conditions, catalyzed by the presence of traces of acid (from ceric ammonium nitrate) in compound **76**. This cyclization is not restricted to **76**, since it was also observed in the thermolysis of the related compound **86** (see its structure below) in the presence of a trace of ceric ammonium nitrate. The overall yield of the eight-step route to **77** was 23%.[56]

For the purpose of establishing structure-activity relationships in the pyridoacridine group, we became interested in the preparation of the pyrido[2,3,4-*kl*]acridin-4-one system common to most cytotoxic marine alkaloids. A literature precedent showed that all attempts at the creation of a C-C bond at the C-4 position of a quinoline lacking a nitro substituent by means of the Stille coupling had to be abandoned due to poor yields in the cross-coupling step.[57] For this reason, we decided to examine the route summarized in Scheme 25, which is based on the less studied Suzuki reaction of 4-halogenoquinolines.

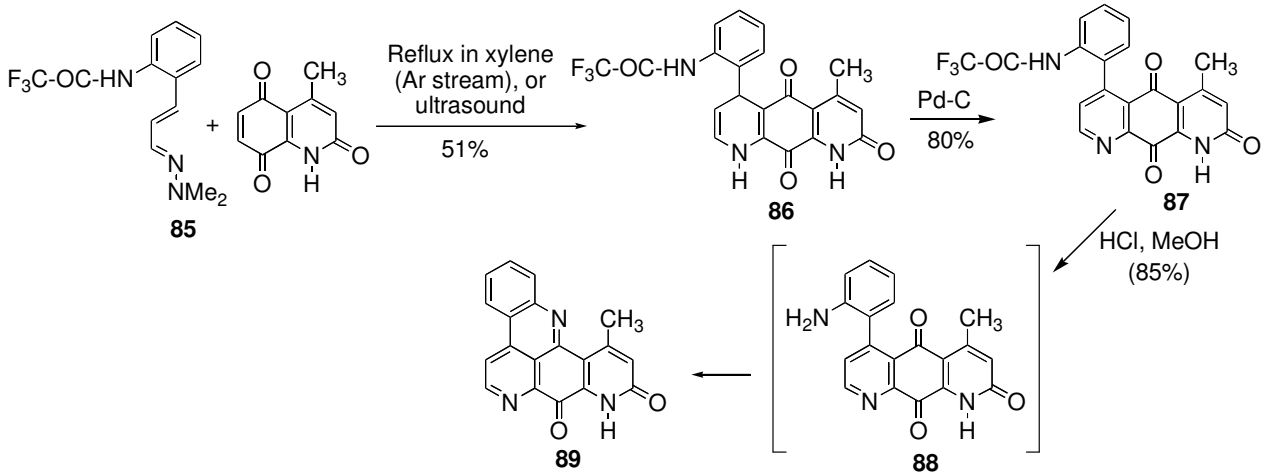


Scheme 25

After some failed attempts with other leaving groups, we found that iodide **79**, prepared from the known triflate **78**, gave smoothly the desired Suzuki coupling with boronic acid **80** in the presence of $(Ph_3P)_4Pd$ and potassium carbonate, affording compound **81** in 81% yield. Attempted oxidative demethylation of this material with CAN in aqueous acetonitrile gave an intractable mixture, a result that was again attributed to competing oxidation of the electron-rich aniline ring. In this case, instead of replacing the pivaloyl group by the more electron-withdrawing trifluoroacetyl unit as in the case of the dehydrolabuanine synthesis, we decided to attempt the search for a less potent oxidant and, after some experimentation with other reagents, we found that cobalt trifluoride[58] was suitable for our purposes. In fact, this reagent was so mild that it allowed an unprecedented oxidative demethylation in the presence of an unprotected amino group. Thus, hydrolysis of the pivaloyl group in **81** afforded amine **82** in 80% yield, and treatment of the latter with potassium fluoride in dioxane, gratifyingly, led to the transformation of **82**

into a non-isolated intermediate aminoquinone **83**, which cyclized spontaneously to the target compound **84** in an excellent 95% overall yield.[59]

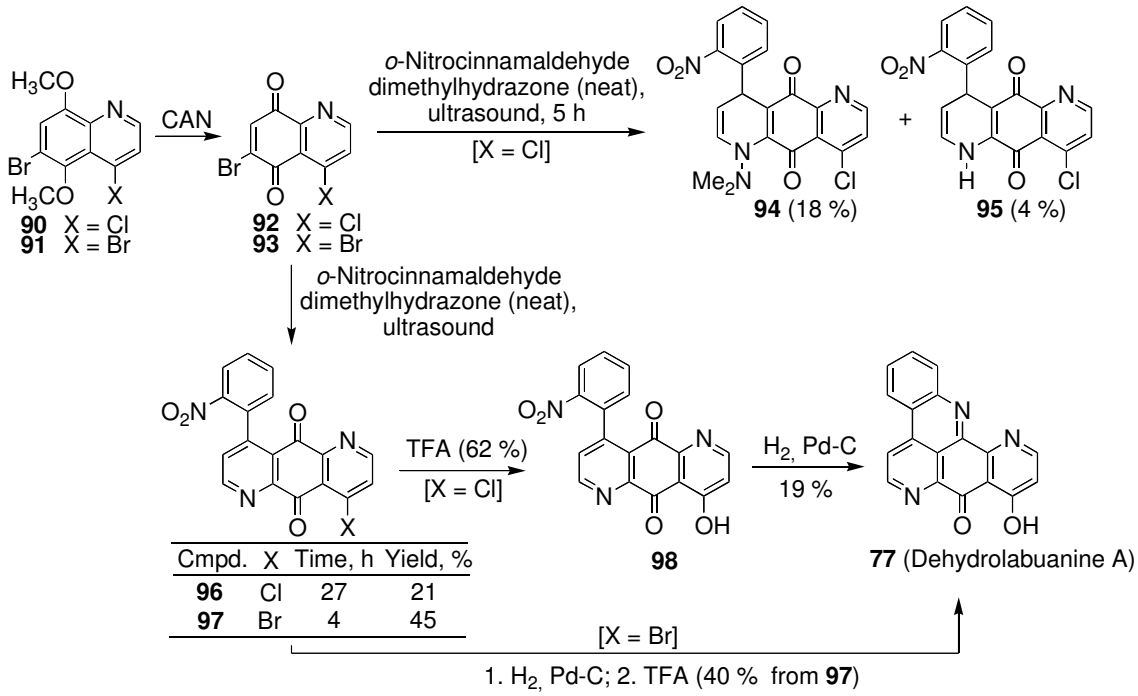
The generation of 4-phenylquinoline precursors to pyridoacridines based on the hetero Diels-Alder reaction between a 4-aryl-1-azadiene bearing a nitrogenated function in the *o*-position and a suitable quinone (strategy B in Figure 5) would be more direct than cross coupling-based methods, but this approach had received very little attention because of the poor reactivity of 4-aryl-1-azadienes and their low stability under forcing conditions. Indeed, the only successful preparation of a pyrido[2,3,4-*kl*]acridine system by the hetero Diels-Alder route had been described in the course of the first total synthesis of meridine, due to Kubo's group.[60] In this synthesis, *o*-nitrocinnamaldehyde dimethyl-hydrazone was used as the azadiene for the key Diels-Alder reaction, which proceeded in only 22% yield, even after considerable optimization work. Another disadvantage of the nitro group was the need for a reductive cyclization step, which gave modest yields. We reasoned that replacement of the nitro group by a trifluoroacetamido unit would lead to an azadiene with an increased electron density and with the additional advantage of being capable of hydrolytic cyclization. After an initial successful study with a model quinone, we sought to apply this method to the synthesis of compound **89**, which can be considered as a regioisomer of both meridine and amphimedine. The Diels-Alder reaction between 4-methyl-carbostirylquinone and azadiene **85** was initially attempted in the presence of the previously mentioned chloroformyl-modified Merrifield resin, but, in this case, reflux conditions were required, under which the desired product **86** became covalently bound to the resin. Hence, the reaction was carried out in refluxing xylene under an argon stream to remove dimethylamine and afforded an acceptable 51% yield of **86**. In small-scale reactions, we found that the optimal procedure involved the use of our previously established ultrasound-assisted conditions.[31b] Finally, dehydrogenation of **86** in the presence of palladium afforded **87**, which was efficiently transformed into the target compound **89** by hydrolytic cyclization, with amine **88** as a non-isolated intermediate.[61]



Scheme 26

In this context, we also investigated a shorter synthesis of dehydrolabuanine A, based on the hetero Diels-Alder reaction between a 4-aryl-1-dimethylamino-1-azadiene bearing a nitrogenated function at the *o*-position and a 4-substituted derivative of 6-bromo-5,8-quinolinequinone, where the presence of the bromine atom at C-6 was expected to revert the natural regiochemistry of the Diels-Alder reactions of

quinolinequinones. In order to increase the reactivity of the quinones as dienophiles, we decided to use a second halogen atom rather than a hydroxy group at C-4 of the quinoline ring and used quinones **92** and **93** as the starting materials for our study. The low stability of these quinones precluded the use of thermal conditions for the hetero Diels-Alder reactions and therefore we chose the previously mentioned ultrasound-assisted conditions. In this case, we found that azadiene **85**, which is a crystalline solid and must be handled as a solution in acetonitrile, was less useful than *o*-nitrocinnamaldehyde dimethylhydrazone, which is an oil and allows the use of solvent-free conditions. Under these conditions, quinone **92** gave the aromatic adduct **96** in 21% yield after 27 h; interruption of the reaction after 7 h allowed to detect intermediates **94**, formed by elimination of HBr from the primary Diels-Alder adduct, and **95**, formed by acid-catalyzed elimination of dimethylamine from **94**. Better results were obtained with the more reactive dibromoquinone **93**, which gave a 45% yield of the aromatic compound **97** after 4 h of irradiation. Two methods were then assayed for the transformation of **96** or **97** into the target compound **77**. In the initial approach, compound **96** was transformed into the hydroxy derivative **98** in 62% yield by brief exposure to wet trifluoroacetic acid; subsequent catalytic hydrogenation of **98** afforded **77** in only 19% yield. The order of these steps was inverted when applied to the bromo derivative **97**, which afforded **77** in 40% yield after catalytic hydrogenation followed by addition of wet trifluoroacetic acid (Scheme 27).[56]

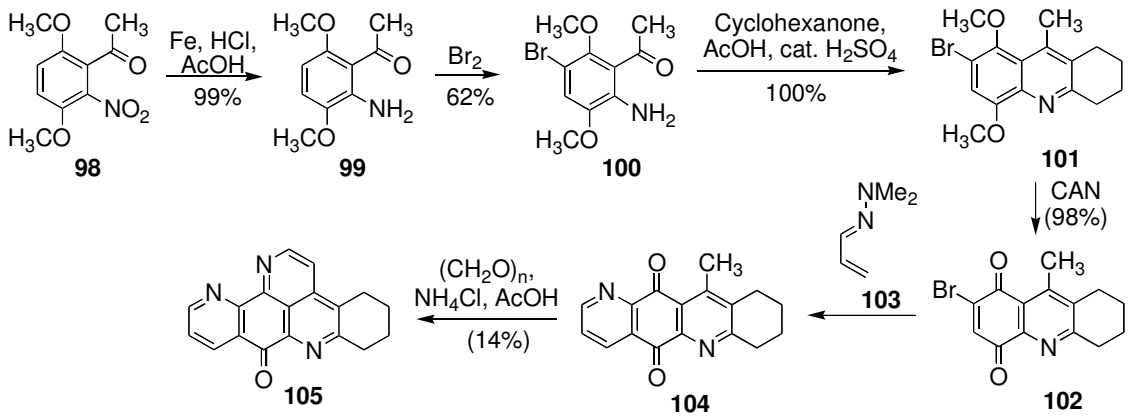


Cmpd.	X	Time, h	Yield, %
96	Cl	27	21
97	Br	4	45

Scheme 27

We will finally discuss the approach mentioned in strategy 3 of Figure 5, which was employed for a synthesis of analogues of ascididemin, based on the combination of the Friedländer and hetero Diels-Alder reactions for the construction of the core linear tetracyclic pyrido[2,3-*b*] acridine system. We were interested in the preparation of tetrahydro derivatives of the parent compound, in an effort to decrease the planarity of the molecule in order to increase its solubility by hampering stacking interactions in the solid state.

Our synthesis of tetrahydroascididemin is summarized in Scheme 28 and started from 2-nitro-3,6-dimethoxy-acetophenone **98**. This compound was reduced to aminoketone **99** in 99% yield by treatment with iron in acetic acid and a catalytic amount of hydrochloric acid. Bromination of compound **99** to give **100** proved troublesome since, as expected, there was interference from the methyl group adjacent to the carbonyl, leading to mono- and dibromo derivatives at that position. After some experimentation, we found that use of a slight deficiency of bromine resulted in a chemoselective bromination of the C-5 position of compound **99**, affording **100** in 62% yield. A Friedländer reaction of **100** with cyclohexanone under Fehnel conditions (acetic acid as solvent and a catalytic amount of sulfuric acid) gave a quantitative yield of the acridine derivative **101**, which was subsequently transformed into bromoquinone **102** by oxidative demethylation with cerium (IV) ammonium nitrate. An hetero Diels-Alder reaction between compound **102** and acrolein dimethylhydrazone **103** yielded the tetracyclic pyrido[2,3-*b*]acridine derivative **104** in 78% yield (48% overall from **98**).[62] Creation of the fifth ring was initially attempted with no success under literature conditions, by reaction with dimethylformamide dimethylacetal followed by addition of ammonium chloride in acetic acid. An alternative approach, based upon a Mannich reaction of the activated methyl group of compound **104**, followed by intramolecular cyclization, afforded tetrahydroascididemin **105** in a modest 14% yield because of competing reactions at other parts of the molecule.[63]



Scheme 28

Some of the pyridoacridine analogues mentioned here showed remarkable antitumour properties. Compound **77** (dehydrolabuanine A) was compared to its regioisomer meridine and it was found that **77** shows a high selectivity for solid tumours that is not present in meridine, proving that the C-ring has a significant role in the activity in these pyridoacridine skeletons. Particularly noteworthy were the high activity and selectivity of **77** towards the human lung carcinoma A-549 ($IC_{50} = 3.10^{-8}$ M). This selectivity constitutes a distinct advantage of this compound over meridine, since a high activity towards all types of tumours is normally considered as a sign of indiscriminate cytotoxicity and therefore is an undesirable feature for a drug candidate. The antitumour activity of the pyridoacridine class of alkaloids is normally associated with their interaction with DNA and subsequent inhibition of the activity of topoisomerase II (topo II). Therefore, we measured the *in vitro* relative ability of meridine and compound **77** to inhibit topo II activity, finding that meridine showed some activity in this test, ($IC_{50} = 3$ μM) but compound **77** was inactive at the highest concentration assayed (33 μM).[56] This different inhibitory activity agrees with the

different cytotoxicity patterns of both compounds and again gives an indication of the importance of the effects of structural variations in the C-ring within this class of pyridoacridines. It must be remarked that the precise mechanism of action of the pyridoacridine alkaloids is far from being fully understood, and that several mechanisms different from topo II inhibition have been described in the literature. The other meridine isomer, compound **89**, also showed high activity and selectivity towards solid tumours such as human colon and lung carcinomas.[64] We are currently involved in the preparation of water-soluble analogues of **89** for *in vivo* testing. Finally, tetrahydroascididemin **105** showed a potent and selective activity in solid tumours, quite similar to that found for natural ascididemin.[63] We believe that this finding will pave the way for the preparation of ascididemin analogues with decreased planarity and hence with improved solubilities, as discussed above. Our results also seem to confirm that the complete pentacyclic framework of the pyridoacridines is important for activity, as shown by the low activities found for analogues lacking one of these rings (*e.g.* compound **84**).

Acknowledgments

The research described here was possible thanks to the hard work and dedication of many coworkers, whose names are in the reference list, and to whom we owe our most sincere gratitude. We also gratefully acknowledge the collaboration of PharmaMar and Bio Mar in the biological testing of the compounds and financial support to the research described here by several Spanish funding agencies, including our current grants from MEC (grant CTQ2006-10930) and UCM-CAM (Grupos de Investigación, grant 920234).

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CATALYTIC INTRAMOLECULAR C-H AMINATIONS: A POWERFUL TOOL FOR THE SYNTHESIS OF VARIOUS HETEROCYCLIC SYSTEMS

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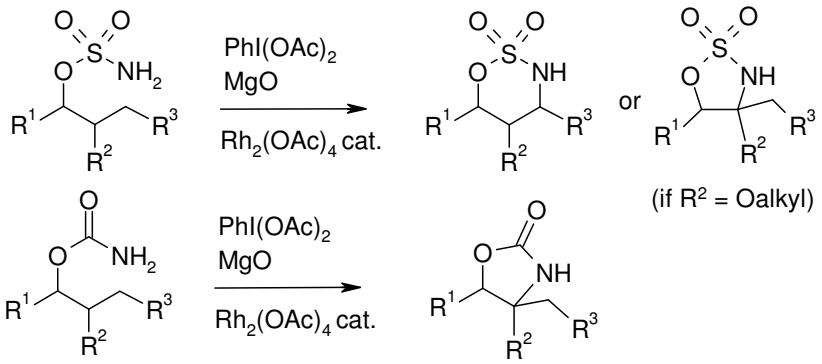
Abstract. *In less than ten years, the intramolecular-catalyzed amination of unactivated C-H bonds using carbamate or sulfamic ester substrates has established itself as a powerful tool for the direct synthesis of a diversity of heterocycles of synthetic and therapeutic interest, such as 5- to 8-membered cyclic sulfamidates, oxazolidine, thiadiazinane or imidazolidinone derivatives. This process has been used as a key step in the total synthesis of complex heterocyclic natural products such as (-)-tetrodotoxin. The purpose of this review is to provide an overview of the main strategic advantages of intramolecular C-H amination in general. Applications to the synthesis of various heterocyclic systems and to the total synthesis of heterocyclic natural products are discussed as well as future potential developments.*

Contents

1. Introduction

The total synthesis of natural products, pharmaceuticals and other relevant targets using the simplest means is a pressing challenge in organic chemistry that combines economic with environmental goals.[1] The aim is indeed to reduce protecting group manipulations and the number of synthetic steps through catalytic and selective processes that produce minimal chemical waste. In addition, the simplicity of a synthetic

strategy is strongly related to its elegance and the quest for beauty has always been a powerful drive for progress in the art and science of total synthesis.[2] In this context, the direct and selective functionalization of unactivated C-H bonds is likely to have a deep impact in the future of many areas of chemistry and to revolutionize the way organic chemists approach synthesis.[3] Unlocking the potential of inert C-H bonds is a strategy of choice to reduce the number of synthetic steps usually required for the incorporation of functional groups or reactive sites. Major simplification of synthetic sequences and unprecedented chemical possibilities are thus expected from this approach. The amino group is probably one of the most important functional group in organic chemistry and biochemistry, from natural products to synthetic pharmaceuticals.[4] Not surprisingly, the high prevalence of nitrogen-based functional groups has stimulated the development of efficient catalytic methods for the amination of unactivated C-H bonds.[5] In the early 1980s, seminal works by Breslow and Gellman demonstrated that cyclohexane could be aminated by using hypervalent iodine reagents, such as PhI=NTs, in the presence of Fe or Mn porphyrin catalysts.[6] Low yields were obtained but, in subsequent work, efficient intramolecular Rh-catalyzed insertion reactions into benzylic C-H bonds were reported from benzenesulfonamide substrates.[7] At the beginning of the 2000s, based on this pioneering study and on the discovery of efficient *in situ* generation of iminoiodinanes,[8,9] the group of Du Bois,[9,10] developed a powerful process for the intramolecular amination of unactivated C-H bonds using carbamate or sulfamic ester substrates (Scheme 1).



Scheme 1. Intramolecular catalyzed C-H amination of sulfamic esters and carbamates.

In the same period, significant studies were independently performed by the groups of Che, Dauban and Dodd, He, Lebel, Müller and others;[5] asymmetric versions of this process were developed, various catalytic systems explored and new insights into its mechanism disclosed.

The strategic advantages of catalytic intramolecular C-H amination reactions in the field of heterocyclic chemistry are numerous. This process may be used to access directly a diversity of heterocycles of synthetic and therapeutic interest, such as oxathiazinane, oxathiazolidine, thiadiazinane or cyclic urea derivatives, or may be exploited as a key step in the total synthesis of heterocyclic natural products and related compounds.[11]

2. A powerful tool for C-H amination

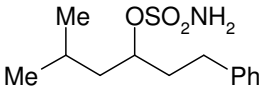
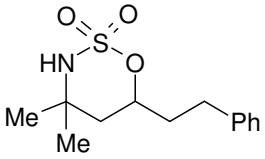
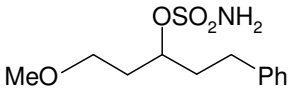
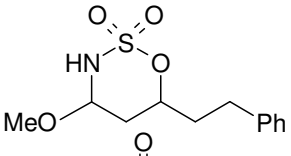
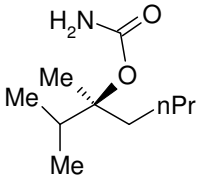
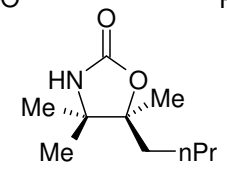
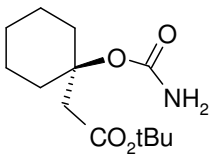
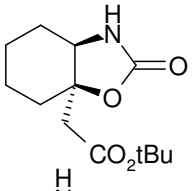
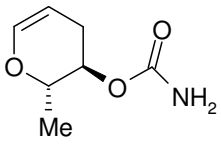
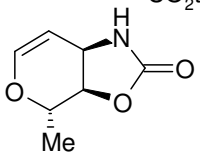
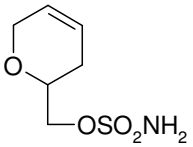
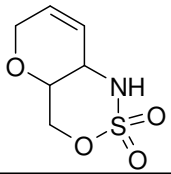
A C-H insertion methodology that would not discriminate among C-H bonds of a given substrate would be essentially useless. The main advantage of the intramolecular-catalyzed C-H amination reactions developed by Du Bois resides on the high level of regio- and stereoselectivity usually observed for this

process. Based on various studies,[5] guidelines may be formulated to predict the selectivity of the insertion reactions, allowing the rational design of synthetic strategies. In addition, the reaction process is stereospecific; intramolecular aminations of enantiopure carbamate or sulfamate substrates proceed with complete retention of configuration at the insertion site.[5] The synthetic interest of sulfamic esters as substrates in C-H amination reactions is further increased by the formation of the cyclic oxathiazinane products. These electrophilic azetidine equivalents indeed offer many opportunities for the diversity-oriented synthesis of 1,3 amino functionalized products.[11]

2.1. Regioselectivity

Amination reactions performed with sulfamate esters lead generally to the formation of the corresponding six-membered ring insertion products whereas carbamates afford only five-membered rings (Scheme 1).

Table 1. Regioselective carbamate and sulfamic ester amination.

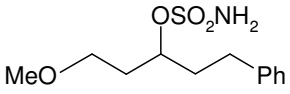
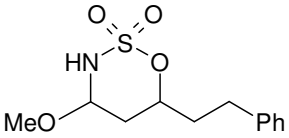
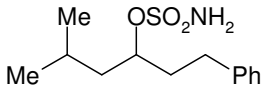
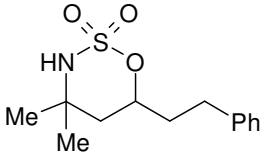
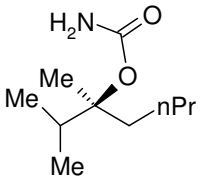
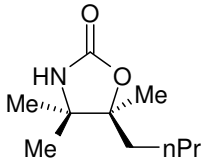
Entry	Substrate	Major Product	Cat.[a]	Regioselectivity
1[5a,10]			A	3°/benz. 60/40
2[13]			B	ether/benz. 93/7
3[9]			A	3°/2°/1° 89/11/0
4[9]			A	2°/2° α-EWG 100/0
5[12]			A	allylic/ether 100/0
6[b]			A	allylic/ether 100/0

[a]Catalyst: A = $Rh_2(OAc)_4$; B = $Rh_2(tpa)_4$ = tetrakis(triphenylacetate) rhodium dimer. [b]Gueyrard, D., unpublished results.

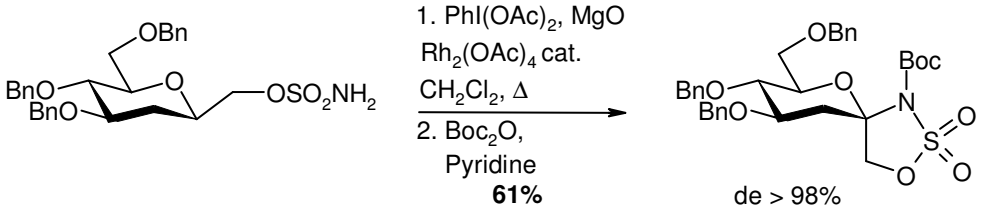
The highly favored formation of the oxathiazinane ring may be rationalized by the elongated S-N and S-O bond length and the N-S-O angle of the sulfamate (~ 103°), which match the metrical parameters of the heterocycle.[5a,b,10] The formation of the oxathiazolidine ring would require an unfavorable compression of

this angle to 95°. Electronic factors play also a decisive role in the regioselectivity of the reaction and may influence the size of the ring formed. Benzylic, allylic and tertiary C-H bonds as well as sites adjacent to electron-donating groups are generally favored. On the opposite, sites adjacent to electron-withdrawing groups are disfavoured (entry 4, Table 1). The order of reactivity for C-H bond insertion may be roughly formulated as follow: allylic > α-amino/α-ethereal ~ 3° > benzylic > 2° >> 1° (Table 1).[5,12,50] In addition, the regioselectivity of the amination reaction may be modulated by the structure of the catalyst and the use of hindered ligands (Table 2).[5a,5b,13] Thanks to these electronic effects, it has been shown recently that it is possible to extend significantly the synthetic scope of sulfamic ester substrates to generate 5-membered rings (oxathiazolidine derivatives, Scheme 2),[10,14] but also 7- and even 8-membered rings (Scheme 3).[15]

Table 2. Catalyst influence on the regioselectivity of carbamate and sulfamic ester amination.

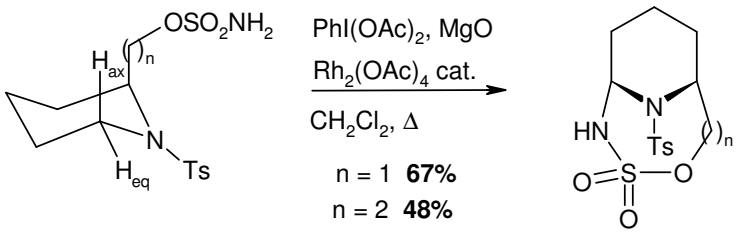
Entry	Substrate	Major Product	Cat.[a]	Regioselectivity
				ether/benzylic
1[13]			A	50/50
			B	93/7
				3°/benzylic
2[5a]			A	60/40
			B	93/7
				3°/2°
3[5b]			A	89/11
			B	50/50

[a]Catalyst: A = $Rh_2(OAc)_4$; B = $Rh_2(tpa)_4$.



Scheme 2. Access to oxathiazolidine derivatives from sulfamic esters.

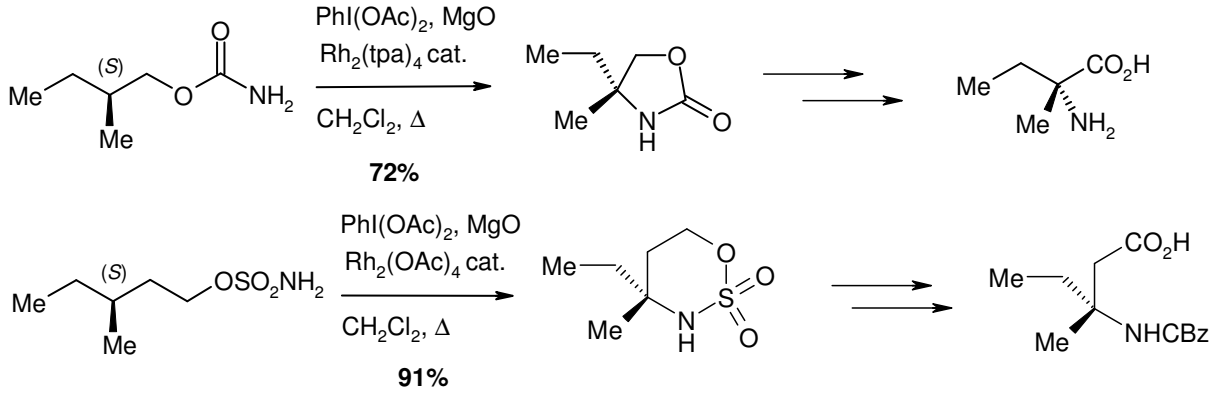
The combination of stereoelectronic effects and conformational factors was found to be decisive in the unexpected formation of bicyclic oxathiazepanes and oxathiazocanes (Scheme 3).[15]



Scheme 3. Access to oxathiazepane and oxathiazocane derivatives from sulfamic esters.

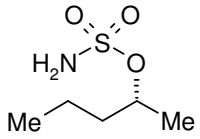
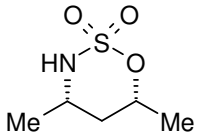
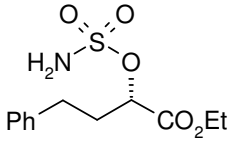
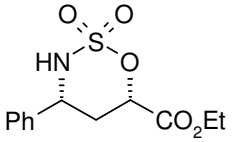
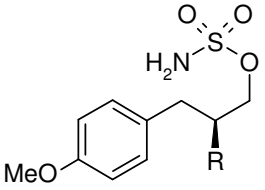
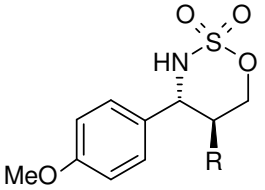
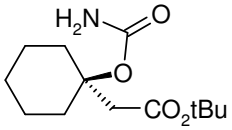
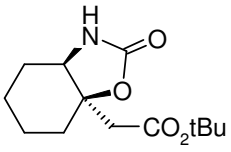
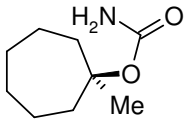
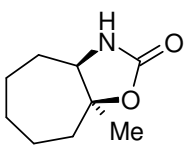
2.2. Reaction stereospecificity

The intramolecular amination reactions of enantiopure carbamate or sulfamate substrates proceed with complete retention of stereochemical configuration at the insertion site (Schema 4).[5,9,10] This result is consistent with a direct concerted C-H insertion of a metallanitrene in the singlet state[5a,b] although an alternative stepwise C-H-abstraction/radical recombination pathway, where the second step is extremely fast,[16] could not be dismissed. Stereospecific amination of 3° C-H groups provide attractive routes to optically active compounds of interest such as quaternary α-amino acids or β-amino acids.



Scheme 4. Stereospecific intramolecular aminations of enantiopure carbamate or sulfamate substrates.

Table 3. Diastereoselective carbamate and sulfamic ester amination.

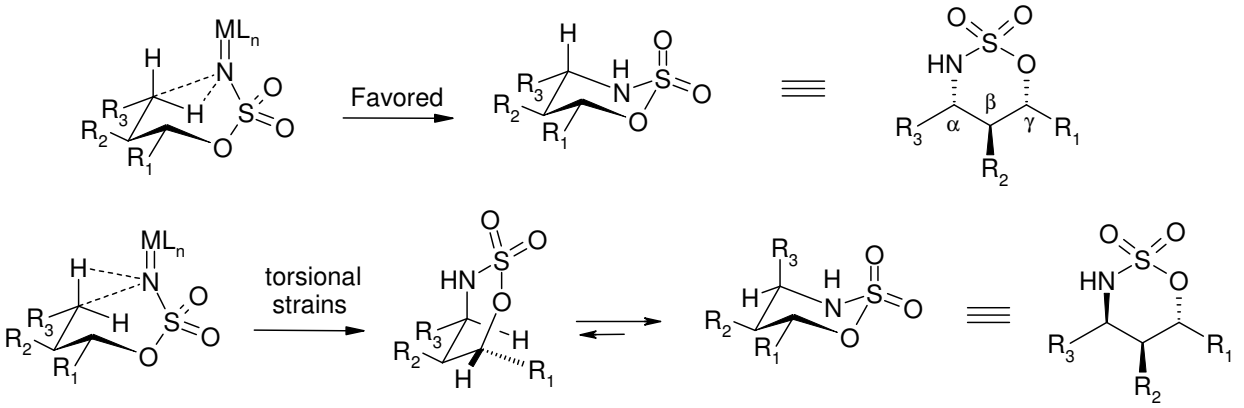
Entry	Substrate	Major Product	Cat.[a]	Yield	*syn*/*anti*
1[17]			A	88%	3/1[17]
2[17]			B	91%	15/1[17]
3[17]			B	65% 77%	1/20 (R = Me)[17] 1/10 (R = OTBS)[17]
4[9]			A	82%	100/0[9]
5[9]			A	83%	8/1[9]

[a]Catalyst: A = $Rh_2(OAc)_4$; B = $Rh_2(Oct)_4$.

2.3. Diastereoselectivity

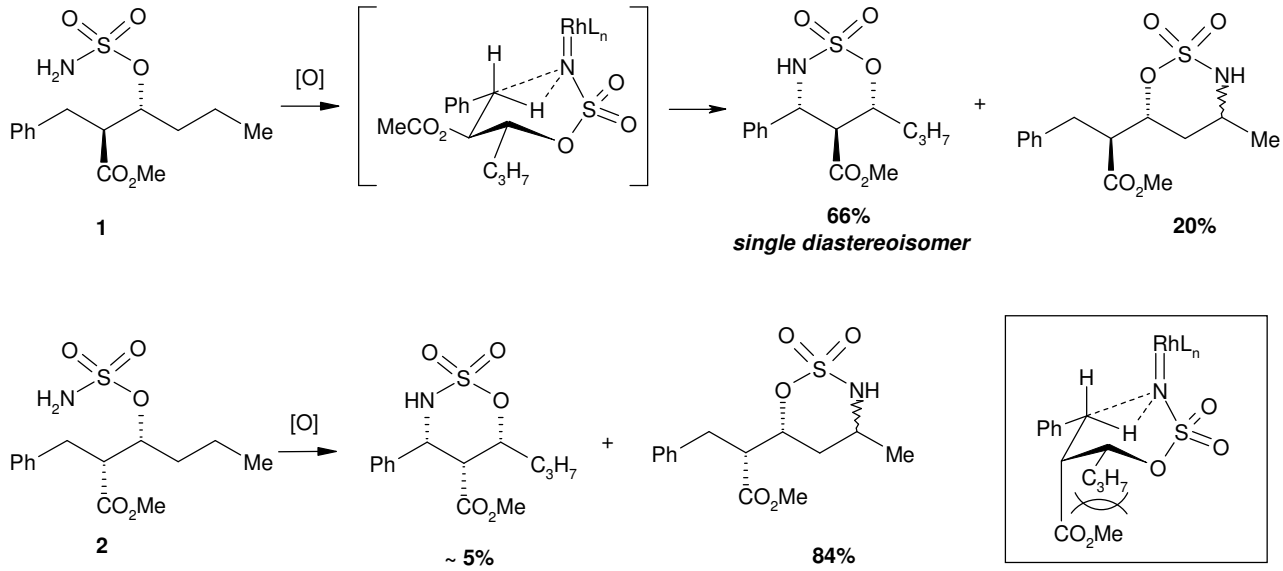
Carbamate or sulfamic esters substrates were prepared from various optically pure secondary and primary alcohols to explore the diastereoselectivity of the intramolecular C-H insertion (Table 3). The amination reaction was found to proceed with high level of stereocontrol (from 3/1 to 100/0). Both cyclic carbamates and α,γ substituted oxathiazinanes are preferentially produced with *syn* diastereoselectivity (entries 1,2,4,5) whereas α,β substituted oxathiazinanes are generated with *anti* diastereoselectivity (entry 3).

The observed diastereoinduction has been rationalized based on a chair-like transition state, to minimize gauche interactions, in which the insertion occurs into the equatorial C-H bond (Scheme 5).[17] Insertion into axial C-H bond would generate torsional strain during the transition to the final chair conformation of the oxathiazinane ring (Scheme 5).



Scheme 5. Stereochemical model for amination reactions of chiral sulfamic esters.

This predictive model has been further validated by experiments in which supplementary steric strains were added (Scheme 6).[17] The amination reactions of compound **1** provide the product corresponding to the insertion into the benzylic C-H bond in good yield and as a single diastereoisomer (favourable chair conformation of the nitrene intermediate in which all substituents are in pseudo-equatorial position).

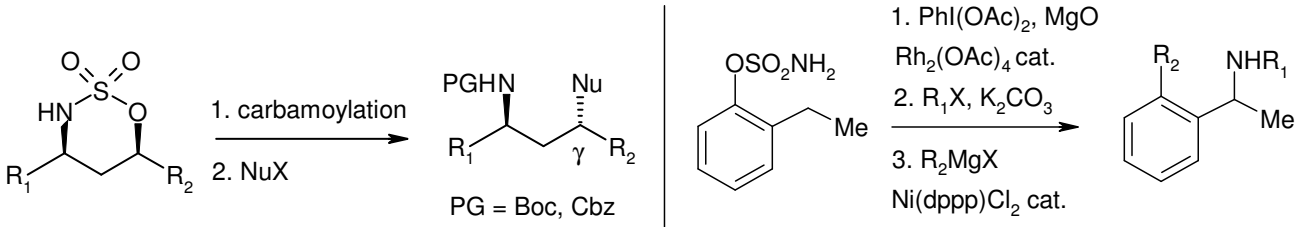


Scheme 6. Stereochemical model for amination reactions of chiral sulfamic esters.

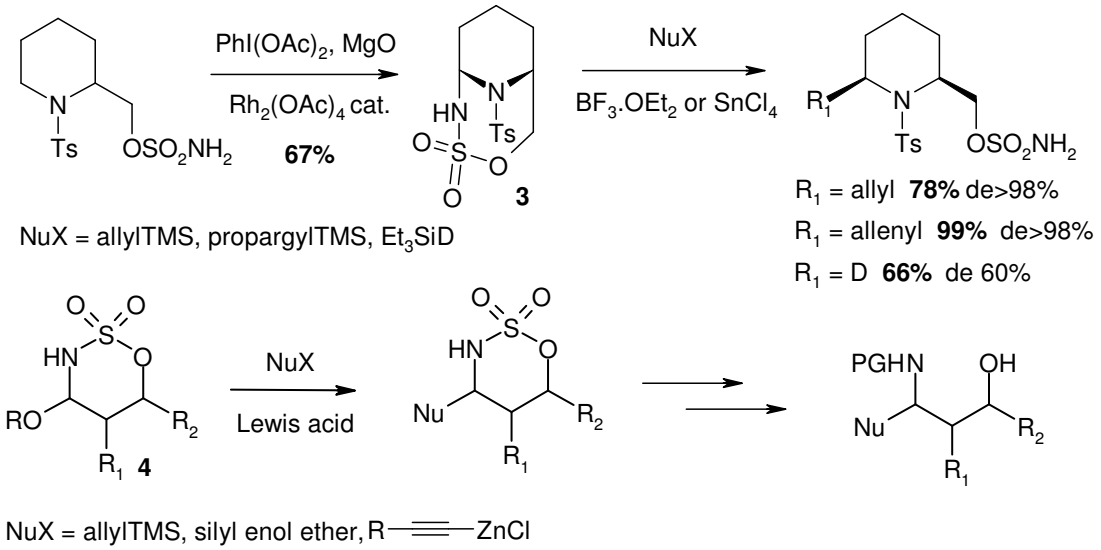
Opposite regioselectivity was observed with the epimer **2** of compound **1**. In this case, defavorable steric strains between the pseudo axial ester substituent and the pseudo equatorial propyl group lead to the product corresponding to the insertion into the theoretically much less reactive 2° γ-C-H center.

2.5. Oxathiazinanes as versatile intermediates

The intramolecular amination of sulfamic ester may be seen as a double-shot weapon. First, this methodology allows the regio- and stereoselective formation of C-N bonds by nitrene insertion into saturated C-H bonds and, secondly, generates a reactive cyclic sulfamidate. According to the structure of the substrate, this key intermediate may be seen as an electrophilic azetidine equivalent (6-membered oxathiazinane ring, Scheme 7) or as a masked iminium ion (R_1 = OR or NRR', Schemes 7 and 8). After activation of the oxathiazinane by carbonylation of the NH moiety, the azetidine equivalent generated may be subsequently opened by various heteroatomic nucleophiles, including TMSCN, NaN_3, KOAc and RSH and carbon nucleophiles.[11] 2-Substituted benzylamines can be obtained by way of amination of *ortho*-substituted phenolic sulfamates followed by Ni-catalyzed cross-coupling with Grignards reagents.[19] These efficient 2-step processes provides a general access to 1,3 amino functionalized products, introducing diversity in γ-position with respect to the amino group (Scheme 7).



Scheme 7. Ring-opening of cyclic oxathiazinane derivatives.



Scheme 8. Nucleophilic addition to iminium ion equivalents.

The reactivity of *N,O* acetal[13,18] or aminal[15] products generated by insertion into C-H bond α to oxygen or nitrogen atom could be exploited to introduce structural diversity in α-position with respect to the amino

group (Scheme 8). As precursors of iminium ions in the presence of Lewis acid, amination products **3** and **4** react with alkynyl zinc reagents or various silylated nucleophiles to produce functionalized 1,3 amino alcohol derivatives. The nucleophilic addition reaction generally proceeds with good to high levels of diastereocontrol.

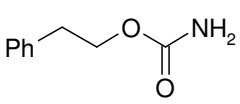
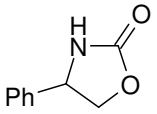
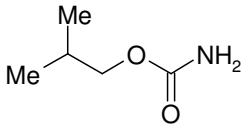
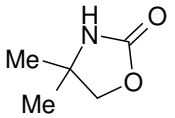
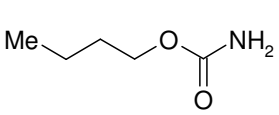
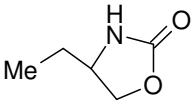
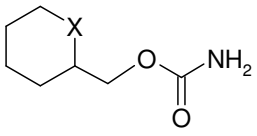
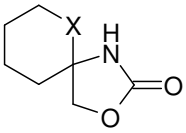
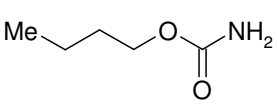
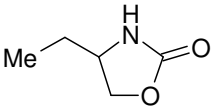
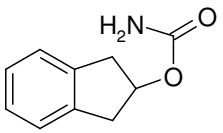
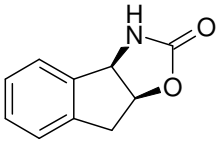
3. Access to cyclic carbamates, sulfamidates and related compounds

In parallel with the study of Du Bois on Rh(II)-catalyzed intramolecular C-H amination, the groups of Che, He, Lebel, Müller and others have developed new sources of metal nitrenes using for example silver catalysts or metal porphyrins complexes. Asymmetric versions of the C-H insertion were also reported and its scope expanded to the synthesis of thiadiazinane and imidazolidinone heterocycles. This review will focus mainly on methods devoted to the amination of unactivated C-H bonds.[20]

3.1. Access to cyclic carbamates

Access to oxazolidinones was performed from acyclic carbamates using rhodium(II)[9] or silver(I) catalysts[21,22] and hypervalent iodine reagents (Table 4).

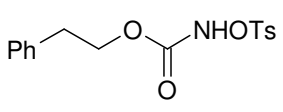
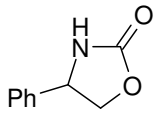
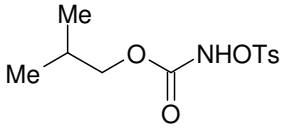
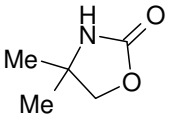
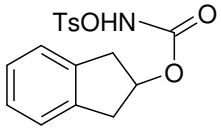
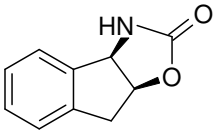
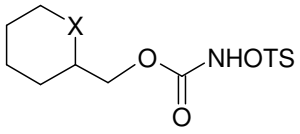
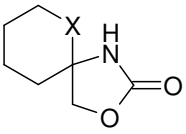
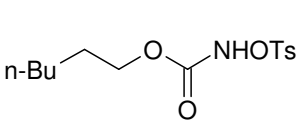
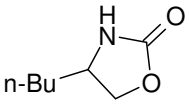
Table 4. 5-Membered cyclic carbamate synthesis by oxidative cyclization of carbamates.

Entry	Substrate	Product	Reaction conditions[a]	Cat.[b]	Yield
1[9]			RC1	B	**74%**
2[9]			RC1	A	**83%**
3[9]			RC1	B	**44%**
4[9]			RC1 RC1	A A	**77%** (X = CH_2) **82%** (X = O)
5[21]			RC2	C	**58%**
6[21]			RC2	C	**83%**

[a]Reaction conditions: RC1 = CH_2Cl_2, 40 °C, cat.:substrate:$PhI(OAc)_2$:MgO= 0.05:1:1.3:2.3; RC2 = CH_3CN, 82 °C, cat.:Substrate:$PhI(OAc)_2$=0.04:1:2.
[b]Catalysts: A= $Rh_2(OAc)_4$; B= $Rh_2(tpa)_4$; C= $[Ag_2(tBu_3tpy)_2(NO_3)]NO_3$.

Alternatively, the group of Lebel[23a] recently reported an interesting approach from *N*-tosyloxycarbamates as a source of nitrenes (Table 5). The advantage of this approach is to avoid one of the major drawbacks associated with hypervalent iodine reagents that is to say the generation of iodobenzene. Two steps are then required from the corresponding alcohol to obtain the *N*-tosyloxycarbamate amination substrate (instead of one to generate the carbamate ester substrate). One year after, the group of Davies[23b] developed an asymmetric version of this method using chiral dirhodium tetracarboxylate catalysts derived from adamantylglycine (see Table 15).

Table 5. 5-Membered cyclic carbamate synthesis by oxidative cyclization of *N*-tosyloxycarbamates.

Entry	Substrate	Product[a,b]	Yield
1[23]			**92%**
2[23]			**71%**
3[23]			**84%**
4[23]			**84%** (X = CH_2) **87%** (X = O)
5[23]			**64%**

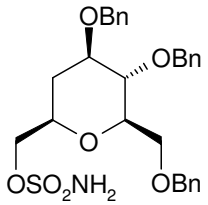
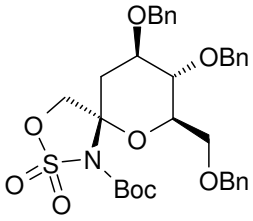
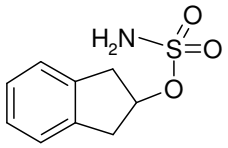
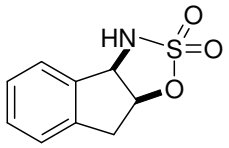
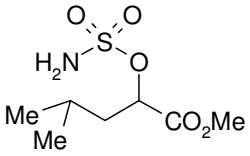
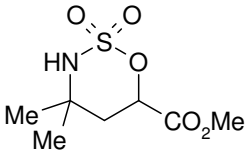
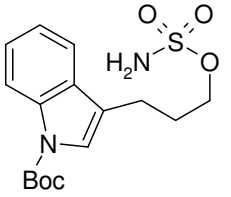
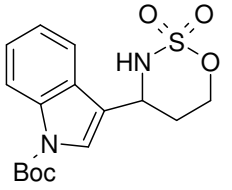
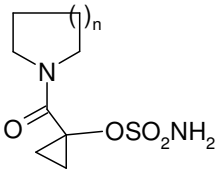
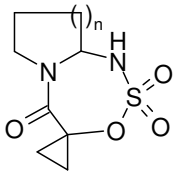
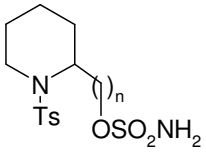
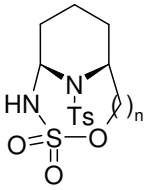
[a] Reaction conditions: CH_2Cl_2, 25 °C, cat.:substrate:K_2CO_3=5-6 mol%:1:2-3.
[b]Catalyst: = $Rh_2(tpa)_4$.

3.2. Access to cyclic sulfamidates

As mentioned in Part 2, Rh-catalyzed amination reactions of sulfamic esters allow the formation of 5- to 8-membered cyclic sulfamidates. According to the structure of the amination substrate, oxathiazolidine, oxathiazinane, oxathiazepane or oxathiazocane derivatives may be obtained in reasonable to very good yields (Table 6). The role of MgO in this process is critical to obtain efficient conversion. This additive is believed to scavenge the AcOH byproduct that is generated during the formation of the iminoiodinane intermediate.[5] MgO might prevent the acid-catalyzed decomposition of the $PhI(OAc)_2$ oxidant and improve the catalyst turnover. It is noteworthy that bases such as K_2CO_3 or $NaHPO_4$ have no beneficial effect on the catalytic process.[5a,b]

The group of He has reported an efficient catalytic system for C-H amination of unactivated C-H bonds based on a disilver(I) complex generated *in situ* by reaction of $AgNO_3$ (4 mol%) with 4,4',4''-tri-*tert*-butyl-2,2':6',2''terpyridine (*t*-Bu_3tpy – 4 mol%).[21,22]

Table 6. Cyclic sulfamidate synthesis by Rh-catalyzed oxidative cyclization.

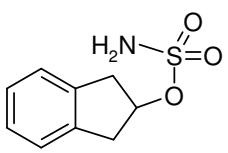
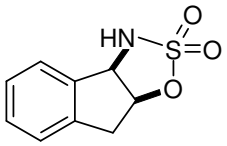
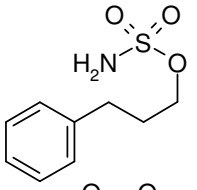
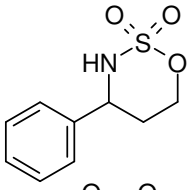
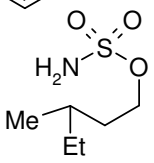
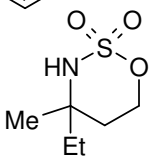
Entry	Substrate	Product[a]	Yield
1[14]			**61%**[b]
2[10]			**60%**
3[10]			**86%**
4[10]			**78%**
5[24]			**24%** (n=2) **86%** (n=1)
6[15]			**48%** (n=2) **67%** (n=1)

[a]Reaction conditions: CH_2Cl_2, Δ, $Rh_2(OAc)_4$:substrate:$PhI(OAc)_2$:MgO=0.05:1:1.3:2.3.
[b]Isolated yield after protection by a Boc group.

The reaction, which is stereospecific, is believed to proceed *via* a silver-nitrene intermediate. By contrast with the Rh-catalyzed amination, no mineral base is required in this process (Table 7). An improved silver-catalyst has been recently developed by the same group by reaction of AgOTf with a commercially available bidentate ligands, the 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline, bp).[22]

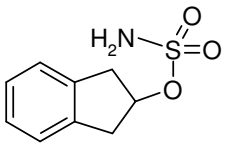
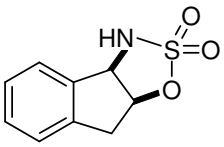
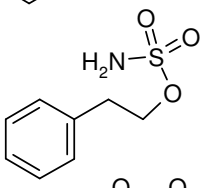
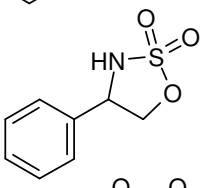
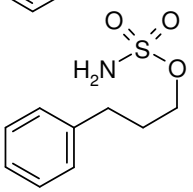
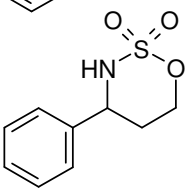
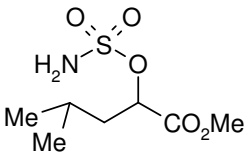
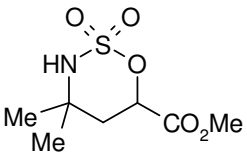
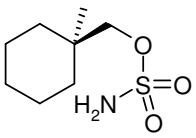
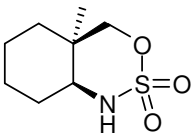
Metalloporphyrins were also found to be efficient catalysts for the intramolecular amination of saturated C-H bonds in sulfamic esters (Table 8). The group of Che used mainly the electron-deficient ruthenium porphyrin [Ru(tpfpp)(CO)] (Figure 1).[25,26] The yields and regioselectivity observed were similar to the ones obtained with rhodium and silver complexes. Better diastereoselectivity could even be observed compared to dirhodium catalysts as highlighted by the result obtained (entry 5, Table 8) (a mixture of *cis*/*trans* diastereosisomers was obtained using $Rh_2(OAc)_4$).[10]

Table 7. Cyclic sulfamidate synthesis by Ag-catalyzed oxidative cyclization.

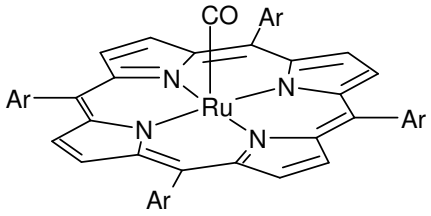
Entry	Substrate	Product[a]	Yield
1[21,22]			**65%**
2[21,22]			**87%**
3[21,22]			**90%**

[a]Reaction conditions: CH_3CN, 82 °C, $[Ag_2(t\text{-}Bu_3tpy)_2(NO_3)]NO_3$:Substrate:$PhI(OAc)_2$=0.04:1:1.4.

Table 8. Cyclic sulfamidate synthesis by ruthenium porphyrin-catalyzed oxidative cyclization.

Entry[24,25]	Substrate	Product[a,b]	Yield
1			**61%** (52%)[c]
2			**56%**
3			**77%**
4			**76%**
5			**88%**

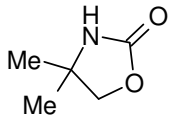
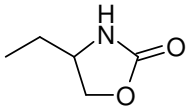
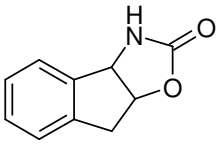
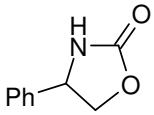
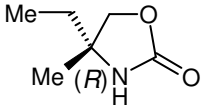
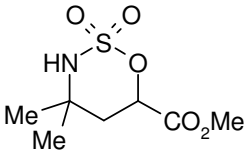
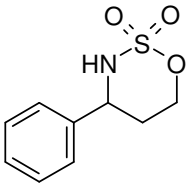
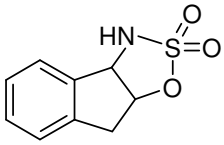
[a]Reaction conditions: CH_2Cl_2, 40 °C, 2h, cat.:substrate:$PhI(OAc)_2$:Al_2O_3=0.015:1:2:2.5.
[b]Catalyst = [Ru(tpfpp)(CO)]. [c]In the absence of Al_2O_3.



[Ru(tpfpp)(CO)]

Figure 1. [Ru(tpp)(CO)] complex.

Table 9. Comparison of amination procedures for the synthesis of cyclic sulfamidates and carbamates.

Entry	Product	Du Bois[5b,9,10]	Lebel[23]	Che[25,26]	He[21,22]
1		83% A	71% B	-	74% E
2		44% B	-	-	58% E
3		86% A	84% B	-	83% E
4		74% B	92% B	-	81% E
5		72% B	73% B	-	73% E
6		86% A	-	76% D	-
7		83% C	-	77% D	87% E
8		60% A	-	61% D	65% E

[a]Catalysts: A = $Rh_2(OAc)_4$; B = $Rh_2(tpa)_4$; C = $Rh_2(Oct)_4$; D =[Ru(tpfpp)(CO)];
E = $[Ag_2(t\text{-}Bu_3tpy)_2(NO_3)]NO_3$.

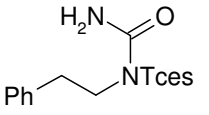
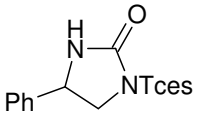
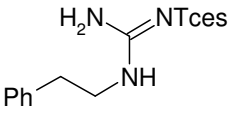
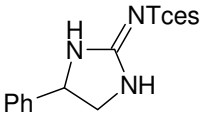
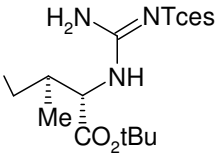
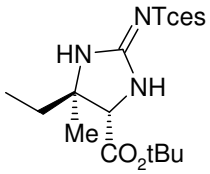
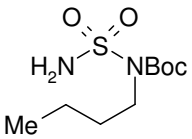
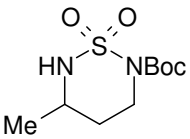
Al_2O_3 was found to be the best additive and to give better yields than MgO or ZnO; K_2CO_3 and NaOH displaying deleterious effects. Other achiral metalloporphyrins such as [M(tpp)Cl] (M= Fe, Mn, Ru; H_2tpp =

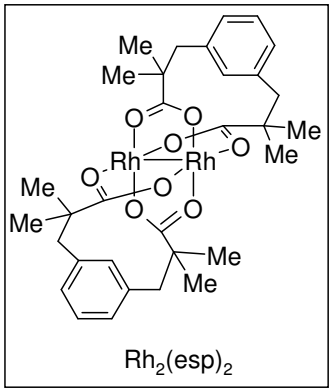
meso-tetraphenylporphyrin) and [Ru(tpp)(CO)] led to lower yields (15–25%), whereas non porphyrin ruthenium complexes such as *trans*-[Ru(pybox-ip)Cl_2(CH_2=CH_2)] (pybox-ip = bis(2-oxazolin-2-yl) pyridine) were ineffective or poor catalysts.[25] The use of enantiopure porphyrins led to the first efficient asymmetric intramolecular C-H amination (see Part 3.5.).[25]

3.3. Comparison of the various amination procedures

The efficiency of the various intramolecular catalyzed-amination procedures may be compared from results obtained with selected substrates (Table 9). Quite surprisingly, whatever the method used, the cyclized products are produced in almost identical yields (see, for example, entries 3, 5 and 8). The main advantage of Lebel's procedure over the other approaches is that the use of hypervalent iodine reagents is not necessary. The major drawback is that two steps are then required from the corresponding alcohol to obtain the *N*-tosyloxycarbamate amination substrate instead of one for the other procedures. Consequently, this method could not be apply to iterative multifunctionalization of saturated C-H bonds (see Part 4.1.).[15b] In addition dirhodium complexes, such as $Rh_2(OAc)_4$, are readily available from commercial sources but very expensive (~ 1 euro/mg). The main advantage of He's procedure is that the silver catalyst is generated *in situ* from less expensive commercially available reagents whereas the ruthenium porphyrin catalysts have to be prepared.[27]

Table 10. Synthesis of thiadiazinane, imidazolidin-2-ones and 2-aminoimidazolines.

Entry[28,29]	Substrate	Product[a]	Yield
1			**87%**
2			**57%**
3			**91%**
4			**83%**



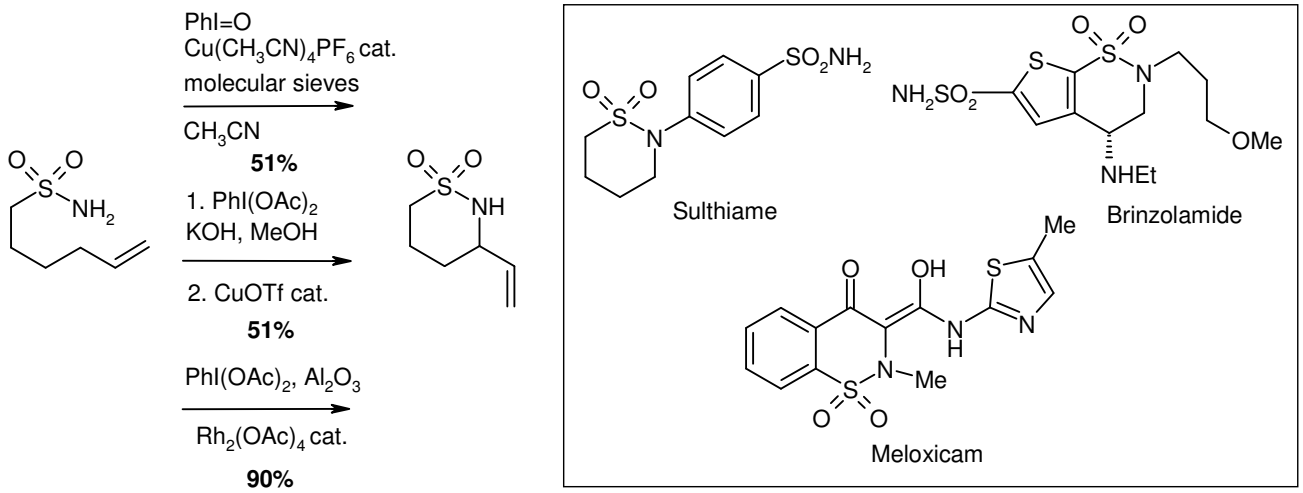
[a]Reaction conditions: toluene 40 °C, $Rh_2(esp)_2$:substrate:$PhI(OAc)_2$:MgO=0.02-0.01:1:1.6:2.5.

3.4. Access to various heterocycles

Very recently, the scope of Rh-catalyzed intramolecular amination has been expanded to the synthesis of thiadiazinane, imidazolidin-2-ones and 2-aminoimidazolines (Table 10).[28,29] Cyclic urea derivatives and

related analogs are known to display various biological activities. Such heterocycles appear in both natural products and potential pharmaceuticals.[30] The success of these syntheses was based on the use of $Rh_2(esp)_2$, a tethered dicarboxylate-derived complex that displays superior catalytic activity for C-H amination[28] and on the use of the electron-withdrawing Tces (2,2,2-trichloroethoxysulfonyl) protecting group. The solvent of choice for this reaction was found to be toluene, much lower yields being obtained using CH_2Cl_2 as solvent.

In relation with their work on aziridination, Dauban and Dodd reported an interesting example concerning the copper catalyzed C-H amination of hex-5-ene-1-sulfonamide (Scheme 9).[31a,31b] In 2002, Che *et al.* reported a similar result using $Rh_2(OAc)_4$ with $PhI(OAc)_2$ and Al_2O_3.[31c]



Scheme 9. Copper catalyzed C-H amination of sulfonamides.

Cyclic sulfonamides appear as structural elements in a growing number of drugs including Sulthiame (antiepileptic), Meloxicam (arthritis) or Brinzolamide (glaucoma).[32] Enantioselective intramolecular C-H amination of sulfonamides were also reported in the literature (see Part 3.5.).

3.5. Enantioselective intramolecular C-H aminations

Chiral ligands in combination with ruthenium, rhodium and manganese complexes have been used to develop efficient enantioselective intramolecular C-H amination reactions. The group of Che was the first to report an asymmetric version of the intramolecular C-H amination based on chiral ruthenium porphyrin complexes such as [Ru(por*)(CO)] (Figure 2).[25]

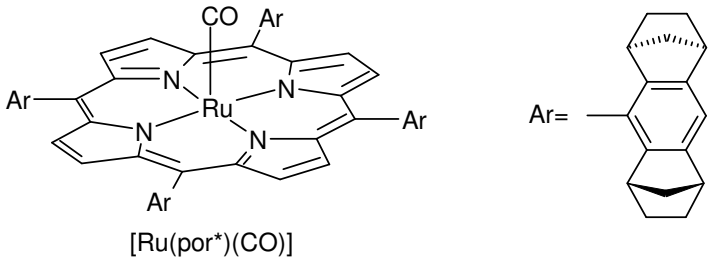
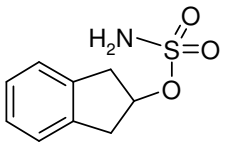
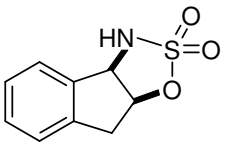
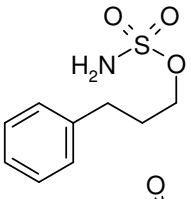
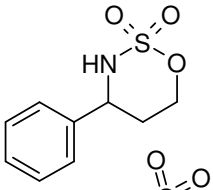
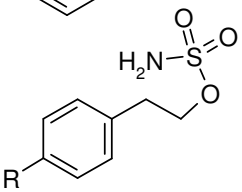
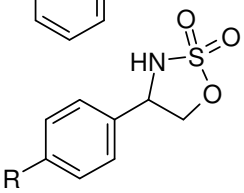


Figure 2. Example of chiral ruthenium porphyrins.

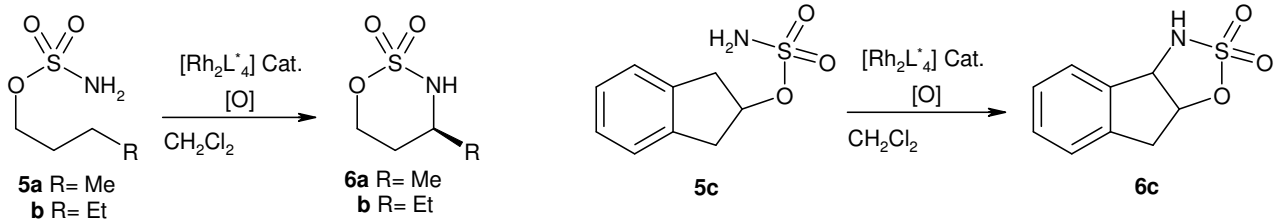
Enantioenriched oxathiazinane and oxathiazolidine derivatives were obtained with good ee, up to 88%, but in lower yields compared to the results obtained with achiral ruthenium porphyrin complexes (Tables 8 and 11).

Table 11. Chiral ruthenium porphyrin-catalyzed synthesis of enantioenriched cyclic sulfamidates.

Entry[25,26]	Substrate	Product[a]	T(°C)	Yield (%)	ee (%)
1			80	**53**	**81**
2			5	**39**	**82**
3			80	**63**	**79**
4			5	**48**	**84**
					
5	R=F		5	**20**	**83**
6	R=Br		5	**31**	**86**
7	R=Cl		5	**72**	**77**
8	R=H		5	**35**	**87**
9	R=Me		5	**89**	**83**
10	R=OMe		5	**75**	**88**

[a] Reaction conditions: C_6H_6, 2-8h, [Ru(por*)(CO)]:Substrate:$PhI(OAc)_2$:Al_2O_3=0.1:1:1.4:2.5.

Table 12. Synthesis of enantioenriched cyclic sulfamidates catalyzed by chiral rhodium complexes.[33,35]



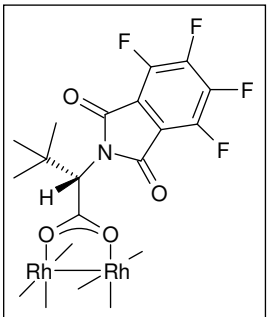
5a R= Me
b R= Et

6a R= Me
b R= Et

5c

6c

Substrate	$[Rh_2L^*_4]$	mol %	T(°C)	Yield (%)	ee (%)
5a[33]	$[Rh_2\{(S)\text{-ptpa}\}_4]$	2.5	40	**97**	**9**
5b[33]		3.5	40	**82**	**<5**
5c[33]		3.5	40	**71**	**18**
5a[33]	$[Rh_2\{(S)\text{-nttl}\}_4]$	3,5	40	**97**	**19**
5a[33]		3.5	-20	**97**	**21**
5b[33]		3.5	40	**60**	**<5**
5c[33]		3.5	40	**62**	**22**
5a[33]	$[Rh_2\{(R)\text{-ntv}\}_4]$	2	40	**80**	**17**
5b[33]		3.5	40	**91**	**<5**
5c[33]	$[Rh_2\{(S)\text{-TFPTTL}\}_4]$	3.5	40	**52**	**30**
5c[35]		2	23[a]	**98**[a]	**48**[a]



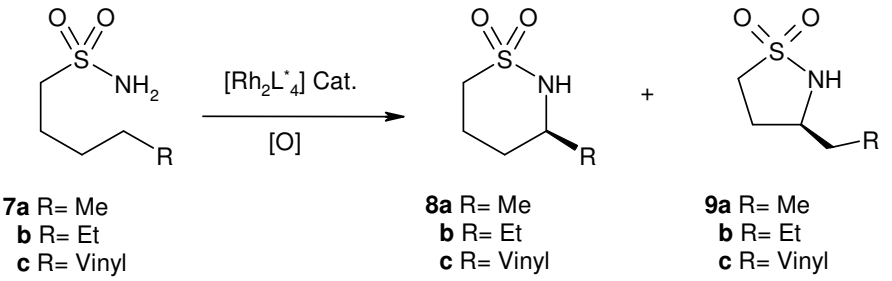
$[Rh_2\{(S)\text{-TFPTTL}\}_4]$

[a]Reaction performed in benzene.

Enantioselective intramolecular amination of sulfamic esters were also reported by Fruit and Muller[33,34] in 2004 and by the group of Hashimoto[35] in 2006 using chiral dirhodium complexes (Table 12). The C-H insertion proceeded in good to very good yields but with modest enantioselectivity compared to chiral ruthenium porphyrin complexes (ee up to 48%).

Fruit and Muller also reported the highly regio- and chemoselective synthesis of enantioenriched cyclic sulfonamides. The C-H amination of sulfonamide substrates was found to proceed with slightly better ee than from the corresponding sulfamic ester substrates (Tables 12 and 13).[33] The group of Che reported that chiral Mn(III) Schiff-base complexes catalyzed intramolecular C-H amination of sulfamic esters more efficiently than chiral ruthenium porphyrin complexes but with lower ee (Tables 11 and 14).[36] It is important to note that the main advantage of this process is the lower cost of manganese *versus* ruthenium or rhodium, and the availability of chiral Schiff-base ligands whereas chiral prophyrin ligands require time-consuming multi-step synthesis. This reaction has been also applied to the amination of unactivated C-H bonds.[36]

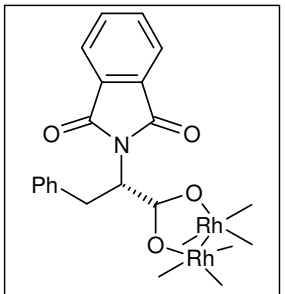
Table 13. Synthesis of enantioenriched cyclic sulfonamides catalyzed by chiral rhodium complexes.[33]



7a R= Me
b R= Et
c R= Vinyl

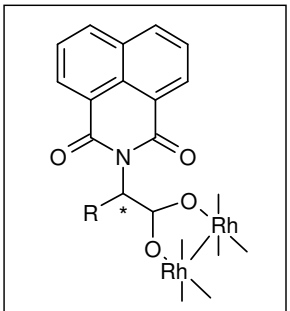
8a R= Me
b R= Et
c R= Vinyl

9a R= Me
b R= Et
c R= Vinyl



$[Rh_2\{(S)\text{-ptpa}\}_4]$

Substrate	$[Rh_2L^*_4]$	mol %	T(°C)	Yield (%)	8/9	ee (%)
7a	$[Rh_2\{(S)\text{-ptpa}\}_4]$	3.5	40	**100**	95/5	**15**
7c		5	-20	**31**	99/1	**10**
7a	$[Rh_2\{(S)\text{-nttl}\}_4]$	3.5	40	**83**	98/2	**57**
7a		3.5	-20	**94**	99/1	**66**
7b		3.5	40	**98**	98/2	**13**
7c		2	40	**23**	99/1	**8**
7a	$[Rh_2\{(R)\text{-ntv}\}_4]$	2	40	**90**	97/3	**54**
7b		3.5	40	**90**	97/3	**22**



$[Rh_2\{(S)\text{-nttl}\}_4]$ R= *t*-Bu
$[Rh_2\{(R)\text{-ntv}\}_4]$ R= *i*-Pr

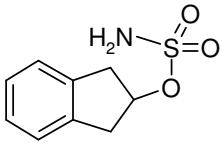
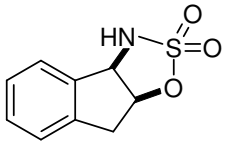
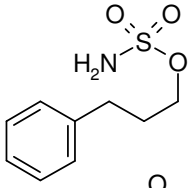
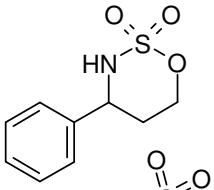
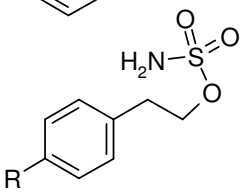
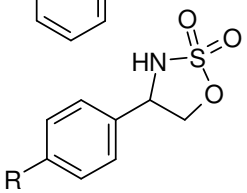
The Lebel's method was extended by Davies *et al.* to the synthesis of enantioenriched cyclic carbamates using Rh_2(*S*-TCPTAD)$_4$ (Table 15).[23b]

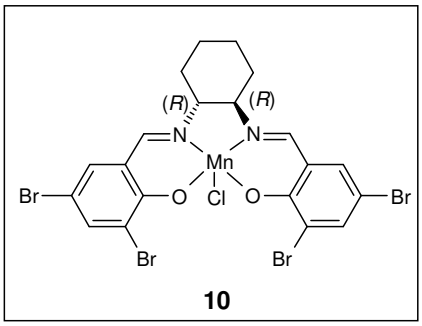
4. Application to the synthesis of natural heterocyclic products and related compounds

The synthetic power of the intramolecular C-H amination reaction has been underscored by the total synthesis of complex natural products such as (-)-tetrodotoxin or (+)-saxitoxin. According to the structure of the synthetic target, carbamate substrates were chosen for their ability to generate exclusively 5-membered ring products and sulfamate substrates for their higher synthetic versatility. Very recently, the amination methodology has been the cornerstone of a unique bond-construction strategy in nitrogen-containing

heterocycles using several C-H bond transformation cycles. Efficient stereocontrolled synthesis of polysubstituted piperidines from simple 2-sulfamoyloxymethyl piperidine derivatives were performed by way of intramolecular Rh-catalyzed amination.

Table 14. Synthesis of enantioenriched cyclic sulfamidate catalyzed by chiral manganese complexes.[36]

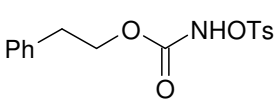
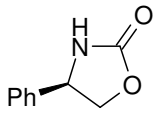
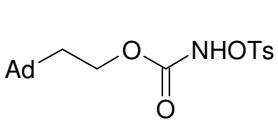
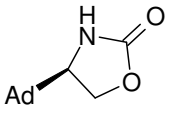
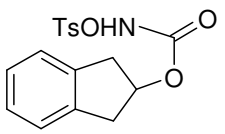
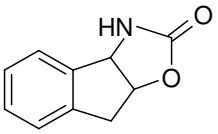
Entry	Substrate	Product[a]	Yield (%)	ee (%)
1			**48**	**52**
2				
3			**68**	**55**
4				
				
5	R=F		**58**	**52**
6	R=Br		**67**	**61**
7	R=Cl		**64**	**71**
8	R=H		**57**	**54**
9	R=Me		**62**	**27**
10	R=OMe		**64**	**23**

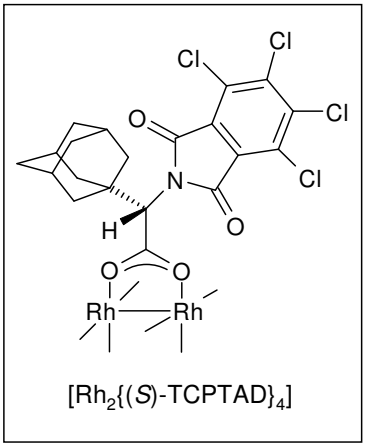


10

[a] Reaction conditions: C_6H_6, 5 °C, **10**:Substrate:$PhI(OAc)_2$:Al_2O_3=0.1:1:1.5:2.5.

Table 15. Synthesis of enantioenriched cyclic carbamate catalyzed by chiral rhodium complexes.[23b]

Entry	Substrate	Product[a,b]	Yield	ee
1			**72%**	**82%**
2[c]			**75%**	**78%**
3			**69%**	**43%**



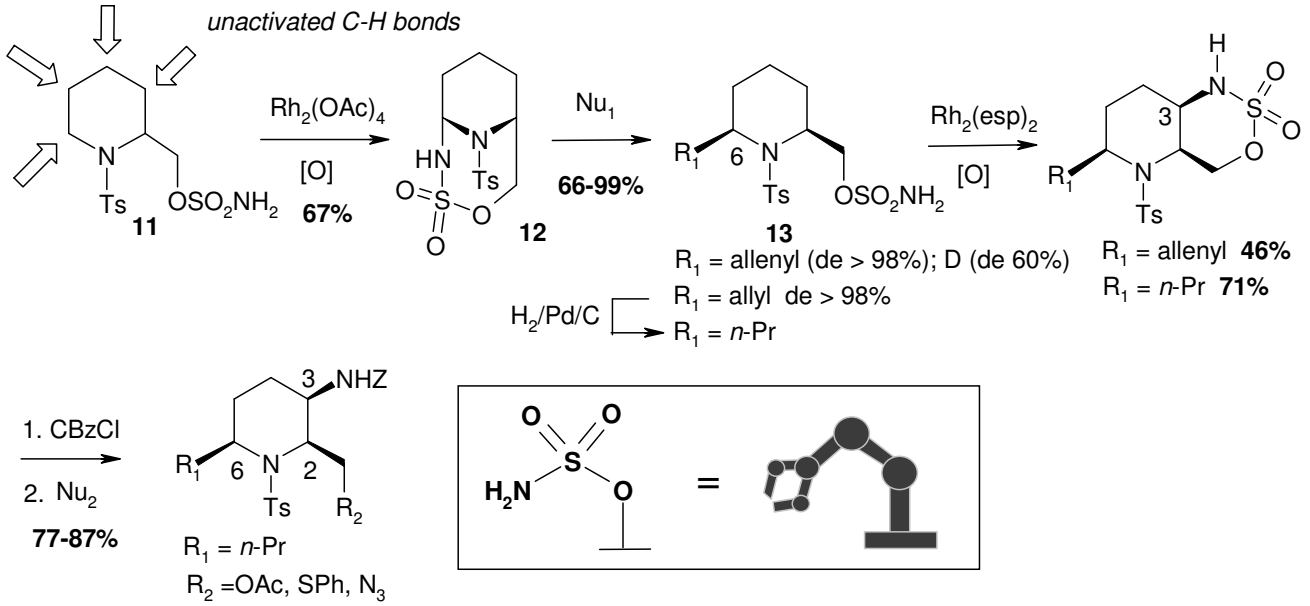
$[Rh_2\{(S)\text{-TCPTAD}\}_4]$

[a] Reaction conditions: CH_2Cl_2, 25 °C, cat./substrate/K_2CO_3=2 mol%/1/3.
[b]Cat = $[Rh_2\{(S)\text{-TCPTAD}\}_4]$. [c]Ad = Adamantyl.

4.1. Iterative multifunctionalization of unactivated C-H bond in piperidines

As mentioned in Part 2.1., Rh-catalyzed amination of sulfamic esters may lead to the formation of seven- and eight-membered rings in nitrogen-containing systems through conformational control of reaction

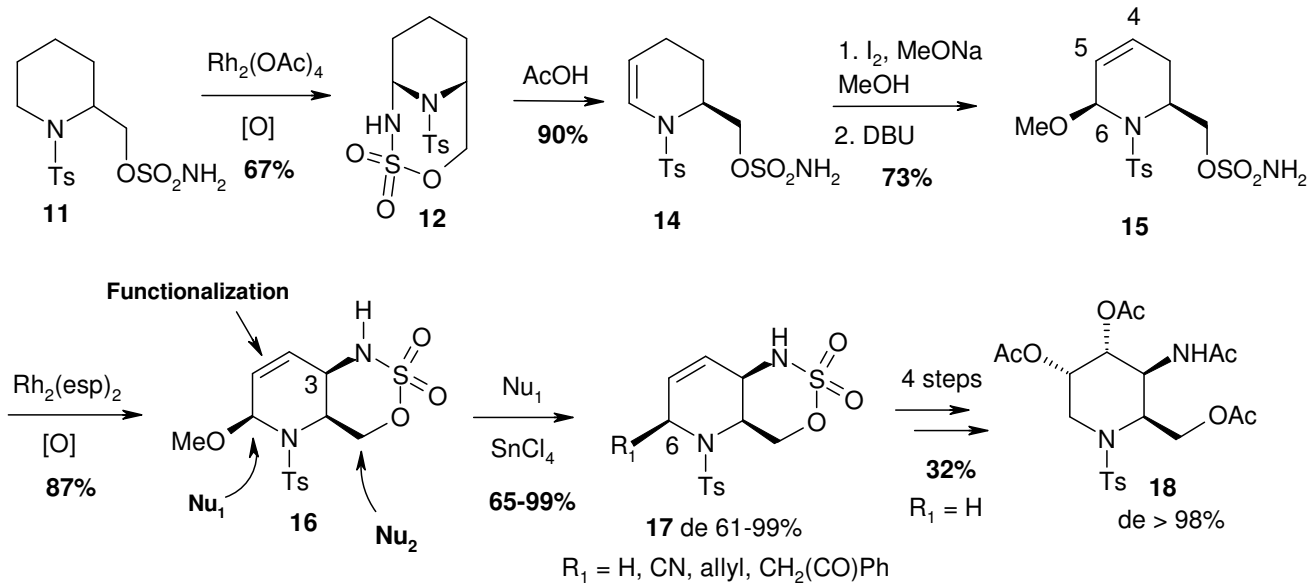
regioselectivity.[15] This reaction provides access to bicyclic aminals such as **12**, allowing the functionalization of a C-H bond in 1,7-relationship with respect to the activating group (Scheme 10). These compounds, as potential precursors of *N*-tosyliminium ions, may react with various nucleophiles. In addition to the stereocontrolled formation of a new bond at C-6, the major advantage of this process is the regeneration of the sulfamoyloxy group that may be used again for further intramolecular C-H amination.



Scheme 10. Synthesis of 2,6-disubstituted 3-aminopiperidines by way of iterative multifunctionalization.

Based on this starting point, it is possible to devise unique bond-construction strategies in nitrogen-containing heterocycles by way of iterative multifunctionalization of unactivated C-H bonds. In this process, the sulfamoyloxymethyl group is used several times as a "molecular activating arm" allowing the formation of C-C, C-N, or C=C double bonds. Preliminary studies have demonstrated very recently the feasibility of this strategy for the general synthesis of polyfunctionalized piperidines (Schemes 10 and 11).[15b]

Piperidines, which constitute a major class of biologically active compounds,[37] are found in many natural products, glycomimetics (iminosugars)[38] and pharmaceuticals. Their impact on medicinal science has been highlighted by the fact that, during a recent 10-year period, there were over 12,000 piperidine compounds mentioned in clinical and preclinical studies.[39] A general access to 2,6-disubstituted 3-aminopiperidines is described on Scheme 10. Nucleophilic ring opening of aminal **12** by silylated nucleophiles in the presence of a Lewis acid afforded the expected 2,6-disubstituted piperidines **13** in good yields and with good to high diastereoselectivity (Scheme 10). This step allowed the stereocontrolled formation of a new bond at C-6 and also regenerated the sulfamate ester that was used again for further intramolecular C-H amination of the piperidine ring.[15b] Selective insertions at C-3 provided the corresponding oxathiazinanes that were opened by various heteroatomic nucleophiles after activation by a Cbz group. A second strategy in which the sulfamoyloxy activating arm is directly or indirectly involved in the functionalization of every saturated methylene of monosubstituted piperidine **11** has been also reported.[15b] This approach exploited the reactivity of cyclic enamine **14** which was readily obtained from **12** by reaction in AcOH in 90% yield (Scheme 11).



Scheme 11. General access to polysubstituted 3-aminopiperidines by iterative multifunctionalization.

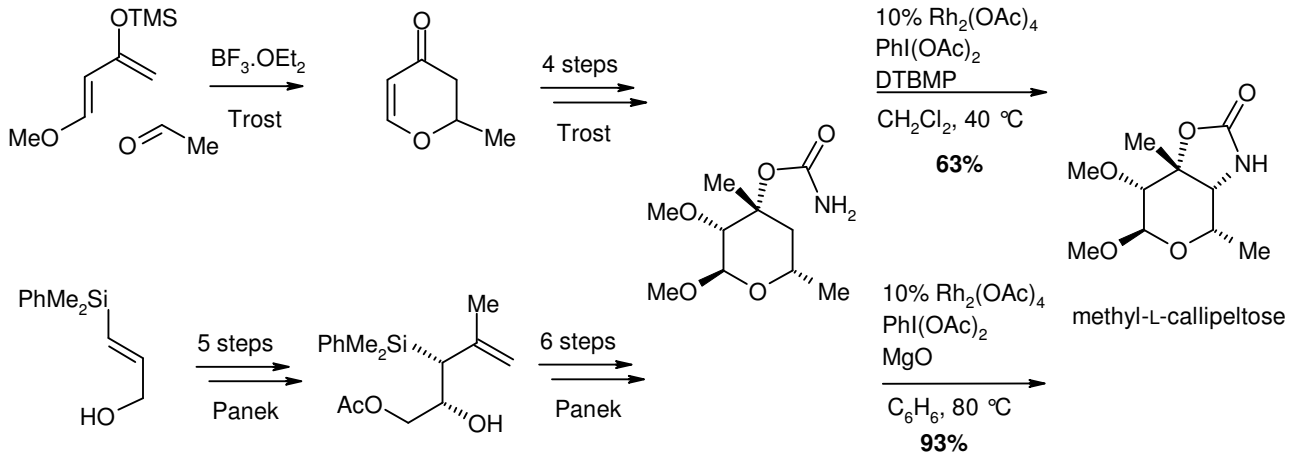
Iodo-methoxylation of α,β-unsaturated *N*-tosylpiperidine **14** using I_2 and MeONa in MeOH, followed by DBU-mediated dehydroiodination provided the desired 6-methoxy-tetrahydropyridine **15** with a double bond tactically positioned at C(4)-C(5).[40] Rh-catalyzed amination of allylic C-H bond at C-3 was then favoured and afforded in 87% yield oxathiazinane **16** as an advanced intermediate for the general synthesis of pentasubstituted piperidines. Nucleophilic additions to the *N,O* acetal **16** were found to proceed with good to high diastereoselectivity and with complete regioselectivity. The versatility of bicyclic intermediate **16** was further probed by stepwise functionalization into more complex structures related to iminosugars[38] such as the fully protected amino iminosugar **18** (in racemic form).[15b] *N*-Acetylation of the oxathiazinane **17** (R_1 = H), followed by the highly diastereoselective dihydroxylation of the endocyclic double bond, direct acetylation of the resulting product and nucleophilic ring-opening with potassium acetate afforded the expected protected iminosugar **18**. The efficient stereocontrolled synthesis of di-, tri-, tetra- and penta-substituted piperidines from simple 2-sulfamoyloxymethyl piperidine derivatives by way of iterative multifunctionalization further demonstrates the tremendous synthetic potential of intramolecular amination of saturated C-H bonds.

4.2. Total synthesis of natural heterocyclic products using carbamate substrates

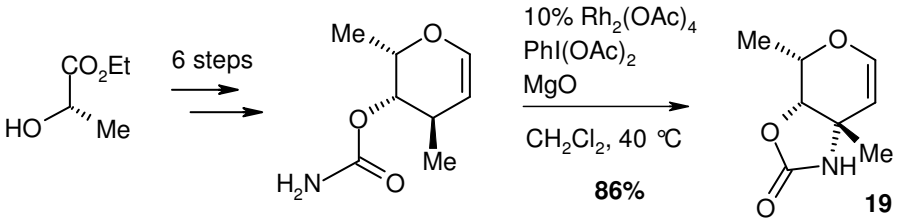
Trost[41] and Panek[42] independently reported the total synthesis of methyl-L-callipeltose, the carbohydrate associated with a cytotoxic glycoside macrolide isolated in 1996, the callipeltoside A (Scheme 12). In both synthetic strategies, the Rh-catalyzed C-H amination allowed the direct synthesis of the key oxazolidine ring of methyl-L-callipeltose. Slight modifications of the standard C-H amination protocol were found to increase the efficiency of the process; 2,6-di-*tert*-butylpyridine were used instead of MgO (57% yield) and toluene instead of CH_2Cl_2. The concise approach to racemic methyl callipeltose described by Trost, could be extended to either enantiomer of the sugar since the asymmetric version of the first cycloaddition step has been developed.[41]

In 2005, Parker and Chang reported the synthesis of the carbamate-protected L-vancosamine glycal **19**, a building block considered as a universal precursor for vancosamine derivatives.[43] The short synthetic

sequence afforded **19** in 7 steps and 44% overall yield by way of Marshall, McDonald and Breslow-Du Bois reactions (Scheme 13). The highly regioselective C-H insertion occurred exclusively at the allylic site, the α-ethereal position being blocked by the methyl group.

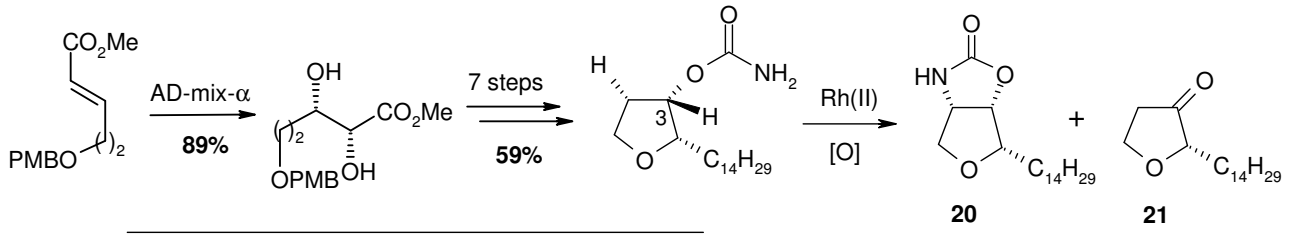


Scheme 12. Synthesis of methyl-L-callipeltose.



Scheme 13. Synthesis of the carbamate-protected L-vancosamine glycal **19**.

Very recently, a simple and short enantioselective synthesis of (+)-pachastrissamine was performed by way of asymmetric dihydroxylation and C-H amination reaction (Scheme 14).[44] Pachastrissamine was isolated from marine sponge and displayed cytotoxic activities against several human carcinoma cell lines.[44]



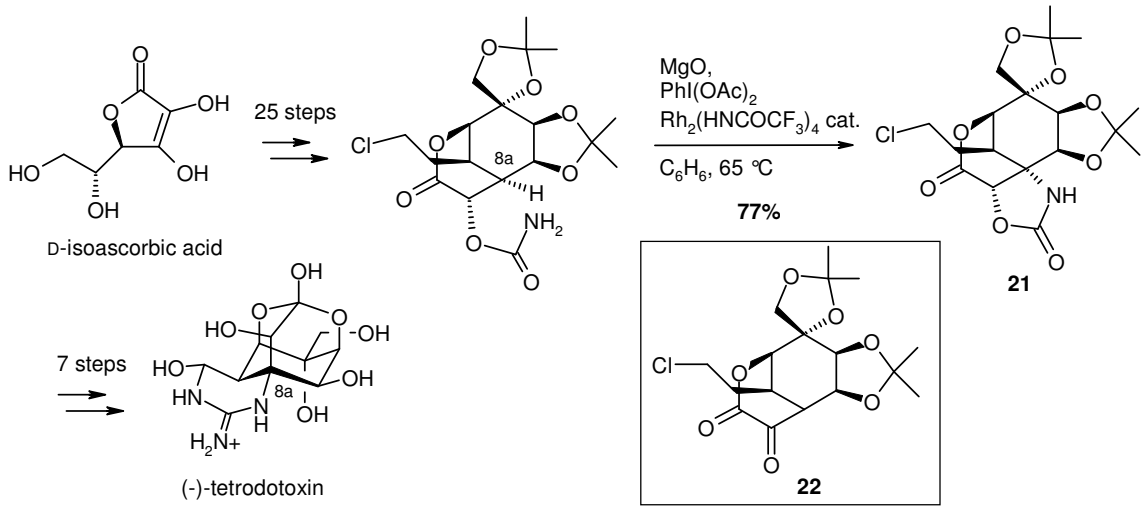
Entry	Rh(II)	Solvent[a]	yield	
			20	21
1	$Rh_2(OAc)_4$	CH_2Cl_2	No reaction	
2	$Rh_2(OAc)_4$	Benzene	0%	58%
3	$Rh_2(tpa)_4$	Benzene	19%	40%
4	$Rh_2(esp)_2$	Benzene	10%	15%

[a]All the reactions were carried out using 10 mol% of catalyst, 4.2 eq. of $PhI(OAc)_2$ and 6.9 eq. of MgO under reflux conditions.

Scheme 14. Synthesis of (+)-pachastrissamine.

The amination reaction proved to be particularly problematic mainly because of probable competitive C-H insertion into the α-oxygenated C-H bond at C-3. The formation of the ketone **21** is indeed believed to proceed from the formation of a four-membered oxazetidinone or by way of direct hydride abstraction by the metal-nitrene intermediate. Theses results underscore problems associated with the intramolecular amination of secondary or primary carbamates.[5b]

Total synthesis of (-)-tetrodotoxin by Hinman and Du Bois is probably the most spectacular illustration of the synthetic power of metal-catalyzed intramolecular C-H amination (Scheme 15).[45] This densely functionalized polycyclic compound, the poisonous constituent of Japanese *fugu*, is one of the most toxic natural products reported to date.[46] After extensive efforts, the first total synthesis of racemic tetrodotoxin was achieved by the group of Kishi[47] in 1972 and the first asymmetric synthesis reported thirty years after by the group of Isobe.[48]



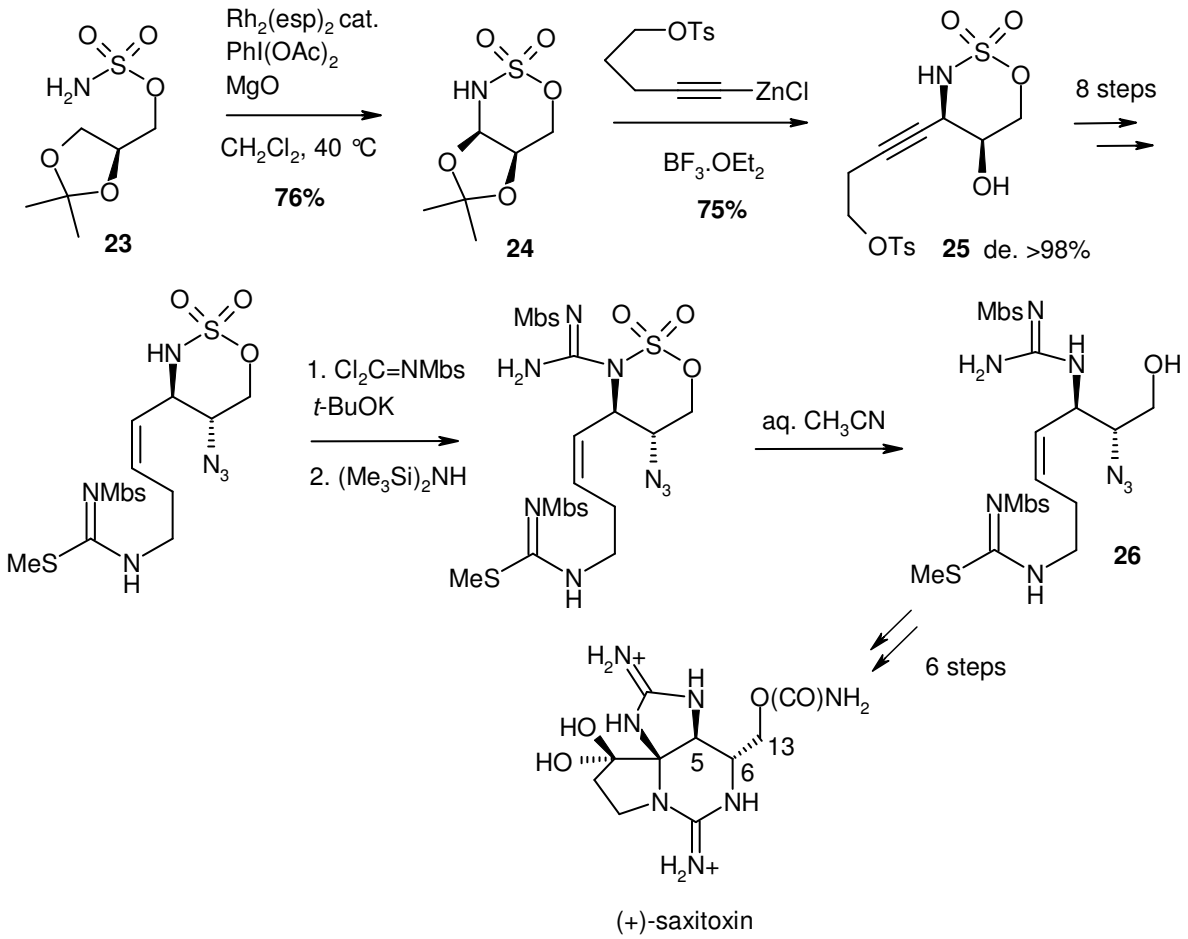
Scheme 15. Stereoselective synthesis of (-)-tetrodotoxin.

The Rh-catalyzed intramolecular amination allowed the late introduction of the key structural element of the guanidine ring and the stereospecific formation of a quaternary stereogenic center at C-8a (Scheme 15). Application of the standard C-H amination protocol using $Rh_2(OAc)_4$ gave moderate yields (50%). Optimized reaction conditions in benzene solvent with 10 mol% of $Rh_2(HNCOCF_3)_4$ provided the expected oxazolidinone **21** in 77% yield along with ketone **22** in 15% yield. This side reaction, typical of secondary carbamate functional groups, may be due to the formation of a four-membered oxazetidinone or to direct hydride abstraction by metal-nitrene intermediate.

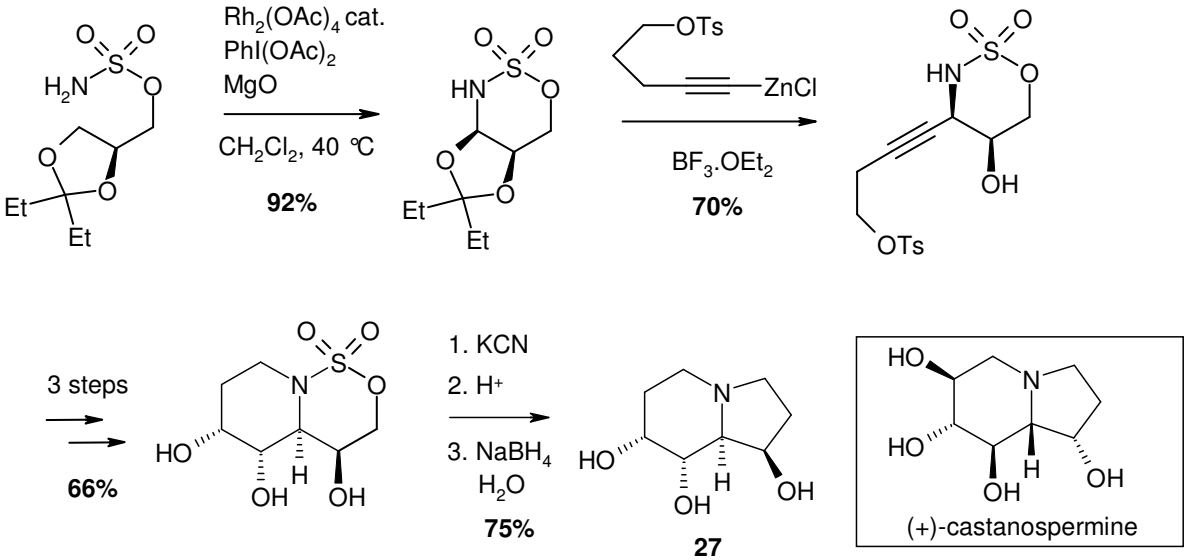
4.3. Total synthesis of natural heterocyclic products using sulfamic acid substrates

In 2006, the group of Du Bois reported the stereoselective synthesis of another guanidinium toxin, the (+)-saxitoxin (Scheme 16).[49,50] The intramolecular C-H amination of the glycerol-derivate sulfamic ester **23** afforded the bicyclic oxathiazinane **24**, a key versatile intermediate. The highly diastereoselective nucleophilic addition of a zinc-acetylide to the *N*,*O* acetal **24** allowed the introduction of all the carbon atoms required for the construction of the pyrrolidine moiety of (+)-saxitoxin. Nine steps later, the oxathiazinane ring was hydrolyzed after direct activation through the guanidinyl function present in the final synthetic target. At this stage, the alcohol **26** obtained contains all the carbons of the tricyclic core of (+)-saxitoxin. The high synthetic potential of sulfamic esters as substrates in C-H amination reactions is superbly

highlighted in this synthesis. The "oxathiazinane-approach" holds many advantages including highly stereoselective formation of a C-C bond at C-5, formation of a cyclic sulfamidate as a masking group of the basic amine at C-5 and a latent electrophile for the introduction of an oxygenated function at C-13.



Scheme 16. Stereoselective synthesis of (+)-saxitoxin.

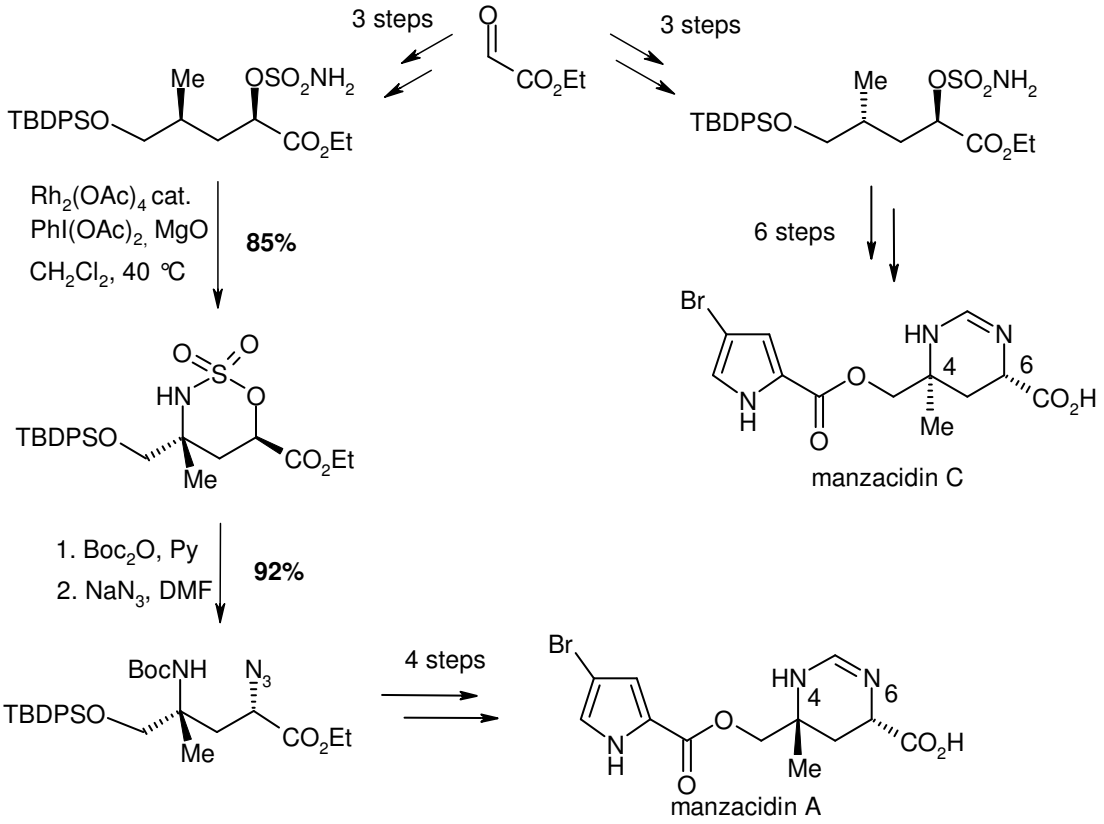


Scheme 17. Stereoselective synthesis of an indolizidine.

Following a similar strategy, the group of Du Bois reported the stereoselective synthesis of indolizidine **27**, a close analog of castanospermine (Scheme 17).[18] This approach could be applied to a general synthesis of indolizidines which constitutes an important class of alkaloids of biological interest.[38,51]

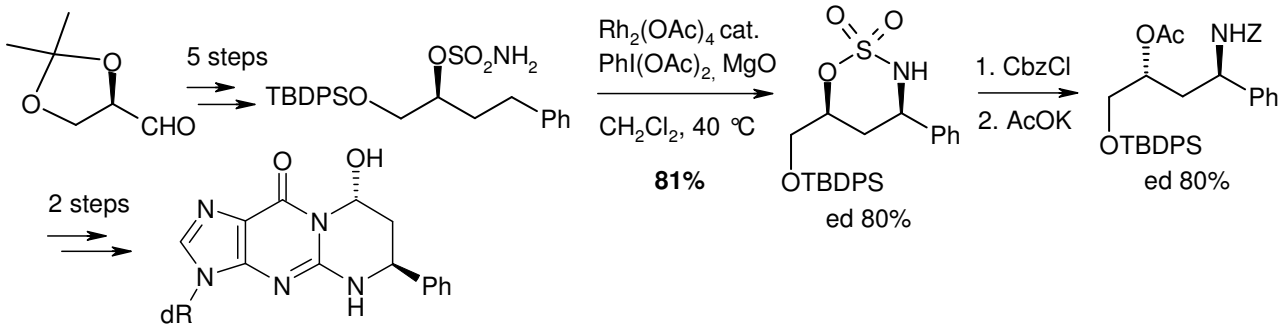
The ability of sulfamic ester substrate to form oxathiazinane product that may be converted to 1,3 diamines has been exploited in the synthesis of manzacidin A and C, two natural products that display various biological activities as serotonin antagonists (Scheme 18).[52]

The two compounds were obtained efficiently following a stereodivergent strategy in 28–32% overall yield in 10 steps from ethyl glyoxylate. The first amino group of manzacidin at C-4 was introduced by way of a stereospecific C-H amination, the second C-N bond at C-6 was generated by the subsequent nucleophilic ring-opening of the oxathiazinane product with NaN_3 after activation by a Boc group.



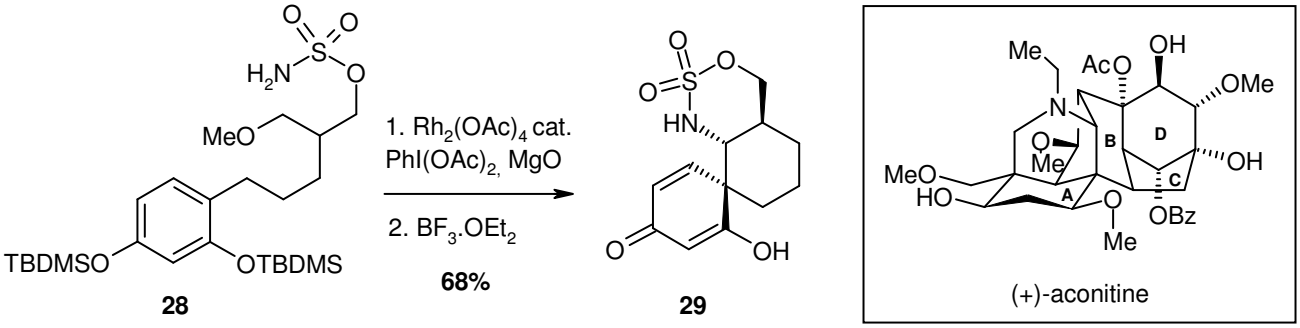
Scheme 18. Stereoselective synthesis of manzacidin A and C.

Pure aminodiols as precursors of 1,N^2-deoxyguanosine were prepared according to a similar strategy (Scheme 19).[53]



Scheme 19. Stereoselective synthesis of 1,3 amino alcohol derivatives.

In the context of the total synthesis of (+)-aconitine, a poisonous constituent of the *Aconitum* genus, Du Bois and Conrad developed an efficient synthetic approach enabling the simultaneous construction of the A and B rings of this polylcyclic product (Scheme 20).[54] A model study performed with sulfamic acid **28** demonstrated the feasibility of this strategy. The spirocycle **29** was obtained from the sulfamic ester **28** by way of intramolecular α-ethereal C-H amination followed by intramolecular arene addition to the oxathiazinane *N*,*O* acetal generated. This 2-step process was found to be remarkably chemoselective, with quantitative conversion for the first amination step, and stereoselective since the tricyclic product **29** was obtained as a single diastereomer. However, application of this strategy to more complex substrates to perform the total synthesis of (+)-aconitine was unsuccessful to date.



Scheme 20. Model study for the simultaneous construction of the A and B rings of (+)-aconitine.

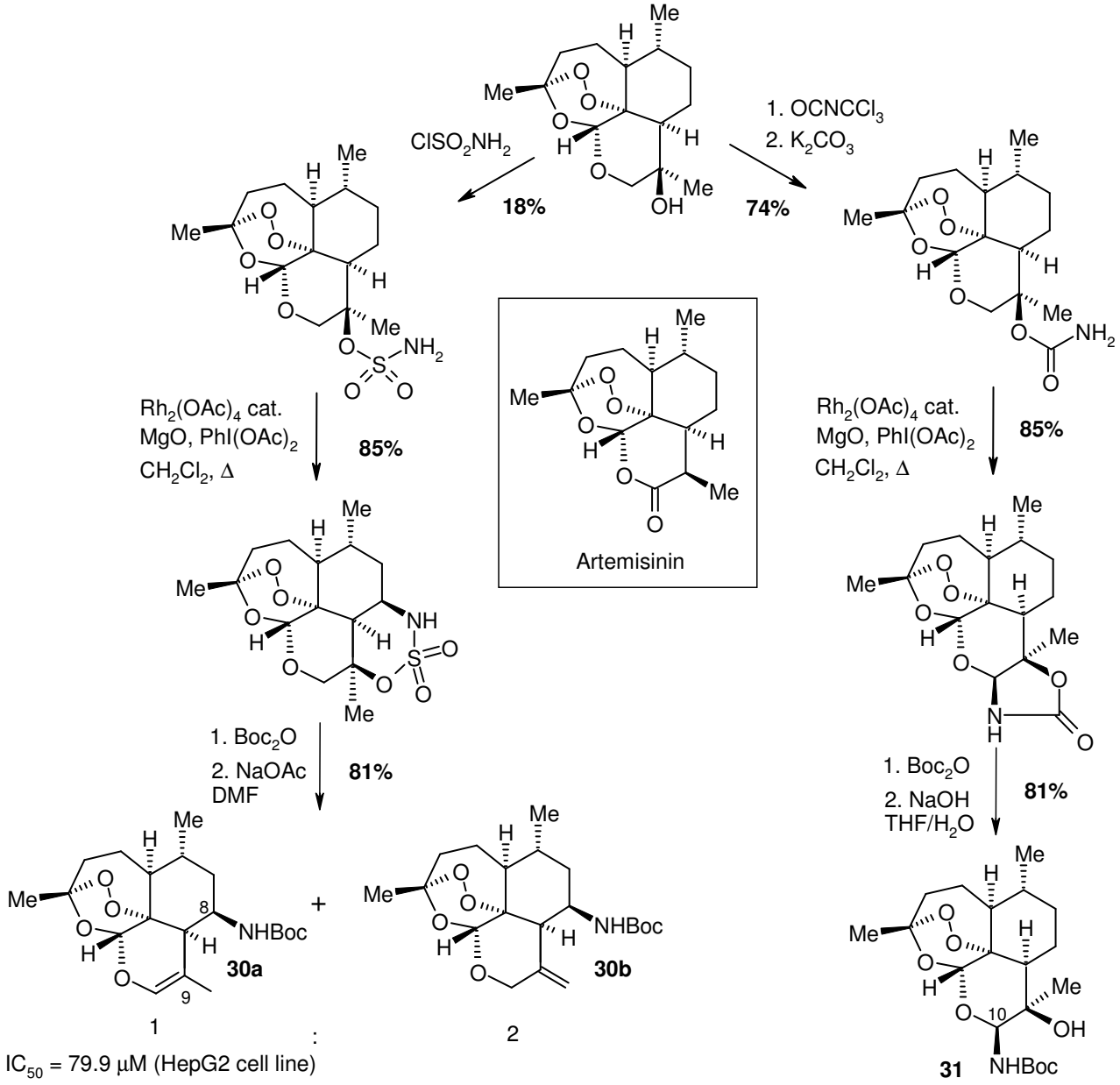
Finally, both carbamates and sulfamic esters were used for the divergent synthesis of various analogs of artemisinin.[55] This natural sesquiterpene lactone endoperoxyde is a well-known antimalarial agent which also displays potent *in vitro* cytotoxicity against cancer cells (Scheme 21).[55,56] Taking advantage of the ability of carbamate substrates to generate exclusively 5-membered ring products and of sulfamate substrates to produce oxathiazinane products, various structural modifications of artemisinin were performed at C-8, C-9 and C-10. The endoglycal **30a** was found to display moderate cytotoxic activity against HepG2 cell line whereas exoglycal **30b** and the *N*,*O* acetal **31** were found to be inactive.[55] Intramolecular metal-catalyzed C-H amination reactions have been also applied to the synthesis of acyclic natural products.[57]

5. Conclusion

The pace of progress in the field of intramolecular-catalyzed amination by way of nitrene insertion has been breathtaking. In the space of only a few years, this process has impressively established itself as a powerful tool for the direct synthesis of a diversity of heterocycles including complex natural products. Major advances have been made including *in situ* formation of iminoiodinane precursors, functionalization of unactivated C-H bonds and new chiral catalysts design allowing enantioselective C-H insertions.

The advantages of intramolecular C-H amination are numerous; the reaction process is stereospecific and the C-H insertions are generally highly regio- and stereoselective. The scope and the power of the intramolecular-catalyzed amination have been increased by the variety of amination substrates that may be used to access cyclic sulfamidate, carbamate or urea derivatives. In addition, the ability of carbamates to generate exclusively 5-membered ring products has been used for the synthesis of 1,2 amino alcohol derivatives. The higher synthetic versatility of cyclic sulfamidate products has been exploited to access a variety of 1,3 amino functionalized derivatives by way of nucleophilic ring opening or addition to iminium

intermediates. The total synthesis achieved to date already define the awesome power of intramolecular C-H amination to construct complex nitrogen-containing natural products. In view of the strategic importance of catalytic C-H bond functionalization and the dynamism of the field, further exciting progress and synthetic applications are yet to come.



Scheme 21. Synthesis of artemisinin analogs.

Acknowledgments

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GALANTHAMINE, A BIOLOGICALLY ACTIVE, NATURALLY OCCURRING HETEROCYCLIC RING SYSTEM

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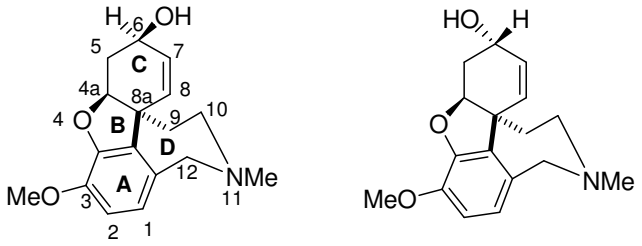
Abstract. *Galanthamine is a heterocyclic target that has attracted the interest of a number of researchers in a collaborative effort aimed at designing novel biologically active compounds for the treatment of Alzheimer's disease. In this account we will present the various syntheses of racemic and enantiomerically pure galanthamine reported so far by using basically two key reaction protocols: the phenol oxidative coupling reaction, and the intramolecular Heck reaction.*

Contents

1. Introduction

(-)-Galanthamine {(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro-[3a,3,2-*ef*][2]benzazepin-6-ol} (**1**)[1] (Figure 1) is a heterocyclic ring system that shows selective, reversible, and competitive inhibition for acetylcholinesterase (AChE)[2] and behaves as an allosteric modulator of the neuronal nicotinic receptor for acetylcholine.[3] Galanthamine is the latest approved AChE inhibitor in Europe and in USA for the treatment of Alzheimer's disease.[4] Owing to the scarce supplies[5] from botanical sources[6] and the high cost of its isolation,[7] several total syntheses have been described to produce this drug.



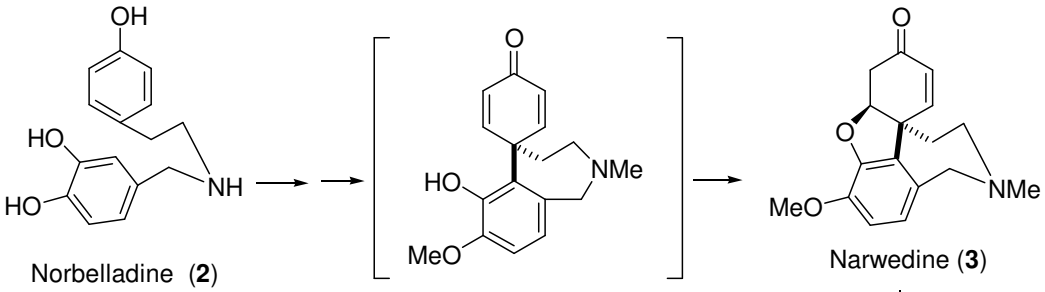
Galanthamine (**1**) *epi*-Galanthamine (*epi*-**1**)

Figure 1

In this account we will summarize and update[8] the current state of the art concerning to the synthesis of galanthamine.[9]

2. Synthesis of galanthamine

The reported synthetic approaches to galanthamine rely on the biomimetic approach *via* the phenolic oxidative coupling in the presence of metal-based oxidating agents,[10] and the intramolecular Heck reaction.[11] In this section we will describe a few synthetic approaches towards galanthamine, highlighting in each case the processes that lead to compound **1** in enantiomerically pure form.



Scheme 1

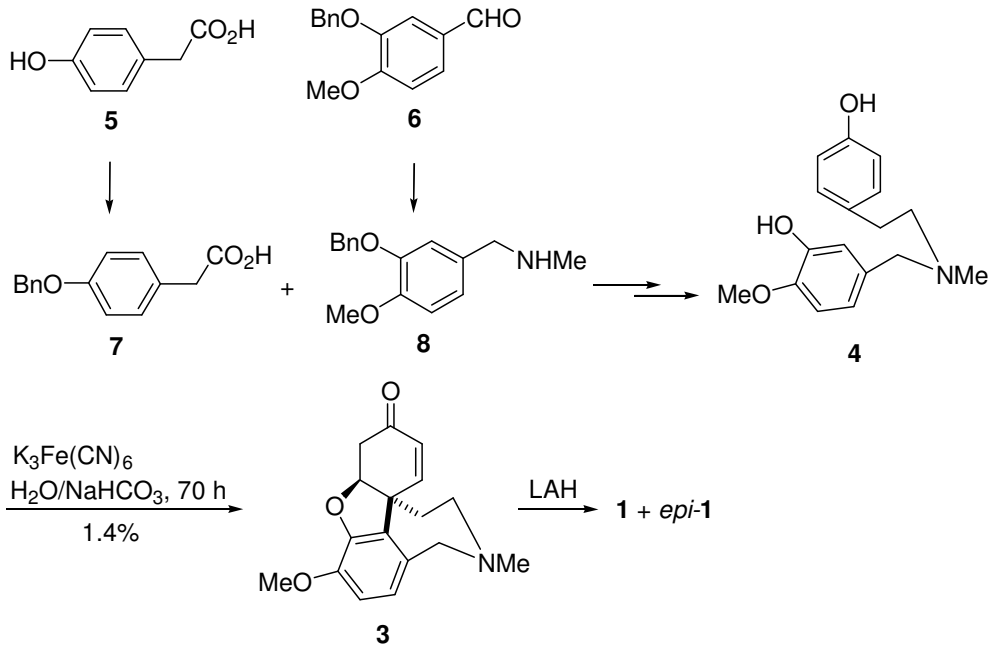
2.1. Synthesis using the phenolic oxidative coupling

In the sixties, Barton[12a] realized that galanthamine could be regarded as derived from norbelladine (**2**) *via* intramolecular oxidative phenol-coupling. Subsequent experiments using α-^{14}C-labelled norbelladine derivatives experimentally confirmed[12b,c] that the oxidative phenol-coupling of norbelladine (**2**) would provide a dienone as the key intermediate leading to narwedine (**3**), postulated as the precursor of galanthamine (**1**) (Scheme 1).[12d,e] The synthesis and resolution of compound **3** have been the object of several patents.[12f–i] A considerable effort was devoted to prove the synthetic feasibility of the proposed biogenetic pathway.[12]

2.1.1. Synthesis of racemic galanthamine

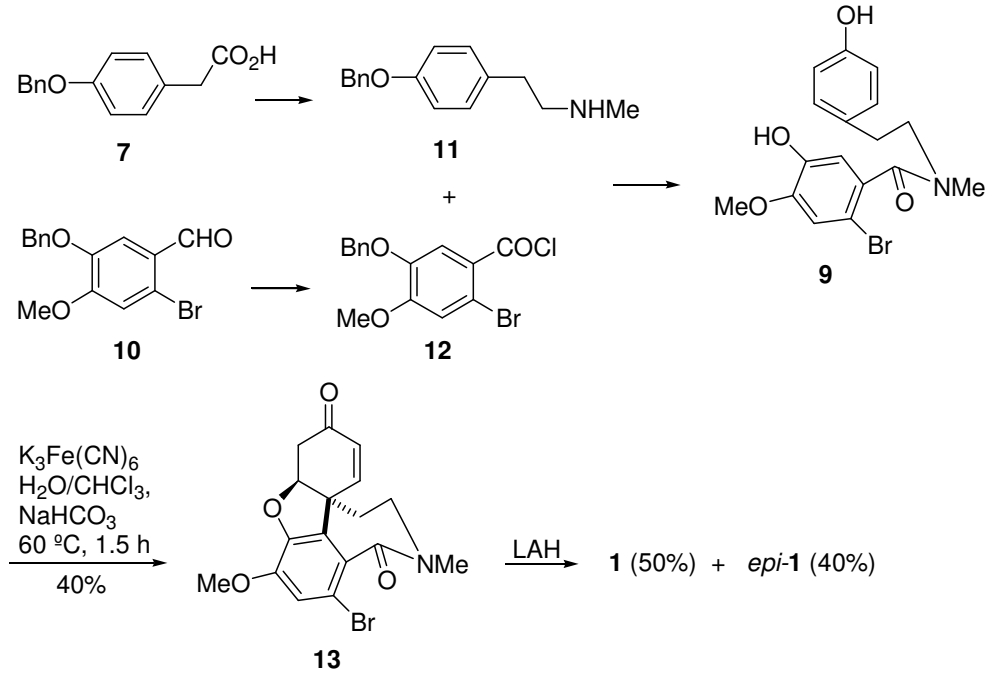
Barton[12b] prepared racemic narwedine (**3**) by phenol oxidation of diphenolic amine **4** using potassium ferricyanide (Scheme 2). The reduction of narwedine (**3**) with lithium aluminium hydride (LAH) represented the first published synthesis of racemic galanthamine and *epi*-galanthamine.[12b] The synthesis of compound **4** was achieved, as shown in Scheme 2, from readily available *p*-hydroxyphenylacetic acid (**5**) and

O-benzylisovanillin (**6**); next, the corresponding acid **7** and the *N*-methylamine **8** were combined to give compound **4**, the needed precursor for the oxidative phenol coupling reaction.



Scheme 2

Kametani[13] proposed diphenol **9** (Scheme 3) as an alternative precursor[14,15] for the synthesis of galanthamine. He assumed that the presence of the bromine atom would prevent the *para* coupling to the hydroxy group, favouring the *ortho* coupling.

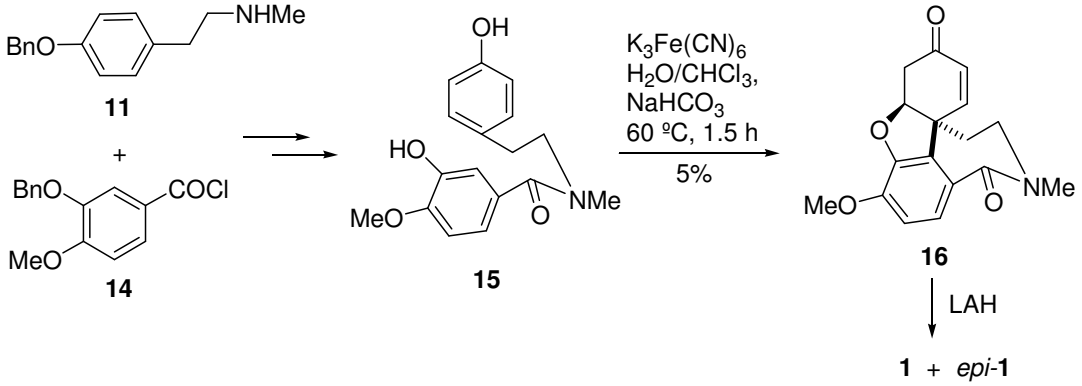


Scheme 3

This compound was prepared starting from *p*-*O*-benzyloxyphenylacetic acid (**7**) and 2-bromo-*O*-benzylisovanillin (**10**), *via* *N*-methylamine **11** and acyl chloride **12**, respectively (Scheme 3). Very

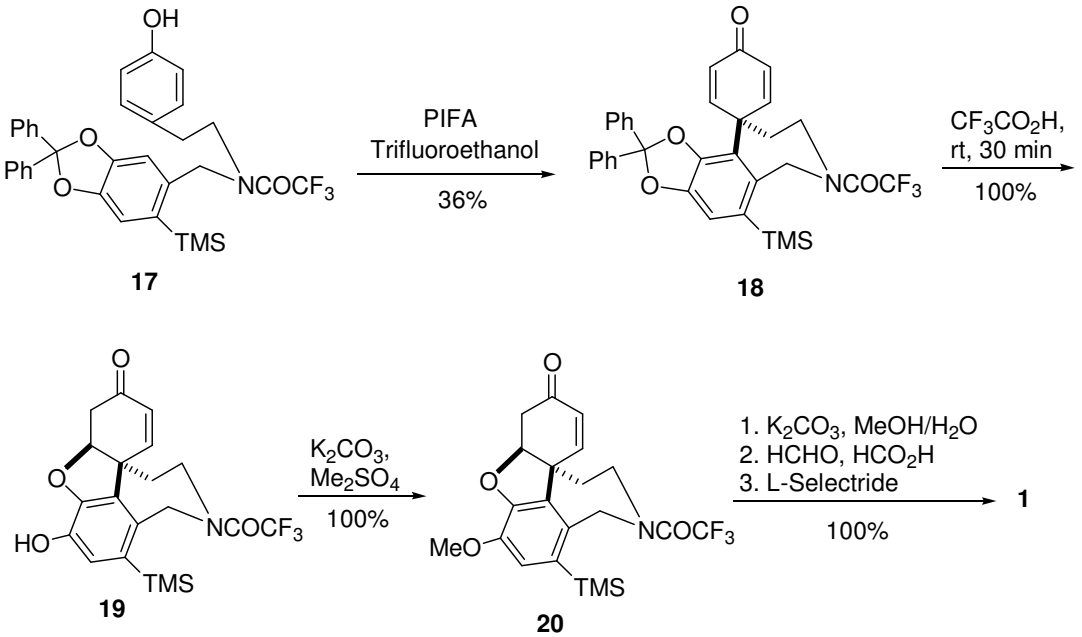
interestingly, the phenol oxidation of compound **9** afforded compound **13** in 40% yield. Reaction of compound **13** with LAH cleaved the carbon-bromine bond, reduced the amide, promoting also the reduction of the keto group, to give galanthamime (**1**) and *epi*-galanthamine (*epi*-**1**) in 50% and 40% yield, respectively (Scheme 3).[13a,b]

Kametani proposed an alternative total synthesis of galanthamine, based on the oxidative phenol coupling of compound **15**,[13c] obtained from *N*-methylamine **11** and 3-benzyloxy-4-methoxybenzoyl chloride (**14**). However, the key oxidative phenol coupling affording compound **16** proceeded in a very poor 5% yield. Final reduction of **16** with LAH gave the expected mixture of galanthamine and *epi*-galanthamine (Scheme 4).



Scheme 4

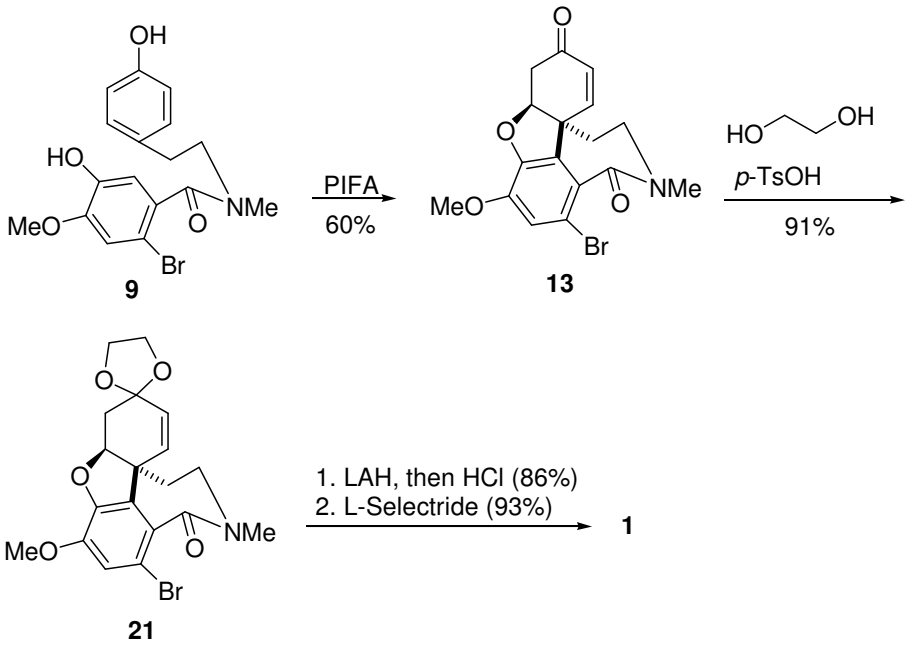
Vlahov and colleagues[16] described the synthesis of the tetracyclic ring system of galanthamine by using the intramolecular *para-ortho* coupling of conveniently functionalized diaryl ethers by anodic oxidation.[16a] In a subsequent communication,[16b] the synthesis of previously synthesised compound **9** (Scheme 3), and its cyclization were reported,[12b] along with the findings that under the same experimental conditions the yield was lower, not superior to 15%.



Scheme 5

In 1998 Kita reported the use of PIFA [phenyliodine(III)bis(trifluoroacetate)] in trifluoroethanol as a suitable oxidant agent that promoted the diphenol coupling on trifluoroacetamide **17**[17] to give compound **18** in a convenient chemical yield (36%); subsequent acid hydrolysis of the acetal, followed by *O*-methylation of phenol **19** afforded methyl ether **20**, which after *N*-deprotection and *N*-methylation, provided galanthamine after stereoselective ketone reduction using L-Selectride (Scheme 5).

Krikorian[16c] has also shown the efficiency of PIFA in the key oxidative coupling reaction for the conversion of amide **9** into derivative **13**, as a higher 60% yield was observed (Scheme 6). After protection of the keto group, acetal **21** was reduced with LAH and the resulting product was submitted to acid hydrolysis to regenerate the ketone, whose reduction with L-Selectride afforded only racemic galanthamine in good chemical yield.

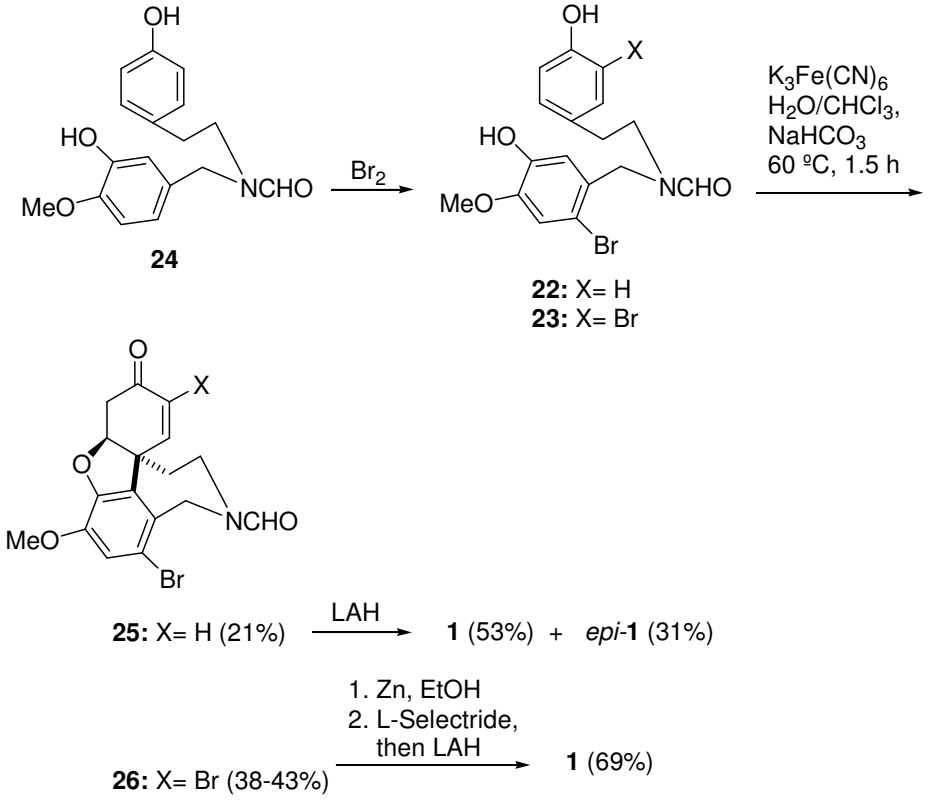


Scheme 6

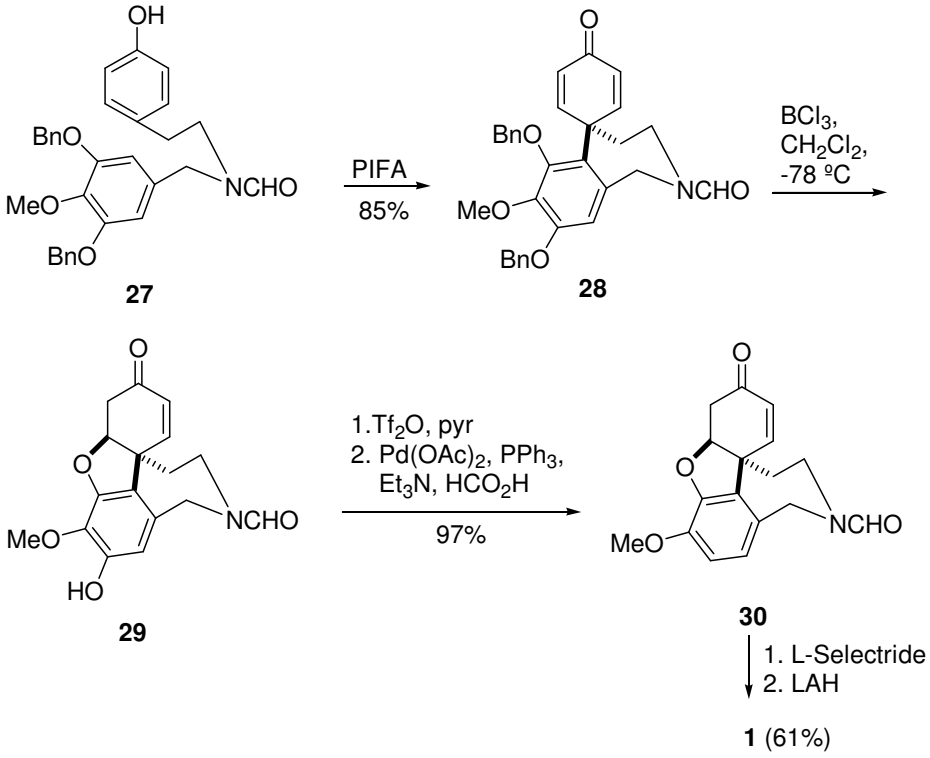
Carroll[18] also described a synthesis of racemic galanthamine using formamides **22**[18a] and **23**[18b] (Scheme 7), prepared by selective bromination reactions (Br_2, –65 ºC for **22**; Br_2, rt for **23**) from a common precursor **24**. Their oxidative coupling reaction using potassium ferricyanide afforded with moderate yields compounds **25** (21%) and **26** (38–43%), respectively. The best yield was obtained from dibromide **23**. Finally, the reduction of compound **25** with LAH gave mixtures of galanthamine and *epi*-galanthamine.[18a] In summary, galanthamine was produced in 11% overall yield, starting from isovanillin and tyramine. Regarding compound **26**, the final steps consisted of the reduction of the carbon-bromine bond with zinc/ethanol, the stereoselective reduction with L-Selectride, and the LAH-promoted reduction of the second carbon-bromine bond.

Node reported a very interesting and efficient approach to galanthamine (Scheme 8).[19] The key points were the use of 3,5-dibenzyloxy-4-methoxybenzaldehyde as a precursor, PIFA-promoted oxidative coupling reaction of *N*-formamide **27** affording dienone **28** in 85% yield, selective *O*-debenzylation, which provided the narwedine-type product **29**, and, finally, *O*-deoxygenation of the extra phenol group *via* the corresponding triflate by palladium(0)-catalyzed reduction with formic acid to give ketone **30** whose final

reduction provided galanthamine (**1**). Note that in this approach the *para* position with respect to the phenol group in precursor **27** is not blocked; instead, two *O*-benzyloxy groups have been attached in *ortho* positions to the methoxy group to make the *para-ortho* coupling the only possible reaction in the treatment with PIFA.



Scheme 7



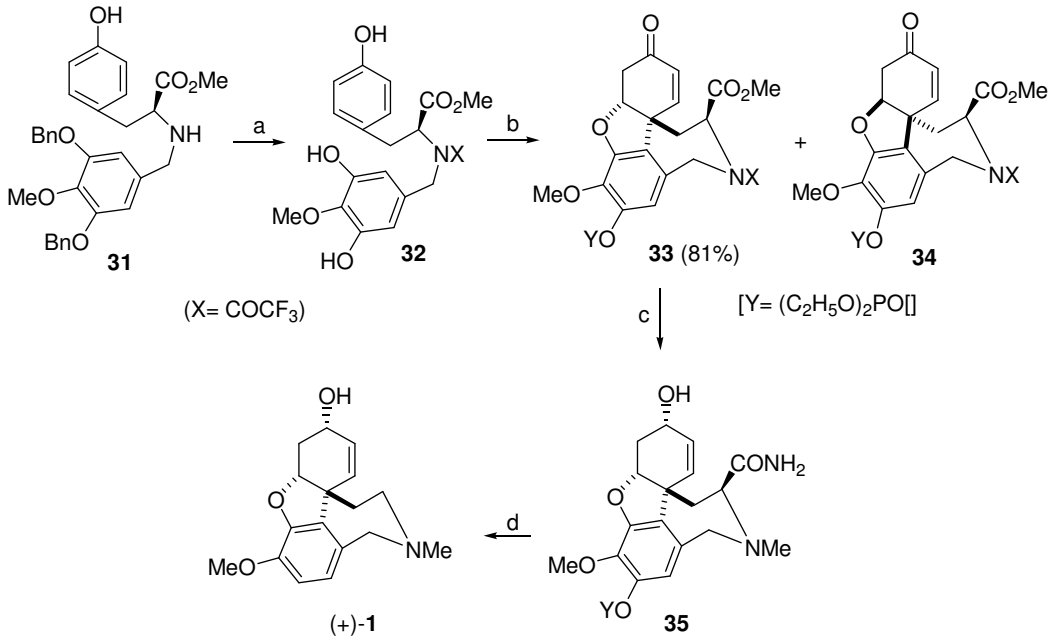
Scheme 8

2.1.2. Synthesis of (-)-galanthamine

Barton and Kirby[12b] were unable to resolve (±)-galanthamine by using standard methods of resolution. However, they obtained (-)-galanthamine by reduction of (-)-narwedine. In the Barton method, (-)-narwedine is isolated by crystallization of a narwedine solution which was mixed with 0.5 equiv of (+)-galanthamine.[12c] The main drawback was the availability of (+)-galanthamine for a large scale preparation. Shieh and Carlson[7] solved this limitation and confirmed that as (±)-narwedine was a racemic conglomerate, a simple crystallization would allow isolation of enantiomerically pure samples without requiring the previous formation of diastereomeric derivatives.

Kametani described the first successful resolution of racemic galanthamine by using optically active di-*p*-tolyl-D-tartaric acid as a resolving agent.[13d] Johnson also reported the resolution of narwedine, using the same agent, and its transformation to (-)-galanthamine.[20] Carroll noticed that the treatment of racemic galanthamine with (-)-camphanic acid chloride gave a mixture of diastereomeric galanthamyl camphenate esters that could be separated to render pure diastereomers. Final reduction with LAH afforded pure enantiomers.[18b]

The first asymmetric synthesis of enantiomerically pure (+) and (-)-galanthamine was reported by Koga.[21] Compound **31**, obtained by reduction of the Schiff base produced from 3,5-dibenzyloxy-4-methoxybenzaldehyde and L-tyrosine methyl ester, followed by reduction with sodium borohydride, was protected as a trifluoroacetamide and submitted to hydrogenation to afford precursor **32** (Scheme 9) for the phenol oxidative *para-ortho* coupling reaction.



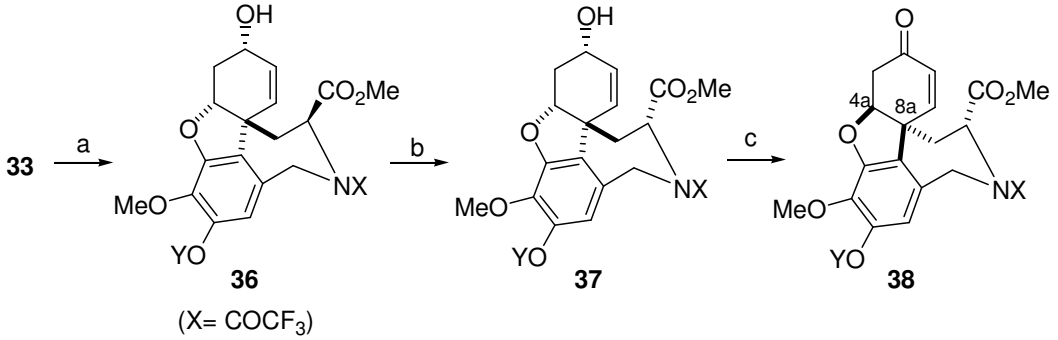
Reagents and conditions. a: i. $(CF_3CO)_2O$, pyr, ii. H_2, Pd/C (90%); b: i. $Mn(acac)_3$ (49%), ii. $(C_2H_5O)_2POCl$, Et_3N; c: i. $NaBH_4$, ii. 35% aq. HCHO, 85% aq. HCO_2H, iii. NH_3 (37%); d: i. Ac_2O, pyr (89%), ii. $POCl_3$, pyr, then LAH (42%), iii. Na, NH_3 (72%).

Scheme 9

This reaction was carried out with five equivalents of manganic tris(acetylacetonate) in acetonitrile, and was efficient since the tetracyclic compound, isolated in 49% yield, gave a mixture of compounds **33** (81%) and **34** (traces) when submitted to phenol protection as the diethyl phosphonate. The absolute

configuration at the new stereogenic center in major isomer **33**, was established after completion of the total asymmetric synthesis of the final product that resulted to be (+)-galanthamine (**1**), the unnatural product. This was achieved in a series of simple reactions, in good overall yield, involving the reduction of the ketone, *N*-methylation, amidation, acetylation, dehydration of the amide **35** to render an unstable, not isolated aminonitrile, reduction with LAH and reaction with sodium in liquid ammonia (Scheme 9).

For the synthesis of the expected natural product (-)-**1**, a simple device was put into practice. As shown in Scheme 10, compound **33** (Scheme 9 and 10) was reduced with sodium borohydride, submitted to full trifluoroacetylation, and the *O*-trifluoroacetate selectively hydrolyzed to produce amide **36**. Next, LDA-promoted epimerization gave compound **37** in poor yield (11%), which after oxidation by PCC afforded a ketone that slowly epimerized to the more stable ketone **38** with the correct and same configuration at carbons 4a and 8a as in the natural product (-)-**1**.[21]



Reagents and conditions. a: i. $NaBH_4$ (99%), ii. $(CF_3CO)_2O$, pyr (92%), iii. 5% aq. $KHCO_3$, MeOH (86%); b: LDA, HMPT (11%); c: PCC (72%).

Scheme 10

Vlahov reported the bio-organic reduction of compound **13** (Scheme 3) for the synthesis of advanced intermediates leading to enantiomerically pure galanthamine.[16b] *Septomyxa affinis DSM 6737* produced pure compound **39** (Figure 2) in 50% yield. *Nematospora corylii CBS 2608* rendered racemic **40** (Figure 2) in 50% chemical yield. *Ashybya gossypii IFO 1355* gave enantiomerically pure **40** and racemic **39** in a 1:2 ratio in total yield over 45%. Finally, *Nocardia alba DSM 43130* and *Bacilus cereus DSM 508* hydrogenated the double bond providing enantiomerically pure (+)-lycoramine derivative **41** (Figure 2).

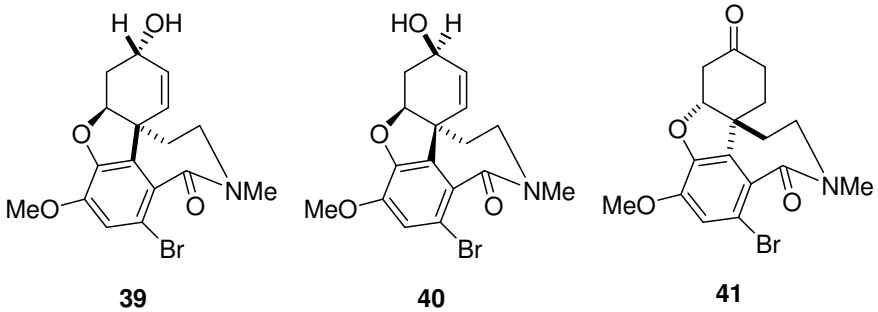
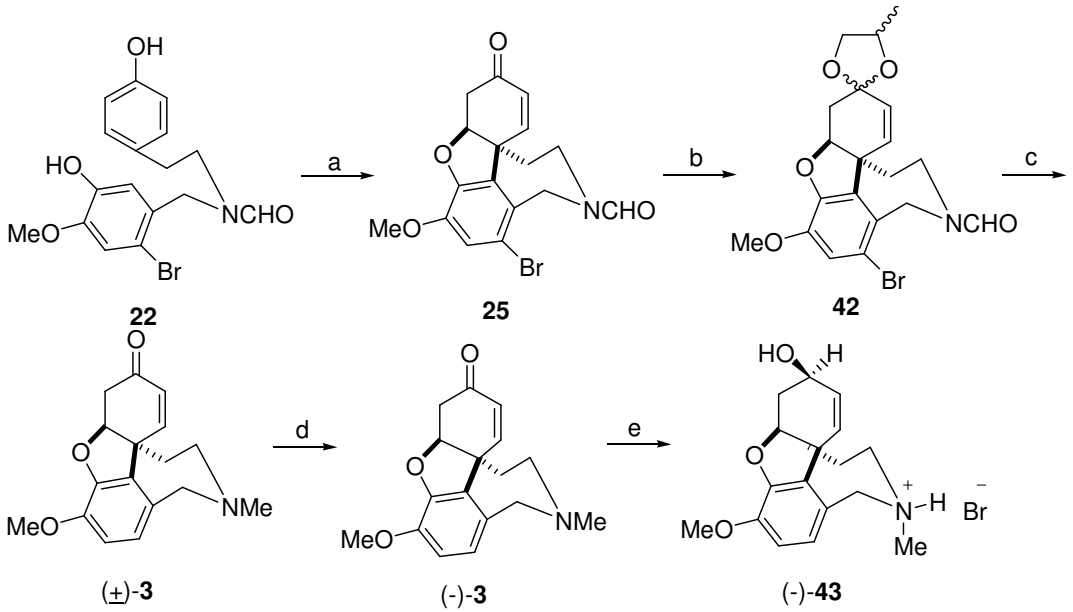


Figure 2

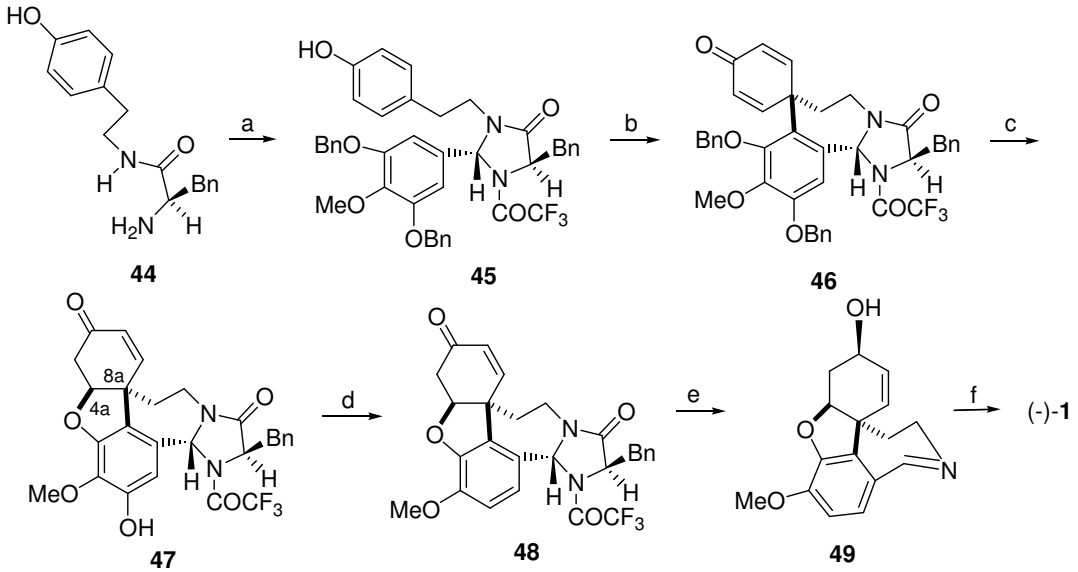
Jordis and colleagues have proposed a new kilogram-synthesis of (-)-galanthamine,[22] starting from compound **22** *via* the known intermediate **25** (Scheme 7).[18a] Protection of the keto group as the acetal using

1,2-propanediol gave a mixture of diastereomers **42** that, without prior separation, were submitted to reduction with LAH, acid hydrolysis and chemical resolution to provide enantiomerically pure compound **3**, whose final reduction with L-Selectride as usual gave galanthamine, isolated as its bromhydrate salt **43**. The protocol is simple, proceeds in nine steps from 3,4-dimethoxybenzaldehyde and requires neither low-temperature reactions nor chromatographic purifications rendering an overall yield of 18–21% (Scheme 11).[22a]



Reagents and conditions. a: $K_3Fe(CN)_6$, H_2O/toluene, Na_2CO_3 (45–50%); b: 1,3-propanediol (89.5%); c: i. LAH, ii. HCl (95%); d: EtOH/Et_3N, cat (-)-3 (80%); e: i. L-Selectride, ii. HBr (99%).

Scheme 11



Reagents and conditions. a: i. 3,5-dibenzyloxy-4-methoxybenzaldehyde, rt, ii. HCl, dioxane (80%), iii. $(CF_3CO)_2O$, pyr (94%); b: PIFA, CF_3CH_2OH, –40 ºC (61%); c: i. BCl_3, –78 ºC (95%); d: i. Tf_2O, pyr (83%), ii. $Pd(OAc)_2$, PPh_3, HCO_2H, DMF (100%); e: i. L-Selectride, THF, –78 ºC (78%), ii. KOH, EtOH (96%); f: i. $NaBH_4$, MeOH, then HCO_2Et (100%), ii. LAH, THF (94%).

Scheme 12

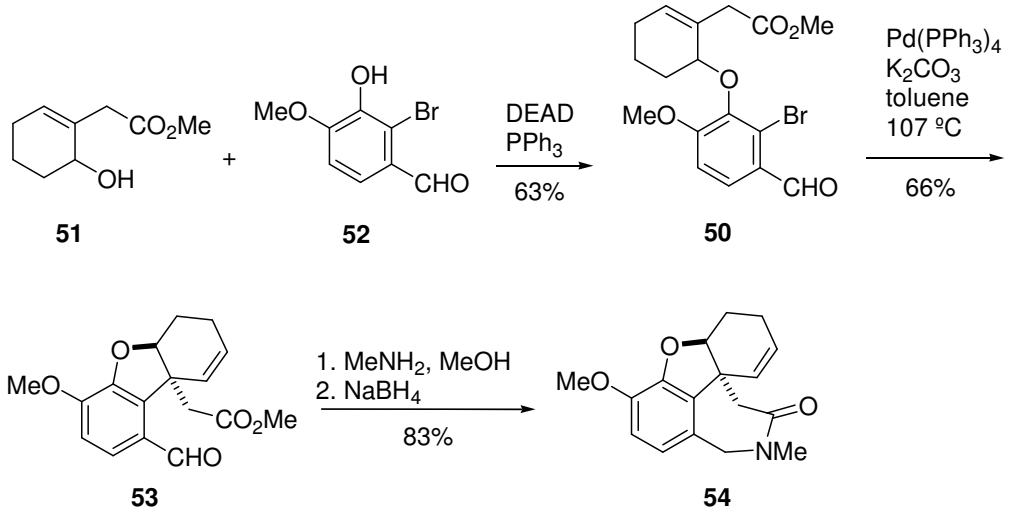
Node has reported a very creative approach to (-)-galanthamine.[19b] The synthesis started with the reaction of tyramine with ®-*N*-Boc-D-phenylalanine providing compound **44** (Scheme 12), whose reaction with 3,5-dibenzyloxy-4-methoxybenzaldehyde gave an imine, which after acid treatment cyclized to yield imidazolidinone **45**, isolated practically as the diastereomerically pure *trans*-isomer. Subsequent oxidative phenol coupling reaction provided dienone **46** in 61% yield. The final steps of the synthesis involved intermediates **47–49**, and are based upon the previous report of his group on the synthesis of the racemate,[19a] with the necessary adjustments for the elimination of the imidazolidinone residue.

2.2. Synthesis using the intramolecular Heck reaction

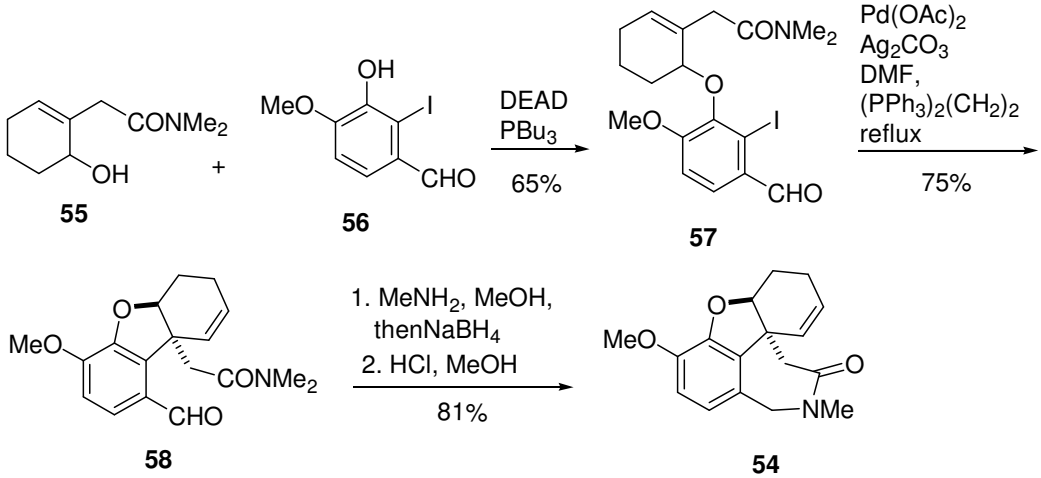
2.2.1. Synthesis of 6-deoxygalanthamine derivatives

In 2000 Fels[23] and in 2001 Parsons[24] described an approach towards the galanthamine heterocyclic ring system based on the intramolecular Heck reaction.[11]

Fels prepared the cyclohexenyl aryl ether **50** from β,γ-unsaturated ester **51** and 2-bromovanillin (**52**), which was submitted to reaction with tetrakis(triphenylphosphine) palladium(0) in the presence of potassium carbonate to give aldehyde **53** (66% yield); final reductive amination with methylamine, followed by *in situ* intramolecular lactamization afforded compound **54** (Scheme 13).[23]



Scheme 13

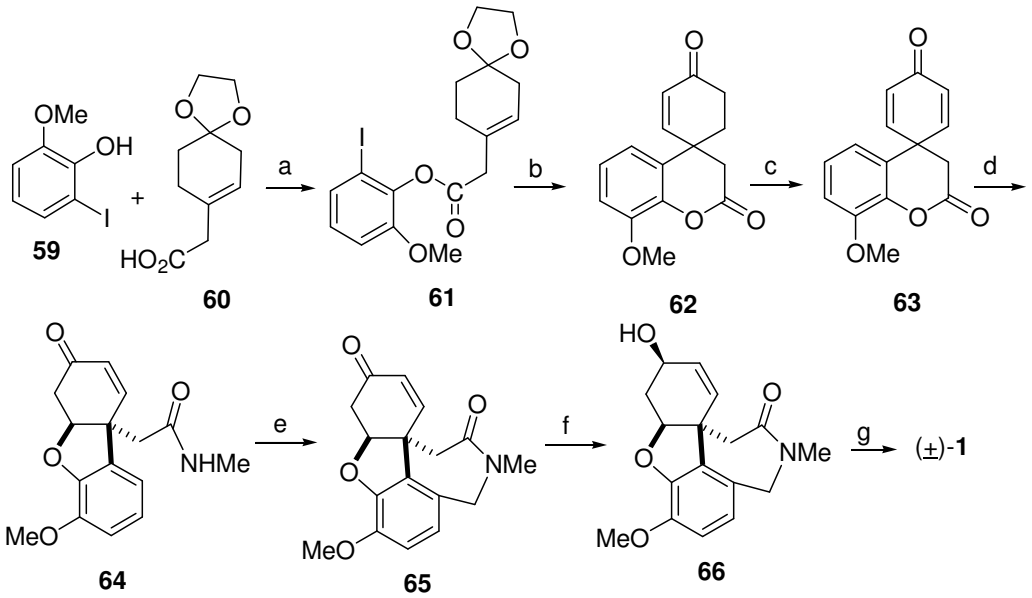


Scheme 14

Similarly, but starting from β,γ-unsaturated amide **55** and benzaldehyde **56**, Parsons[24] synthesized the iodide **57**. Thereafter, benzofurane **58** was obtained in 75% yield by refluxing iodide **57** with $Pd(OAc)_2$ and silver carbonate in DMF (Scheme 14). Finally, compound **58** was transformed into lactam **54** by using the same methodology reported by Fels. [23]

2.2.2. Synthesis of racemic galanthamine

Based on the results obtained in the formal synthesis[25] of related alkaloid lycoramine,[25a] Guillou reported[25b] the total synthesis of racemic galanthamine by using an intramolecular Heck reaction.[25c] This group has described the first use of this intramolecular reaction as an alternative for creating the spiro quaternary carbon atom of galanthamine-type of alkaloids. In contrast with other approaches,[23,24] the aryl iodide partner **59** was coupled within acid **60** and the β,γ-unsaturated ester **61** did not show an allylic alcohol, but a protected ketone (Scheme 15). Heck reaction, promoted by palladium-*trans*,*trans*-dibenzylideneacetone in the presence of 1,2-bis(diphenylphosphanyl)ethane and tallium acetate, afforded compound **62** in 67% yield. The formation of dienone **63** was more difficult than envisaged, but the use of $(PhSeO)_2O$ in the presence of molecular sieves solved the problem affording the product in 50% yield. The stereoselective transformation of dienone **63** into benzofurane **64** is one of the most interesting and original contributions of this synthetic approach. Finally, the tetracyclic ring system of galanthamine was assembled by simple electrophilic aromatic substitution of an iminium ion formed in the reaction of amide **64** with paraformaldehyde in the presence of trifluoroacetic acid. The resulting ketone **65** was reduced with L-Selectride, and racemic galathamine was finally obtained by LAH-reduction of amide **66**.



Reagents and conditions. a: EDCI, DMAP, CH_2Cl_2, (80%); b: i. $Pd_2(dba)_3$, dppe, TlOAc, CH_3CN (67%), ii. Ph_3CBF_4, CH_2Cl_2 (100%); c: $(PhSeO)_2O$, CH_2Cl_2 (50%); d: 40% aq. $MeNH_2$, THF (100%); e: $(CH_2O)n$, TFA, (63%); f: i. L-Selectride, THF, –78 ºC (93%), ii.KOH, EtOH (96%); g: LAH, DME (80%).

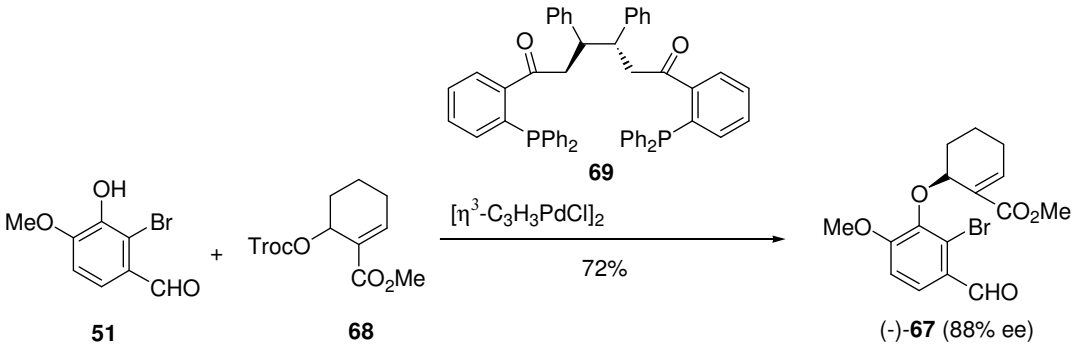
Scheme 15

2.2.3. Synthesis of (-)-galanthamine

Trost and Toste published the second asymmetric synthesis of (-)-galanthamine in 2000[26a] and an improved version of this synthesis in 2002[26b] by using as key steps the formation of the O4-C4a bond by a

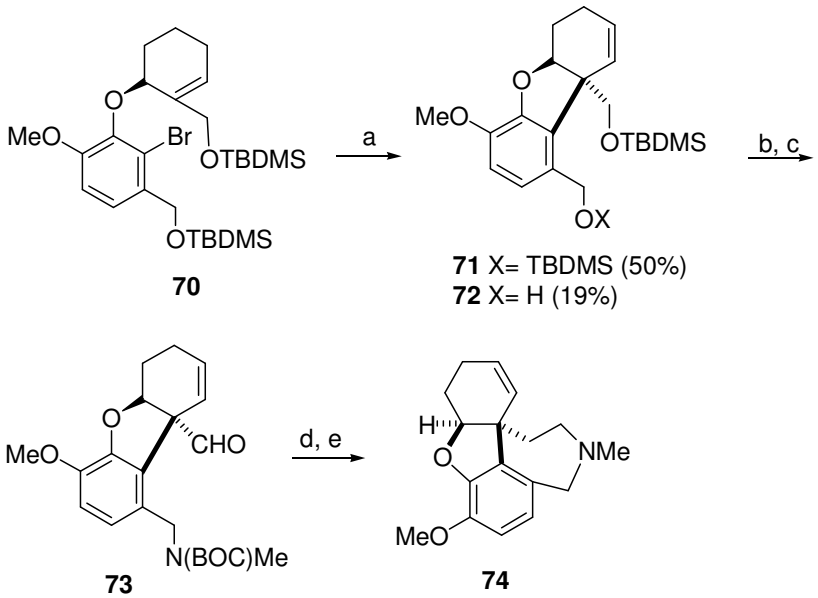
palladium-catalyzed asymmetric allylic alkylation,[27] and an intramolecular Heck reaction to prepare the quaternary center C8a. A full paper has been recently published.[26c]

First generation synthesis of (-)-galanthamine started with intermediate (-)-(**67**), prepared in 72% yield and 88% ee (Scheme 16), in the reaction of 2-bromovanillin (**51**) with carbonate **68**, in the presence of ligand **69**.[26a]



Scheme 16

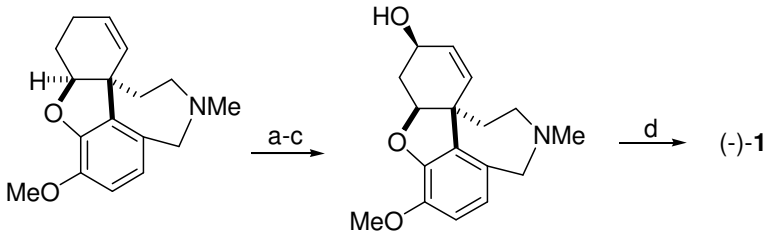
All attempts to carry out the intramolecular Heck reaction on compound (-)-**67** failed, probably due to the fact that the presence of the ester on the olefin was detrimental to the Heck reaction.[28] Therefore, the authors prepared compound **70** from **67** by total reduction (DIBAL-H) (92%), followed by persilylation (97%). Although the Heck reaction of unsaturated aryl bromide **70** was still problematic, critical experimental conditions [20 mol% $Pd(OAc)_2$, 18 mol% 1,2-(dicyclohexylphosphino)-ethane (dcpe), 0.1 M dimethylacetamide, 3.0 equiv proton sponge, 12 h] were found to provide the expected heterocyclic derivative as a mixture of compounds **71** (50%), **72** (19%), and unreacted starting material **70** (7%) (Scheme 17).



Reagents and conditions. a. See Text; b. i: TBAF (99%), ii: MnO_2 (97%), iii: $MeNH_2$, then $NaCNBH_4$ (83%); c. Dess-Martin (92%); d. i: Ph_3P=CHOMe (64%),
e. i. TFA, ii. 4 Å MS, MeOH, iii. $NaCNBH_4$ (53%).

Scheme 17

Next, the mixture of compounds **71**+**72** was submitted to a complete desilylation reaction, followed by selective benzylic oxidation with manganese dioxide; then, reductive amination of the resulting aldehyde using methylamine to form the imine and reduction with sodium cyanoborohydride, followed by *N*-Boc protection and oxidation of the alcohol, gave the key intermediate **73** (Scheme 17). Then, Wittig reaction and acid hydrolysis afforded an aldehyde that was submitted to a reductive Mannich amination to produce compound **74** in 16% overall yield from the mixture **71**+**72** (Scheme 17). At this stage of the synthetic sequence, it was only necessary to functionalize the C-ring. In order to do so, the allylic oxidation was investigated but without success. Thus, an alternative, tedious, four-step protocol was developed from compound **74** to incorporate the C6 hydroxyl group in place, which ended with the synthesis of alcohol **75** (Scheme 18). Finally, when this compound was treated with Osborn's rhenium(VII) catalyst a product, identical to natural galanthamine (-)-**1** (Scheme 18), was obtained.

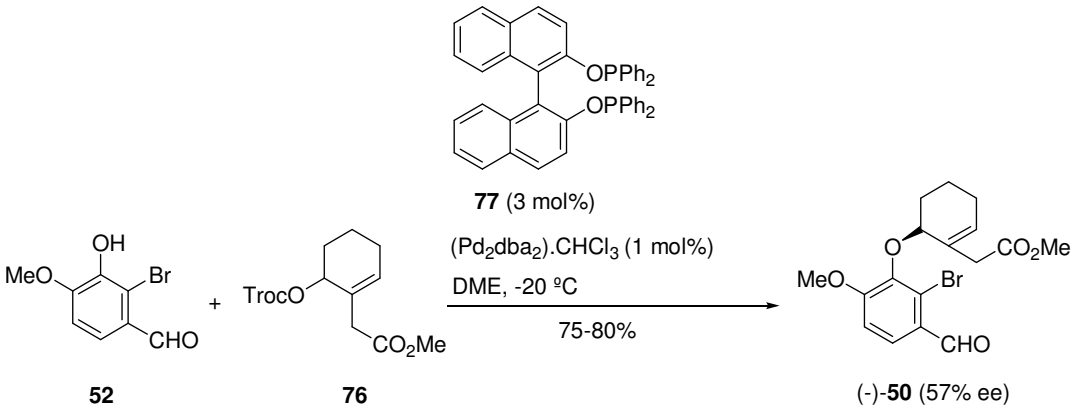


74 **75**

Reagents and conditions. a: i. TsOH, ii. DMDO/acetone, iii. DBU (45%); b: PhSeSePh, $NaBH_4$ (98%); c: $NaIO_4$, then 80 ºC (64%); d: $Ph_3SiOReO_3$ (50%).

Scheme 18

Second generation synthesis of (-)-galanthamine started[26b] with compound (-)-**50**, the same intermediate previously synthesized by Fels[23] (Scheme 13), but now obtained in enantiomerically pure form from compounds **52** and **76** using the chiral inductor **77**, in the presence of a palladium salt as the catalyst for the key Heck reaction (Scheme 19).

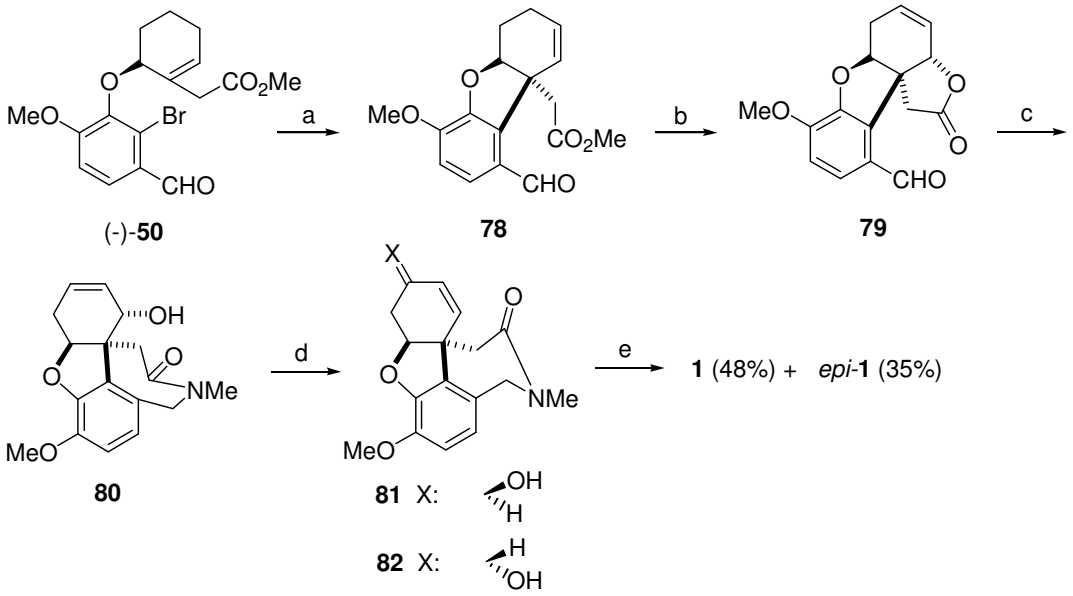


52 **76** (-)-**50** (57% ee)

Scheme 19

Aryl ether **50** was then cyclized to give **78**, whose absolute configuration at the new formed stereocenters was assigned based on the analogy of Heck cyclization of related compound **70** (Scheme 17). Direct iodolactonization of **78** was impossible; however, hydrolysis and iodolactonization followed by elimination of HI afforded lactone **79** (Scheme 20). Reductive amination and amidation were carried out in a

single operation leading to lactam **80** in 92% yield, whose reaction with methanosulfonyl chloride followed by basic hydrolysis provided a mixture of compounds **81** and **82** in a ratio of 1.5:1. Finally, reduction with LAH and separation gave galanthamine (-)-**1** and 3-*epi*-galanthamine (*epi*-**1**) in 48% and 35% yield, respectively (Scheme 20).



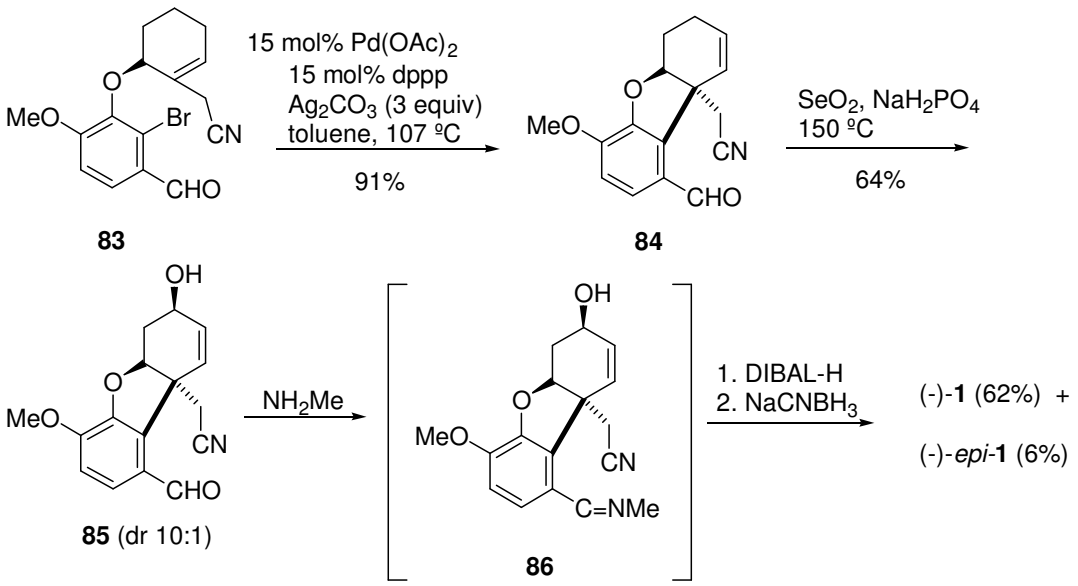
Reagents and conditions. a. 15 mol% $Pd(OAc)_2$, 15 mol% dppp, toluene, Ag_2CO_3 (3 equiv) (82%); b. i: 1 N NaOH, ii: NIS, DMAP, MeCN, iii: DBU (64%); c. $MeNH_2$/MeOH, then $NaBH_4$ (92%); d. i: MsCl, Et_3N, ii: Cs_2CO_3 (45%); e. LAH.

Scheme 20

The low overall efficiency and selectivity of both approaches prompted the authors to investigate a third generation synthesis of (-)-galanthamine.[26b,c] Based on the success of the Heck reaction for substrates such as **70** (Scheme 17) and **50** (Scheme 20) bearing a carboxaldehyde function, aldehyde (**83**) bearing a nitrile moiety (Scheme 21) was easily prepared from intermediate **67** (Scheme 16) using standard protocols. As expected, after cyclization compound **84** was obtained in 91% yield. Next, the allylic oxidation of compound **84** using SeO_2 rendered compound **85** in moderate yield, as a mixture of isomers. This mixture was converted to galanthamine (**1**)/*epi*-galanthamine (*epi*-**1**) (Scheme 21) after reaction with methylamine to give intermediate **86**, followed by reduction with DIBALH/$NaCNBH_3$. Note that in a single operation, the imine was reduced to a secondary amine, and so was the nitrile to an aldehyde that was trapped *in situ* to yield a presumed hemiaminal that was again reduced with sodium cyanoborohydride to afford the target molecules.

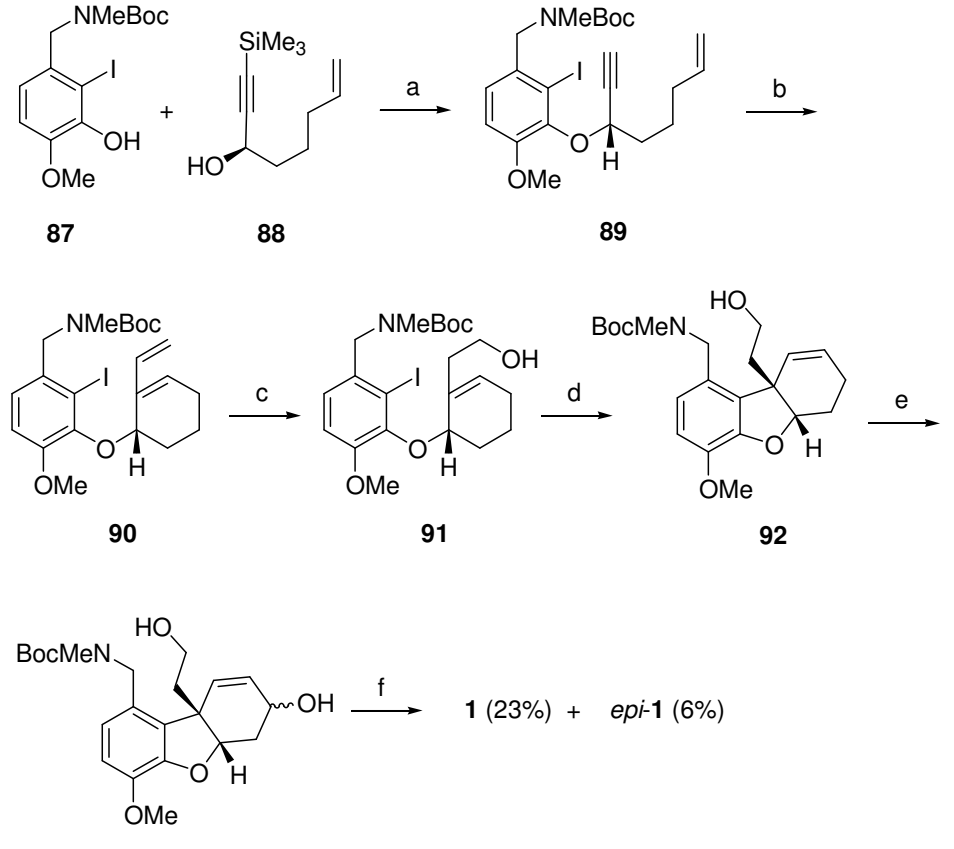
Brown and co-workers have recently reported an efficient synthesis of (-)-galanthamine (**1**)[29] on 11 steps from isovanillin, and an easily available, enantiomerically pure propargylic alcohol derivative to control and direct the absolute and relative configuration at the diferent stereocenters, featuring as key steps an enyne ring-closing metathesis, and the Heck reaction. As shown in Scheme 22, starting from phenol **87** the Mitsonubu reaction with enantiopure alcohol **88** gave enyne **89**, which underwent an efficient ring-closing metathesis reaction in the presence of the first-generation Grubbs' catalyst (3 mol%). The hydroboration of the resulting diene (**90**) afforded the homoallylic alcohol **91** in excellent yield (91%). Allylic oxidation according to Trost[26,27] provided a mixture of diastereomers (**92**) in 4.8:1 ratio favoring the

α-isomer, that without separation were transformed into (-)-galanthamine (**1**) and minor *epi*-galanthamine, after activation of the primary alcohol **93** as mesylate, amine deprotection of ring annulation.



83 **84** **85** (dr 10:1) **86**

Scheme 21



87 **88** **89** **90** **91** **92** **93**

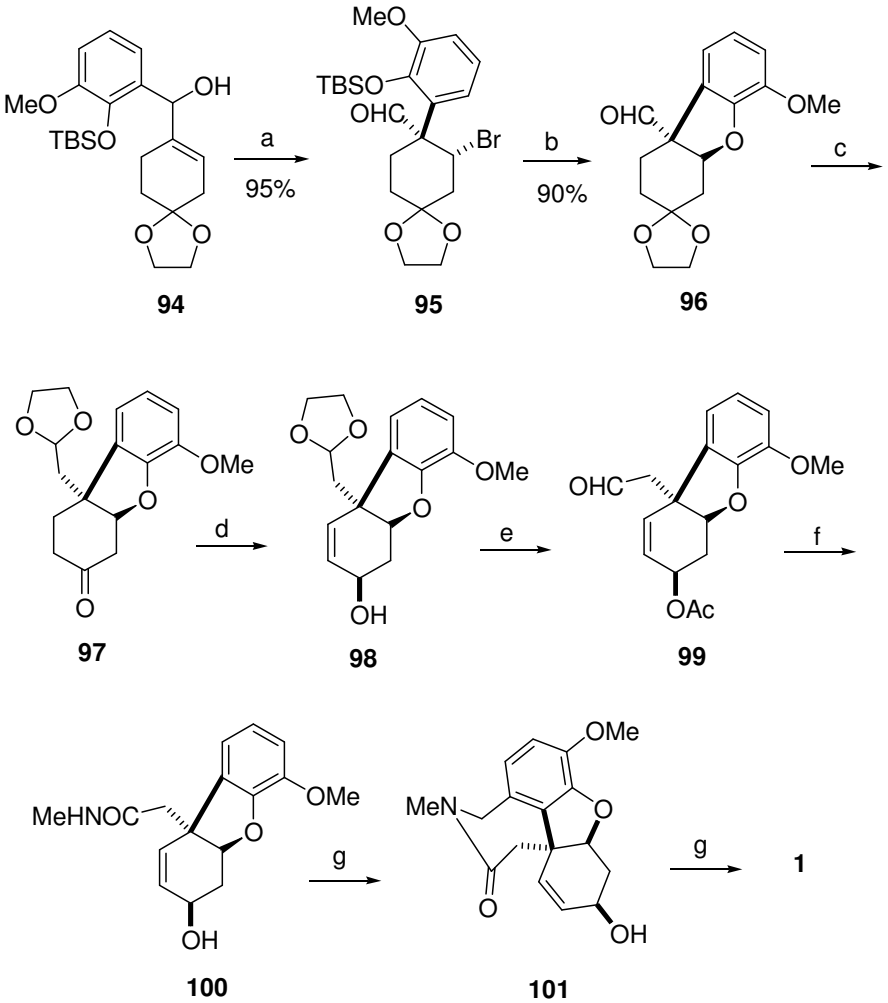
Reagents and conditions. a. i: Ph_3P, DIAD, THF (74%), ii: K_2CO_3, MeOH (97%); b. Grubbs' catalyst (3 mol%), DCM (85%); c. 9-BBN, H_2O_2, NaOH (91%); d. $Pd(OAc)_2$, dppp, Ag_2CO_3, PhMe (58%); e. SeO_2, $NaHPO_4$, dioxane, 150 ºC (61%)(a: b / 4.8:1); f. i: MsCl, Et_3N, DCM, ii: TFA, $NaHCO_3$, H_2O.

Scheme 22

2.3. Miscellaneous

More recently, Tao and co-workers[30] have achieved the semi-synthesis of the target compound **1** from lycoramine by selective dehydrogenation, in the presence of rare earth metal hydride (9%) at 240 ºC, in 46 % chemical yield and 97% of optical purity.

On the other hand, a recently reported synthesis of racemic galanthamine was based on a successive semipinacol rearrangement/desilylation/cyclization strategy.[31] Starting from readily available intermediate **94**, the reaction with NBS afforded compound **95**, whose treatment with DBU in DMSO gave the key intermediate **96** bearing the basic core of galanthamine in place (Scheme 23). One-carbon homologation and a very curious but extremely efficient protection/deprotection sequence of ketal groups provided precursor **97**, ready for the Saegusa-Ito oxidation.[32] Under the usual experimental conditions, the expected α,β-unsaturated ketone was isolated and reduced to the allylic alcohol **98** in good overall yield. Trivial acid hydrolysis and acetylation provided aldehyde **99**, which was transformed into the *N*-methylamide **100** by amidation with *N*-methylamine on the presumed intermediate acyl bromide and deacetylation.

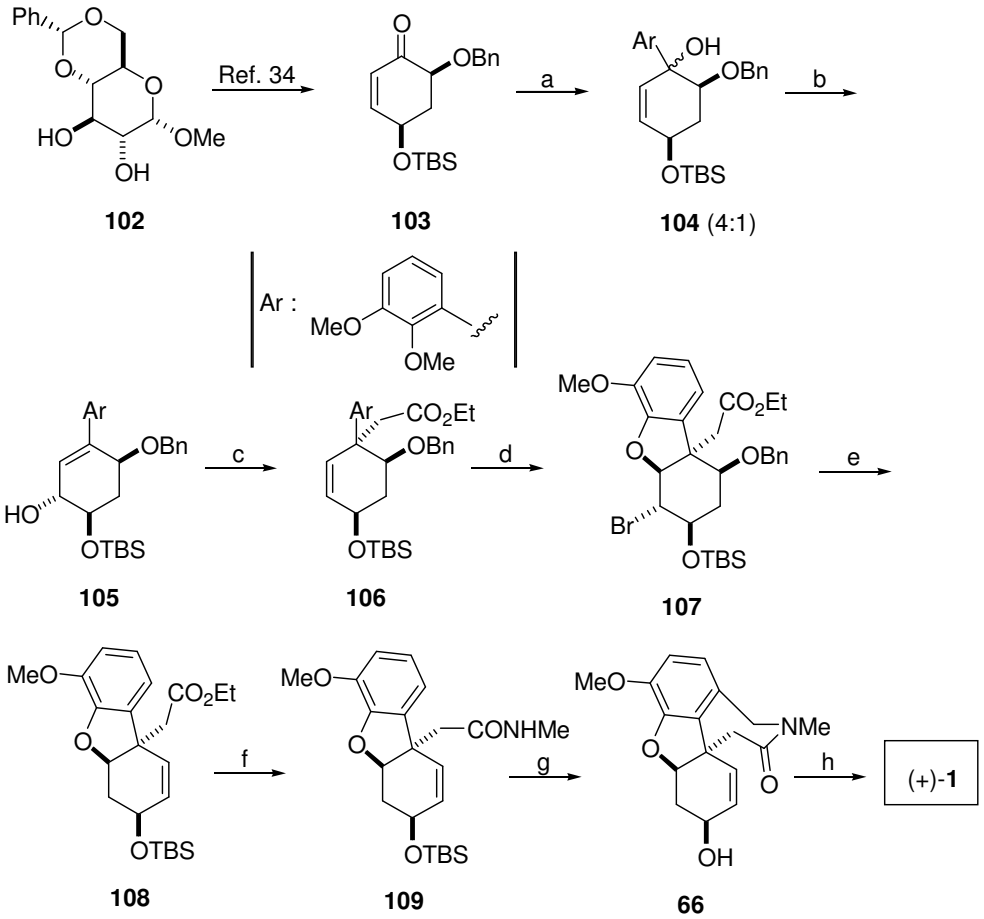


Reagents and conditions. a. NBS, DCM (95%); b. DBU, DMSO (90%); c. i: Ph_3P=CHOMe, *t*-BuOK (98%), ii: ethylene glycol, acetone, PTS (75%); d. i: LDA, TMSCl, ii: $Pd(OAc)_2$, Na_2CO_3, MeCN (76.5%); e. i: 1N HCl (99%), ii: Ac_2O, py (80%); f. i: NBS, AIBN, then $MeNH_2$ (75%); g. $(CH_2O)n$, TFA (82%); h. LAH (76%).

Scheme 23

The final steps of the synthetic sequence consisted of the Pictet-Spengler reaction of **100** with *para*-formaldehyde to provide lactam **101** with the new cycle incorporated, followed by reduction with LAH to give racemic galanthamine. Globally, this new synthesis of compound (**1**) has been achieved in 13 steps in 12% overall yield.

A stereoselective synthesis of (+)-galanthamine **1** starting from D-glucose has been recently reported by Chida and co-workers.[33] In Scheme 24 we show the synthetic sequence with the most significant key intermediates. Following a protocol (8 steps, 38% overall yield) described by the same authors[34] for the transformation of commercially available 4,6-*O*-benzylidene-α-D-glucopyranoside (**102**) into (4*R*,6*S*)-6-benzyloxy-4-(*t*-butyldimethylsilyloxy)-2-cyclohexene (**103**), the reaction of this chiral enone with 2,3-dimethoxyphenylmagnesium bromide at low temperature in THF afforded a mixture (4:1) of tertiary alcohols that without separation was submitted to oxidation and stereoselective reduction to give major allylic alcohol (**104**), the minor β-isomer (not shown) being isolated in 9% yield.



102 **103** **104** (4:1) **105** **106** **107** **108** **109** **66**

Reagents and conditions. a. 2,3-dimethoxyphenylmagnesium bromide, THF, –78 ºC (85%); b. i: PCC, NaOAc, $(CH_2Cl)_2$, 60 ºC, (75%), ii: $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH/ DCM (2 / 3), –78 ºC (89%); c. Nitrophenol, $CH_3(OEt)_3$, 140 ºC, 60 h (80%); d. NBS, DMF, 0 ºC (84%); e. i: H_2, 10% Pd/C, EtOH; then, H_2, 10% Pd/C, K_2CO_3, EtOH (85%), ii: (thiocarbonyl)diimidazole, DMAP, 1,2-dichlorobenzene, rt to reflux (72%); f. i: LiOH, MeOH, H_2O, ii: $MeNH_2$•HCl, Et_3N, $(EtO)_2P(O)CN$, THF, –10 ºC (93%); g. $(CH_2O)n$, TFA, $(CH_2Cl)_2$ (67%); h. LAH, THF, reflux (88%).

Scheme 24

Next, Johnson-Claisen rearrangement[35] of compound **105** with triethylorthoacetate in the presence of nitrophenol provided compound **106** in good yield. In the next step the formation of the benzofuran moiety

was attempted by using NBS in a process that included phenol deprotection and intramolecular etherification *via* a bromonium ion intermediate. The compound **107** so obtained was fully reduced in a "one-pot-two-step" process, implementing sequential debromination and de-*O*-benzylation reactions; the resulting secondary alcohol was dehydrated to give product **108**, that was transformed, *via* amide **109**, into the tetracyclic lactam **66**, identical to the compound previously described by Guillou and colleagues.[25b] Finally, reduction of **66** with LAH afforded (+)-galanthamine (**1**) in 88% yield. The spectroscopic data of this compound were similar with those from natural (-)-galanthamine (**1**), but showing an opposite $[\alpha]_D$ value [+ 111.5 (*c* 050, EtOH)]. In summary, the new synthesis of non-natural (+)-galanthamine (**1**) required 11 steps with a 12.8% overall yield from compound **103**, featuring elegant Claisen-type rearrangement on a chiral cyclohexenol derivative to stereoselectively generate the quaternary carbon, and simple and effective NBS-promoted dealkylation plus bromination strategy to form the key benzofuran ring system.

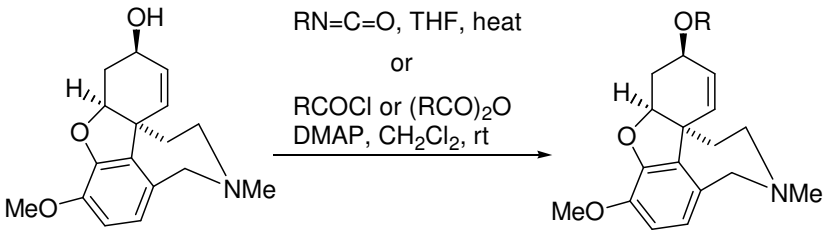
K. R. Buszek, and D. L. Bixby[36] have described synthetic studies toward the total synthesis of galanthamine. The key step involves the application of a tandem [2+2] aryne cycloaddition-rearrangement sequence to generate the key tricyclic core. Subsequent ring expansion *via* a highly regioselective Beckmann rearrangement provides the seven-membered heterocycle. Finally, ring-closing metathesis strategies for the construction of the cyclohexenoid unit would afford galanthamine.

3. Synthesis of galanthamine analogues and derivatives

Several galanthamine analogues and derivatives have been reported and the synthetic pathways used for their preparation are brevely commented below.

^{3}H- and ^{14}C- stable isotopes of galanthamine found to be useful in the following of their pharmacokinetic have been reported by Linnemann *et al.*[37] and Janssen and co-workers.[38]

Han *et al.*[39] prepared several esters and carbamates (**110**) starting from galanthamine (Scheme 25). In order to compare their pharmacological properties as AChE inhibitors, compounds **110** were tested, the carbamates generally being more potent than the corresponding esters, but less actives than galanthamine.



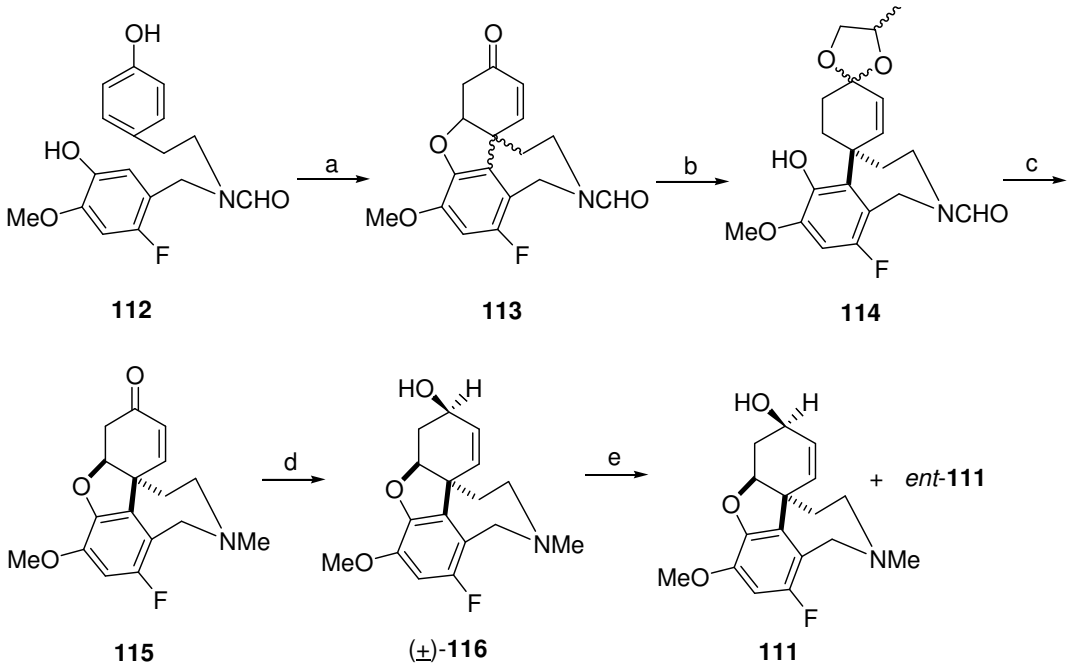
1 **110**

Scheme 25

The Austrian group led by Jordis has achieved important results on the chemistry of galanthamine analogues.[40] In the same way, more recently, Jordis has reported[41] the synthesis of (-)-8-fluorogalanthamine (**111**) and its enantiomer (*ent*-**111**). They have applied the same synthetic sequence for the preparation of (-)-galanthamine on a kilogram scale,[22b] but now starting from fluorinated derivative **112**, *via* the analogous intermediates **113–116** (Scheme 26).

Fröhlich and co-workers[42] reported a novel serie of alkyl derivatives of 1-methyl-galanthamine and 1-methyl-*epi*-galathamine. Scheme 27 shows the synthetic approach leading to 1-methyl-galanthamine (**117**)

starting from compound **118**, prepared by reductive amination of 5-hydroxy-4-methoxy-2-methyl-benzaldehyde with tyramine, followed by formylation, *via* intermediate **119**.

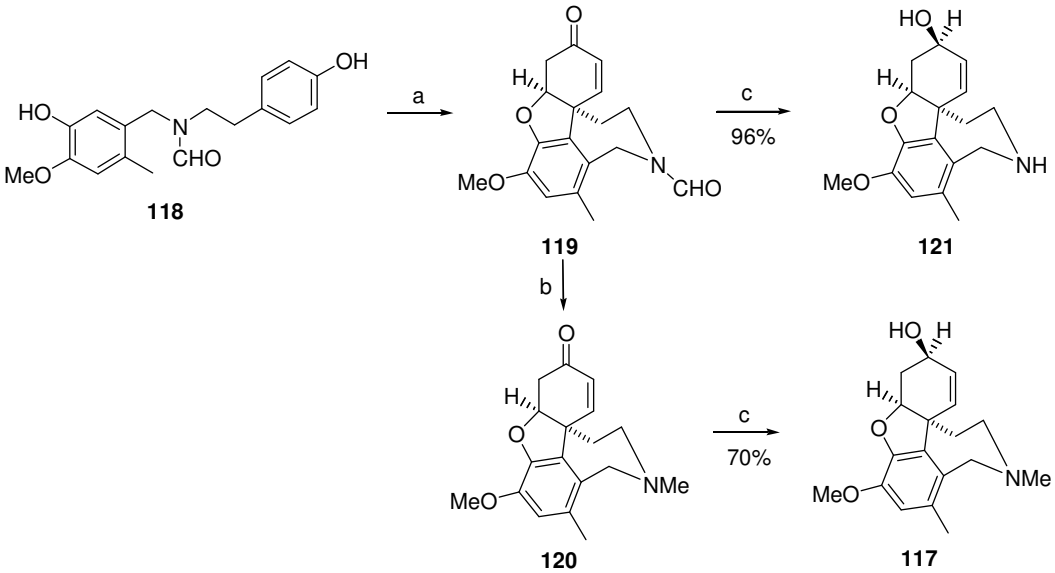


112 **113** **114** **115** (±)-**116** **111**

Reagents and conditions. a. $K_3Fe(CN)_6$, H_2O/toluene, Na_2CO_3, 50 ºC (40%); b. 1,3-propanediol; c. LAH; d. L-Selectride; e. preparative separation and chiral column.

Scheme 26

The protection of the ketone group in compound **119** followed by reduction with LAH and acid hydrolysis gave compound **120**, whose final reaction with L-Selectride provided the target **117**. On the other hand, the reaction of compound **119** with L-Selectride produced the reduction of keto group as well as a deformylation reaction leading to the corresponding demethylated analogue **121** (Scheme 27).

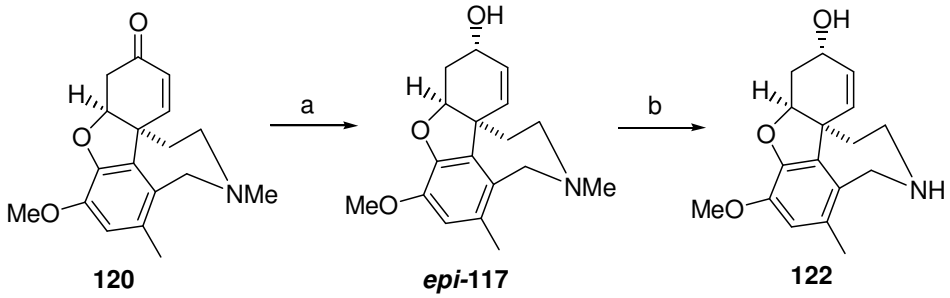


118 **119** **121** **120** **117**

Reagents and conditions. a. $K_3[Fe(CN)_6]$, K_2CO_3 (55%); b. i: propylene glycol, p-TsOH (73%), ii: $LiAlH_4$, iii: HCl (93%); c. L-Selectride.

Scheme 27

The stereoselective reduction of **120** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ afforded 1-methyl-*epi*-galathamine (*epi*-**117**), which was demethylated by using bis(1,1-dimethylethyl)azo-dicarboxylate to yield compound **122** (Scheme 28).

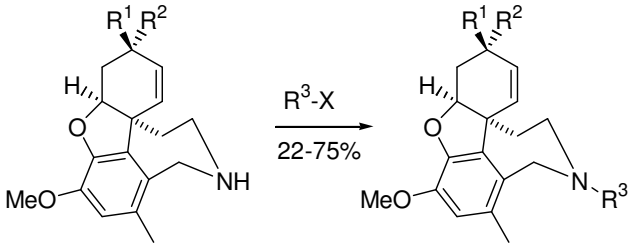


120 ***epi*-117** **122**

Reagents and conditions. a. $NaBH_4$, $CeCl_3 \cdot 7H_2O$ (67%); b. bis(1,1-dimethylethyl)azo-dicarboxylate (53%).

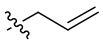
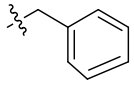
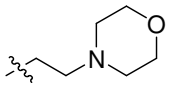
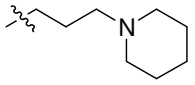
Scheme 28

The corresponding *N*-alkyl derivatives **123** and the quaternary ammonium salts **124** were obtained by alkylation of the appropriate derivatives, as shown in the Schemes 29 and 30.

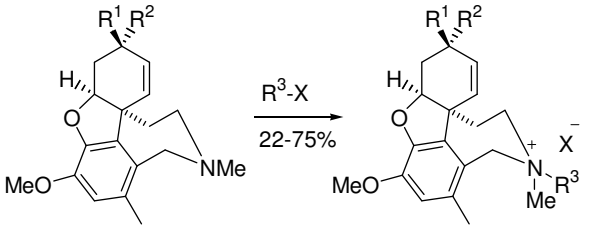


121 (R^1 = OH, R^2 = H)
122 (R^1 = H, R^2 = OH)

123a-d (R^1 = OH, R^2 = H)
123e (R^1 = H, R^2 = OH)

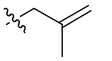
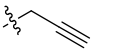
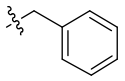
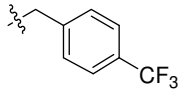
	R^3
a	
b	
c	
d,e	

Scheme 29



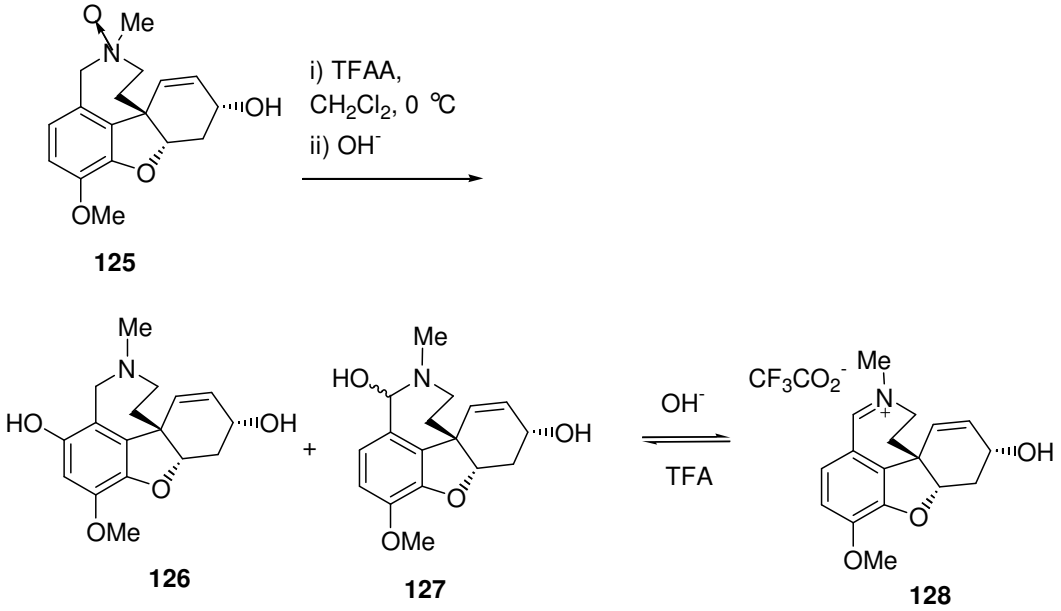
117 (R^1 = OH, R^2 = H)
***epi*-117** (R^1 = H, R^2 = OH)

124a-d (R^1 = OH, R^2 = H)
124a-f (R^1 = H, R^2 = OH)

	R^3	X
a		Cl
b		Br
c		Br
d		I
e		Br
f		Br

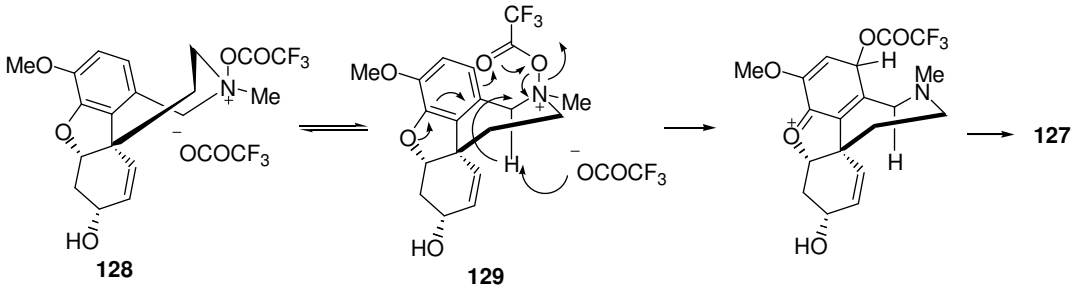
Scheme 30

Renko *et al.*[43] prepared new galanthamine derivatives from galanthamine *N*-oxide **125** through modified Polonovski reaction (Scheme 31). Thus, treatment of **125** with trifluoroacetic anhydride (TFAA), in dichloromethane at 0 ºC, followed by basic hydrolysis afforded the hydroxy-galathamine **126** and a mixture of α/β isomers of the carbinols **127**, which were dehydrated in TFA to give the corresponding iminium trifluoroacetate **128**. The unexpected compounds **127** were probably formed from the trifluoroacetoxyammonium salt **128** which is in equilibrium with **129** followed by abstraction of H9α. Oxygen transfer took place through the trifluoroacetoxy group with the participation of the furan oxygen lone pair (Scheme 32).



125 **126** **127** **128**

Scheme 31



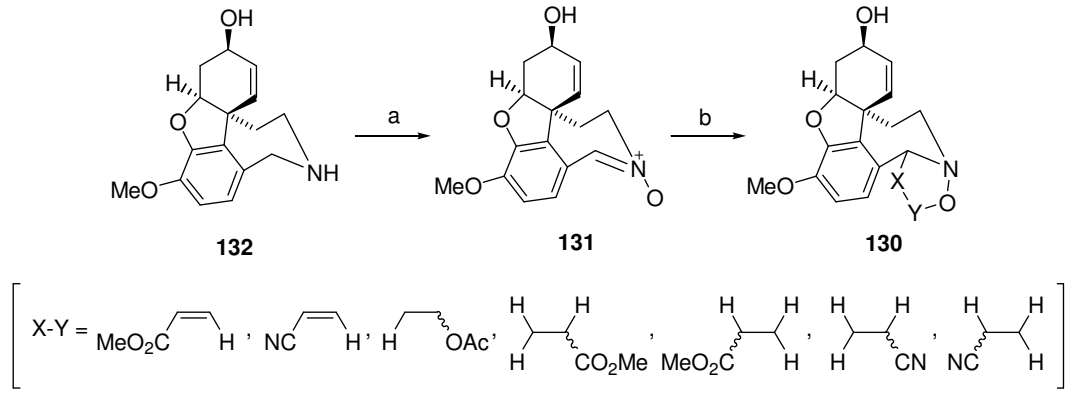
128 **129** **127**

Scheme 32

Fröhlich and co-workers synthesized a few examples of 4a,5,9,10-tetrahydro-6*H*,14a*H*-benzofuro-[3a,3,2-*ef*]isoxazolo[3,2-*a*][2]benzazepines **130** starting from galanthamine nitrone **131** (Scheme 33),[44] prepared by oxidation of nor-galanthamine **132** with H_2O_2 and catalytic amounts of SeO_2, which underwent 1,3-dipolar cycloaddition reaction with various dipolarophiles leading to the benzazepines **130**.

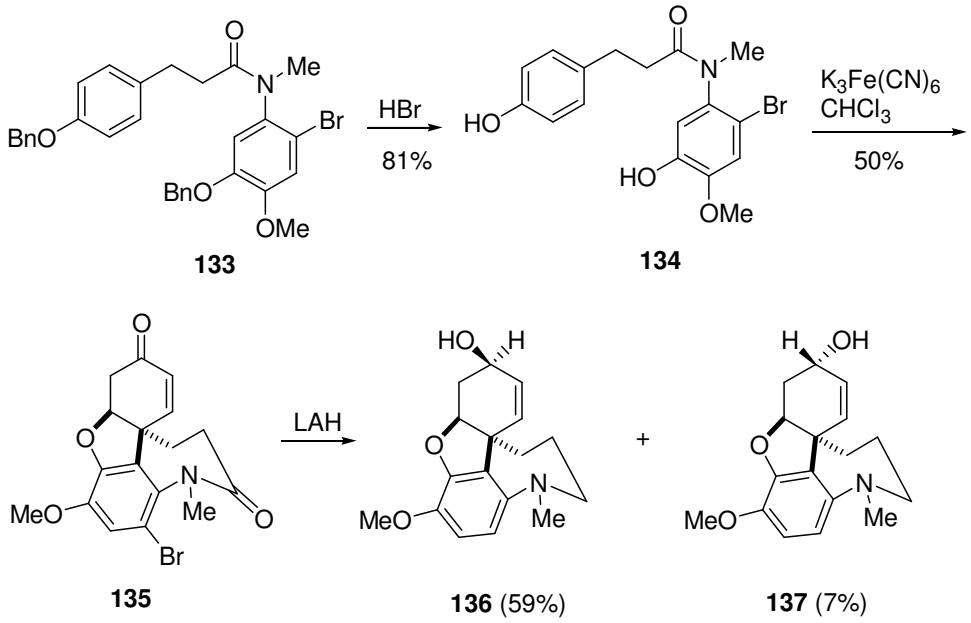
Carroll has described the synthesis of new galanthamine analogues bearing the 6*H*-benzofuro[3a,3,2-*e*,*f*][1]benzazepine and 6*H*-benzofuro[3a,3,2-*e*,*f*][3]benzazepine skeletons.[45] Starting from open-chain precursor **133**, the reaction with bromhydric acid gave diphenol **134**, whose treatment with potassium ferricyanide afforded the heterocyclic ring system **135** in moderate yield; finally, reduction with LAH gave

the expected analogues **136** and **137**, after cleavage of the carbon-bromine bond and unselective ketone reduction (Scheme 34).



Reagents and conditions. a. SeO_2/H_2O_2 (79%); b. methyl propiolate (100%); 2-propynenitrile (97%), ethynyl acetate (98%), methyl acrylate (99%), acrylonitrile (97%).

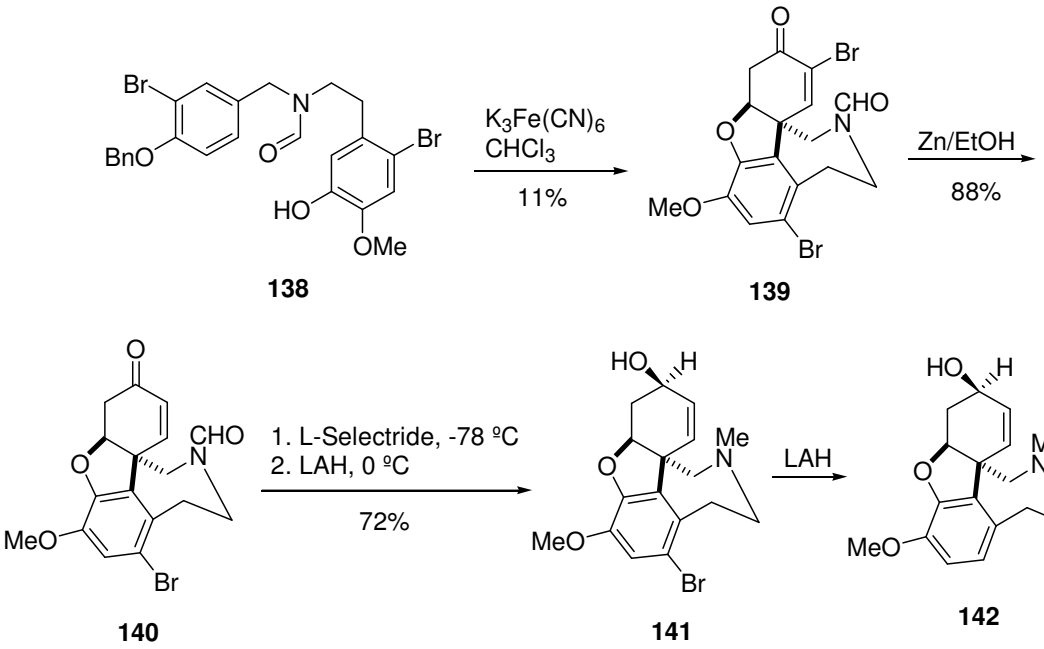
Scheme 33



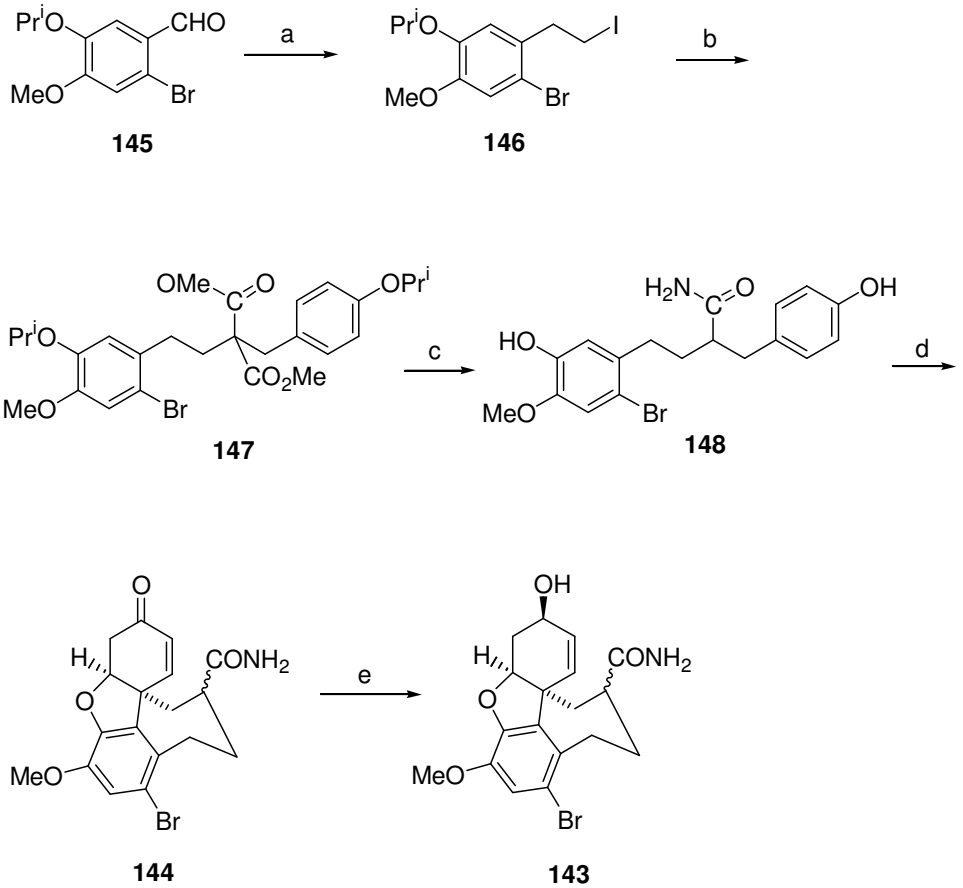
Scheme 34

Similarly, starting from precursor **138**, after reaction with potassium ferricyanide, compound **139** was isolated in poor yield; next, reduction with zinc gave the monobromide **140**; final reduction with L-Selectride afforded stereospecifically alcohol **141**, whose reduction with LAH provided galanthamine analogue **142** after cleavage of the carbon-bromine bond (Scheme 35).[45]

Interestingly, Treu and Jordis[46] reported the synthesis of carbocyclic galanthamine **143** from norbelladine analog **144** (Scheme 36). Aldehyde **145** was easily transformed into iodide **146**, which was coupled with ethyl malonate, followed by reaction with 1-(chloromethyl)-4-(1-methylethoxy)benzene yielding compound **147**, which was hydrolyzed, decarboxylated and converted into the key intermediate **148** by amidation with ammonia and subsequent deprotection of both phenolic groups. Finally, oxidative cyclization of **148** and treatment with L-Selectride gave the galanthamine derivative **143**.



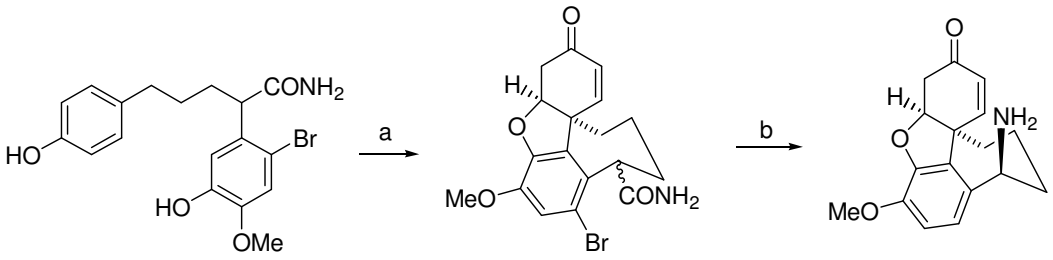
Scheme 35



Reagents and conditions. a. i: PPh_3CHOMe, KO*t*Bu, THF, 0 °C (85%), ii: aq HCl/THF, reflux, (98%), iv: $NaBH_4$, EtOH (99%), v: imidazole, I_2, PPh_3, (77%); b. i: dimethyl malonate, K_2CO_3, DMF (72%), ii: 1-(chloromethyl)-4-(1-methylethoxy)-benzene, K_2CO_3, DMF 80 °C (91%); c. i: 1) KOH, EtOH reflux, 2) H_3O^+, 3) 160 °C (84%), ii: 1) $(COCl)_2$, CH_2Cl_2 0 °C, 2) NH_3, (83%), iii: BCl_3, CH_2Cl_2 –78 °C, (86%); d. $K_3Fe(CN)_6$, K_2CO_3 (6%); e. L-Selectride (85%).

Scheme 36

The authors have used a similar synthetic approch in order to prepare other unnatural carbocyclic galanthamine analog **149** (Scheme 37).[47] Thus, from intermediate **150**, easily synthesized from commercial 3-(4'-hydroxyphenyl)-propionic acid and 1-bromo-2-cyanomethyl-5-methoxy-4-(1-methyloxy)benzene, a mixture of epimeric amides **151** were obtained and transformed into the desired amine **149** by using PIFA and subsequent treatment with Cu/Zn and $CaCl_2$.

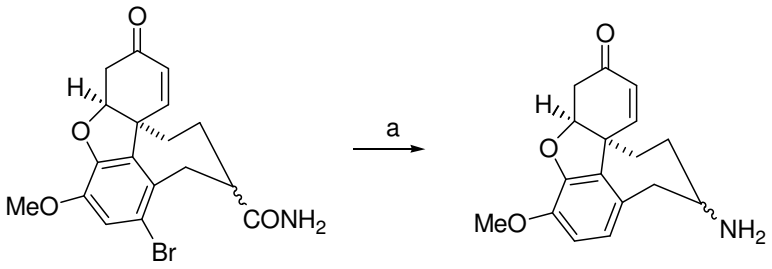


150 **151** **149**

Reagents and conditions. a. $K_3Fe(CN)_6$, K_2CO_3 (8%); b. i: L-Selectride (83%), ii: PIFA (58%), iii: Cu/Zn, $CaCl_2$ (78%).

Scheme 37

In the same way, amine **152** was synthesized from intermediate **153** by using a similar synthetic sequence (Scheme 38).[48] Although these compounds showed no AChE or butyrylcholinesterase (BuChE) inhibition, their evaluation allowed the authors to draw some pertinent conclusions about the binding mechanism for galanthamine, and valuable insights into the structure-activity relationships.



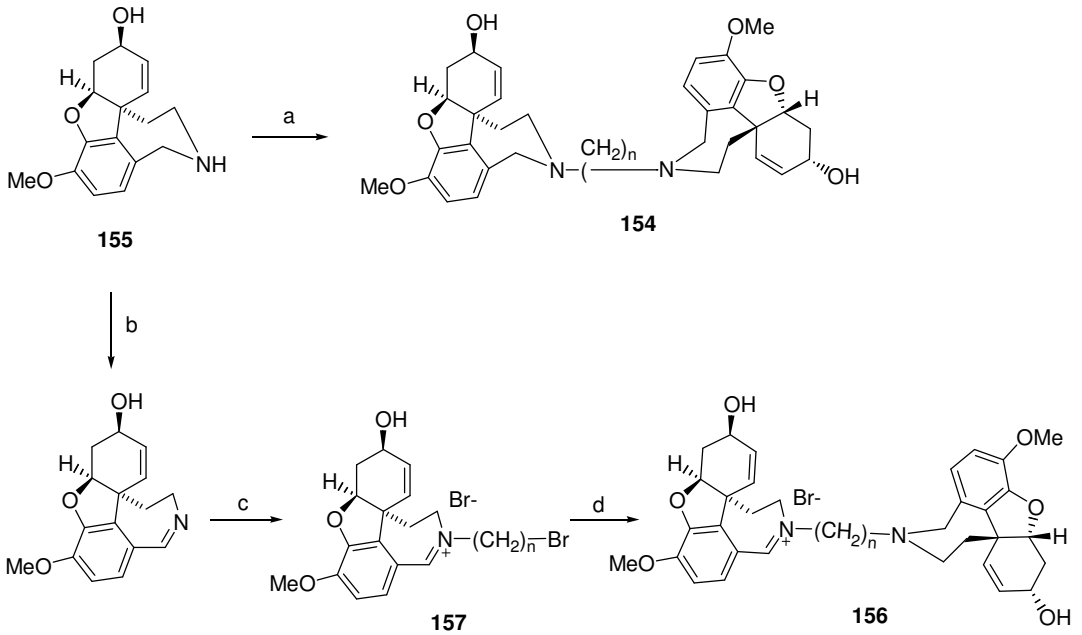
153 **152**

Reagents and conditions. a. i: L-Selectride (86%), ii: PIFA (75%), iii: Cu/Zn, $CaCl_2$ (59%).

Scheme 38

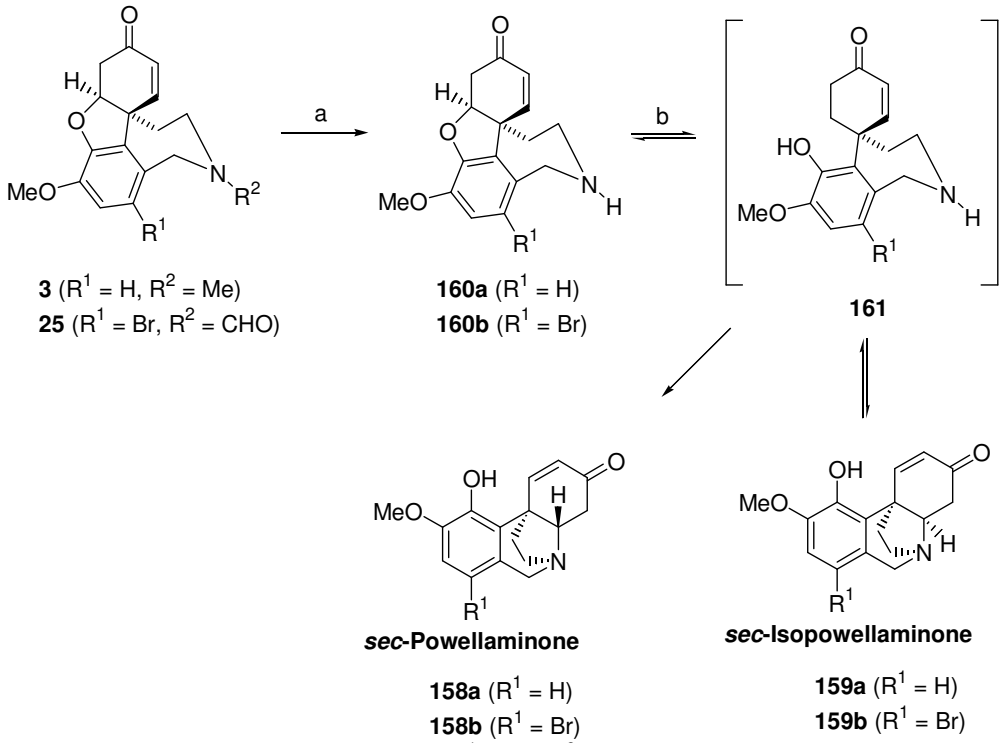
Guillou and co-workers[49] have synthesized two new series of AChE inhibitors with dimeric galanthamine structure, some of them with higher activity than the reported for galanthamine or tacrine. Thus, bis-galanthamines **154** were prepared from norgalanthamine **155** by alkylation with the corresponding 1,*n*-dibromoalkane, while their heterodimeric analogues **156** were synthesized by oxidation of **155** followed by alkylation giving the corresponding iminium salts **157**. Finally, coupling of norgalanthamine **155** with compounds **157** afforded the bis-galanthamines **156** with chemical yields in a range of 60–86% (Scheme 39).

sec-Powellaminone and *sec*-isopowellaminone derivatives **158** and **159** were synthesized when investigating the transformation of nor-narwedine analogues **160** in the presence of the mildly acidic catalyst such as $CaCl_2$ (Scheme 40).[50]



Reagents and conditions. a. $Br(CH_2)_nBr$, n = 6, 8, 10, Et_3N, CH_3CN, 25 °C; b. NBS, CH_3CN, 25 °C (70%); c. $Br(CH_2)_nBr$, n= 6, 8, 10, Et_3N, CH_3CN reflux; d. 155, Na_2CO_3, CH_3CN, 25 °C.

Scheme 39



3 (R^1 = H, R^2 = Me)
25 (R^1 = Br, R^2 = CHO)

158a (R^1 = H)
158b (R^1 = Br)

159a (R^1 = H)
159b (R^1 = Br)

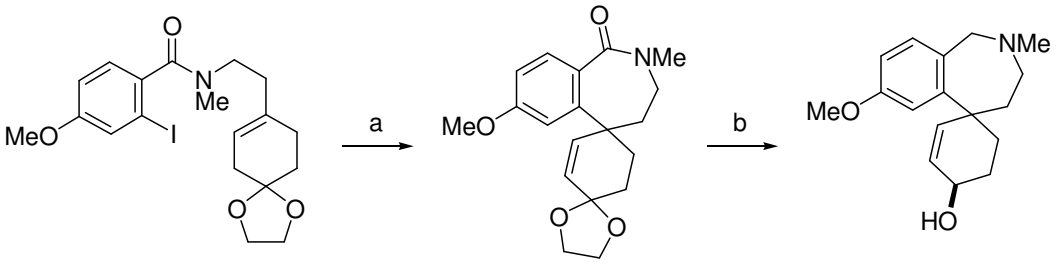
Reagents and conditions. a. from **3** (R^1 = H, R^2 = Me) i: m-CPBA, ii: $FeSO_4 \cdot 7H_2O$; from **25**(R^1 = Br, R^2 = CHO) cc. HCl, b. $CaCl_2$, EtOH reflux.

Scheme 40

Thus, compound **160b**, prepared from **25** by treatment with concentrated HCl, was transformed into derivative **159b**[40b] in a few seconds, while its analogue seco-powellaminone **158b** was only detected after one week reaction time. This fact was explained in terms of the more stable conformation to produce compound **159b** through an equilibrium process involving the tricyclic intermediate **161**. In the same

reaction conditions, nor-narwedine **160a**, obtained from compound **3** by oxidation using *m*-CPBA followed by treatment with $FeSO_4 \cdot 7H_2O$, provided a mixture of compounds **158a** and **159a**.

Spiro-cyclohexanebenzazepine (**162**)[51] is a galanthamine analogue lacking the benzofuran ring system. This is probably the reason of its weak inhibitory activity against AChE [IC_{50} 150 μM; compare with natural galanthamine (IC_{50} 2.4 μM) or tacrine (IC_{50} 0.5 μM)]. The synthesis of compound **162** has been described starting from advanced intermediate **163**, readily available by a series of routine transformations from *p*-anisaldehyde.[51] When compound **163** was submitted to standard Heck reaction conditions (Scheme 41) product **164** was isolated in 66% yield. The authors remarked that this is the first reported example of the direct construction of the seven-membered azepine ring in galanthamine by the Heck reaction. Finally, acid hydrolysis followed by stereoselective ketone reduction with L-Selectride and lactam reduction afforded the desired molecule **162**.

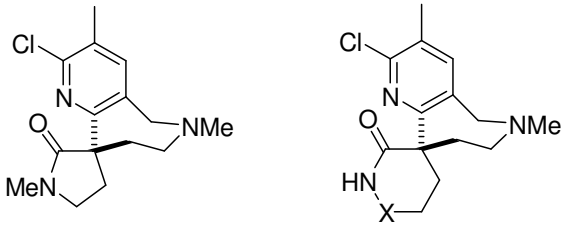


163 **164** **162**

Reagents and conditions. a. $Pd(OAc)_2$, Ph_3P, K_2CO_3, MeCN, 130 ºC, 35 h (66%); b. i: 1N HCl, MeOH, rt, 1 h (88%); ii: L-Selectride, THF, –78 ºC, 30 min (46%), iii: LAH, 1,4-dioxane, reflux, 2 days (66%).

Scheme 41

In a recent preliminary communication, Compernolle and co-workers have reported the synthesis and biological activity of a series of simplified galanthamine analogues (**165–167**) (Figure 3), as in the case of azepeine **162** (Schem 39), where the benzene ring has been replaced by a pyridine unit.[52] The crucial step in this synthetic approach relied on the intramolecular nucleophilic aromatic substitution (INAS) reaction of suitable functionalized 3-substituted 2-chloropyridines.



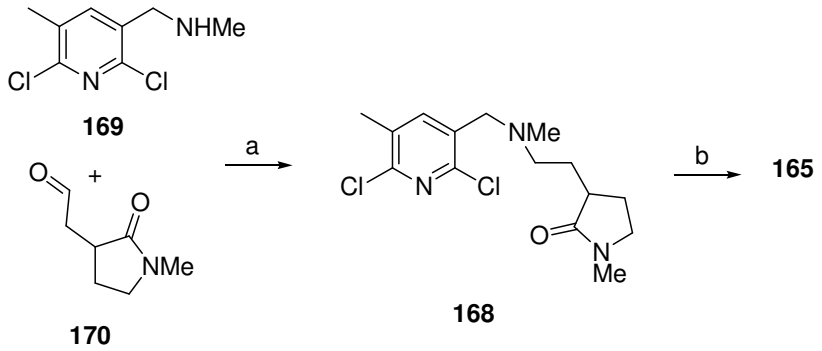
165

166: X = CH_2
167: X = CO

Figure 3

For compound **165**, and according to the general INAS strategy, the key intermediate was compound **168**, readily available in one step from simple precusors **169** and **170** (Scheme 42). This conversion could be achieved by applying microwave irradiation with $KN(SiMe_3)_2$ as a base in toluene; under these conditions compound **168** was isolated in 85% yield. However, this reaction seems to be very structure dependent, because the homologue of intermediate **166** with an additional carbon in the lactam ring did not afford the

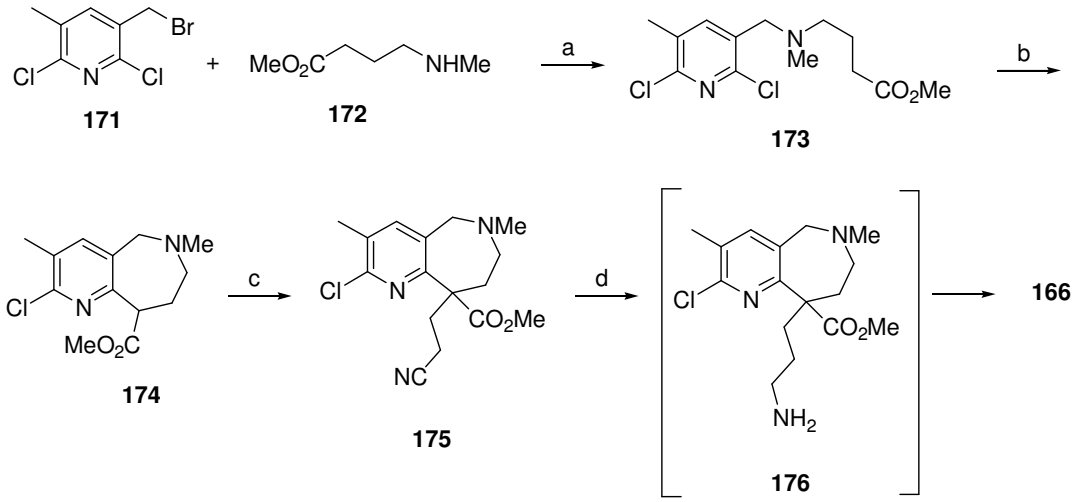
expected molecule, under the same experimental conditions. In view of the failure to produce the desired molecule, an alternative strategy was investigated.



Reagents and conditions. a. $NaCNBH_3$, MeOH, AcOH, rt, 15 min (85%),
b. $KN(SiMe_3)_2$, toluene, MWI (85%).

Scheme 42

As shown in Schemes 43 and 44, instead of forming the spirocyclic ring system by INAS in the final ring closure step, spirocyclic pyridoazepines **166** and **167** were formed by transformation of an appropriate bicyclic pyridoazepine. This intermediate can be formed by INAS of the corresponding 3-[(4-methoxy-4-oxobutyl)(methyl)amino]-substituted 2-chloropyridine.

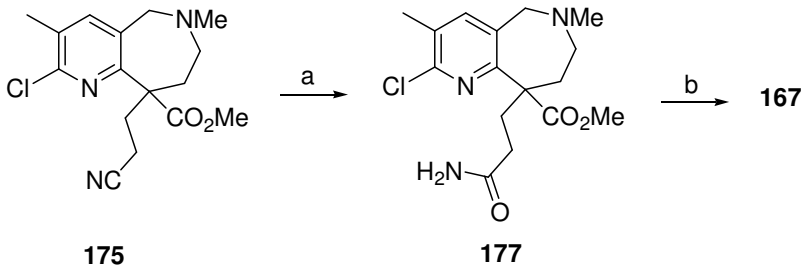


Reagents and conditions. a. Et_3N, MeOH, rt, 4 h (85%), b. i: $KN(SiMe_3)_2$, toluene, 80 ºC,
ii: NH_4Cl, 5 min (90%); c. i: KO*t*Bu, THF, rt, 10 min, ii: acrylonitrile, *t*BuOH, rt, 15 min (61%);
d. i: $CoCl_2$, $NaBH_4$, MeOH, rt, overnight, ii: MeOH, reflux, overnight (57%).

Scheme 43

As shown in Scheme 43, the reaction of 3-(bromomethyl)pyridine **171** with methyl 4-(methylamino)butanonate (**172**) gave compound **173**, which smoothly underwent the INAS reaction to form the pyridoazepine **174** under conventional heating conditions. To construct the spirolactam ring of the target compounds **166** and **167**, the authors planned a Michael reaction of pyridozepine **174** with either acrylonitrile, acrylamide or methyl acrylate. Finally, acrylonitrile was the successful choice affording the key intermediate **175** in 61% yield. Next, reduction of the nitrile group with sodium borohydride in the presence of cobalt(II) chloride provided amine **176**, which underwent ring closure in refluxing methanol to

give product **166**. Finally, target molecule **167** was obtained from the same intermediate **175** *via* amide **177** after treatment with potassium *t*-butoxide in *t*-butanol (Scheme 44).

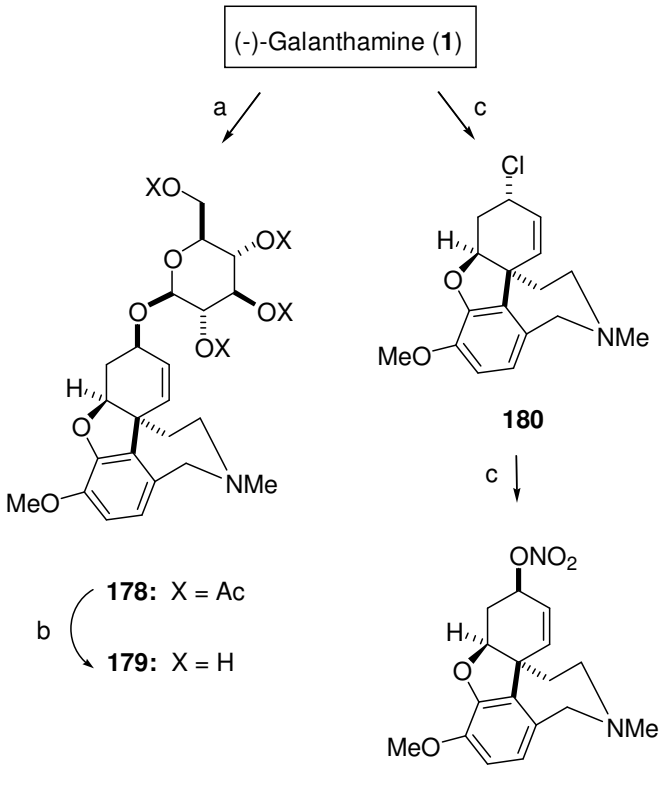


175 **177**

Reagents and conditions. a. $MeSO_3H$, toluene, 100 ºC, 2 h (83%),
b. i: KO*t*Bu, THF, rt, 1 h, ii: NH_4Cl, H_2O (60%).

Scheme 44

Compounds **165–167** (Figure 3) were tested for their inhibition activity against AChE, showing significant K_I values in the range 70–514 μM, but lower than the value obtained for galanthamine (K_I 3 μM).



Reagents and conditions: a. 2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl bromide, AgOTf, CH_2Cl_2, –10 ºC;
b. 0.1M NaOMe, MeOH; c. $SOCl_2$, toluene, 55 ºC; c. $AgNO_3$, CH_3CN, rt, 48 h

Scheme 45

An italian group has reported on the synthesis and biological activity of some new galanthamine analogues in order to evaluate the role of the hydroxyl group at C-6. Accordingly, two galanthamine derivatives (**178** and **179**) have been synthesized incorporating a glucosyl motif in the natural product, and a nitroxy galanthamine analogue (**180**) has been obtained as a potential NO donor.[53]

The synthetic sequence was very simple, and afforded the target compounds in good yields. As shown, reaction of (-)-galanthamine (**1**) with commercial 2,3.4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide under typical glycosylation reaction conditions afforded stereoselectively the β-isomer **178**, which on treatment with sodium methoxide in methanol gave the fully deprotected 6-*O*-glucolylated galanthamnine analogue **179** (Scheme 45). The reaction of (-)-galanthamine (**1**) with thionyl chloride afforded the corresponding chloride (**180**) with the inverse configuration at C-6, which after reaction with silver nitrate produced the target analogue **181** (Scheme 43).

Unfortunately, only compound **181** proved to be an AChE inhibitor showing a IC_{50} (45.09 μM) value significantly lower to the measured for (-)-galanthamine [IC_{50} (5.86 μM)].[53]

4. Conclusions and perspectives

Galanthamine is an alkaloid that has attracted both the interest of organic chemists and pharmacologists, in a collaborative effort aimed at designing, preparing and evaluating novel biologically active compounds for AD treatment. In this account we have shown how an apparently complex molecule such as galanthamine can be very efficiently prepared in a few steps, in racemic or in enantiomerically pure form, by using either the phenol oxidative coupling reaction or an intramolecular Heck reaction. In spite of the obvious reported advances on this subject and the present sophisticated state of the art concerning the synthesis of galanthamine, in the future new synthetic strategies are sought to accomplish the challenging synthesis of this molecule. In adition, we think and wait that more and new efforts to prepare synthetically accesible analogues of galanthamine with improved biological profiles for the treatment of Alzheimer's disease will be documented.

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GENERATION OF NITROSO SPECIES AND THEIR USE AS DIENOPHILES IN THE HETERO DIELS ALDER REACTION

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Abstract. *Acylnitroso and nitroso dienophiles participate in hetero Diels Alder cycloadditions when reacted with dienes. This process constitutes an important means to introduce heteroatoms in an all carbon framework. Recently, several mild methods of generation were reported allowing the synthetic chemist using nitroso species for the preparation of stereo defined small molecules and complex natural products. Aim of the present review is to furnish the reader with an update of the most recent findings and applications.*

Contents

1. Introduction

The Diels-Alder reaction emerged as a key step in organic synthesis as in one step two new C-C bonds are formed in a stereoselective fashion. The scope of reaction is wide and several enantioselective methodologies have been developed.[1] The hetero Diels Alder (HDA) is an important class of reactions that allows incorporating heteroatoms (O, N, S) in a carbon framework.[2] In recent past, the HDA reaction of nitroso dienophiles and dienes has been extensively studied.[3,4] We would like here to furnish the reader with an update of the most recent findings together with some notable synthetic applications.

Acylnitroso species **1** and **2**, α-chloronitroso **3**, arylnitroso **4** and iminonitroso species **5** have been repeatedly described as efficient dienophiles. A discussion on species **1–5** could not begin without an analysis of their reactivity (Figure 1), that correlates with the electron-withdrawing character of the group attached. For example, nitroso formate esters **1** and acylnitroso compounds **2** are the most reactive dienophiles and could only be generated *in situ*. On the contrary, some of the α-chloronitroso **3**, arylnitroso **4**

and iminonitroso **5** are stable and could be isolated and stored. In compounds **4–5** conjugation stabilised the nitroso moiety.

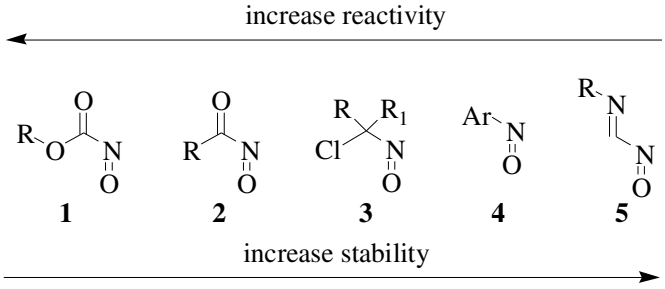
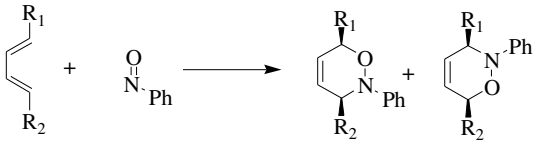


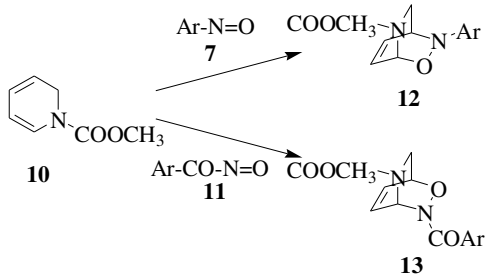
Figure 1

The HDA reaction of nitroso species **1–5** with dienes is a concerted process that occurs with complete stereoselectivity.[3c,4] For example, when nitrosobenzene **7** was reacted with a 1,3-diene of general formula **6**, the corresponding 1,4-*cis*-3,6-dihydro-1,2-oxazines **8** and **9** were obtained in good yields (Scheme 1).[5] Additionally, when the diene component was electronically dissymmetric, the reaction occurred with high regioselectivity.



Scheme 1

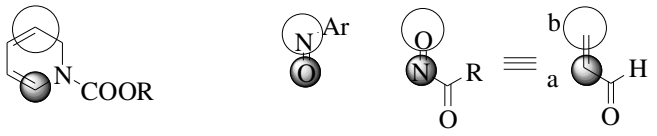
Arylnitroso **4** and acylnitroso **2** displayed an opposite regioselectivity when reacted with dissymmetric dienes. For example, the reaction of 1,2-dihydropyridine **10** with nitrosobenzene **7** gave regioisomer **12** only and in high isolated yield.[6] Conversely, the reaction of **10** with benzoylnitroso **11** gave exclusively regioisomer **13** (Scheme 2).[7]



Scheme 2

This result could be explained considering the shape of the FMO in arylnitroso **4** and acylnitroso **2** (Figure 2) and assuming the reaction to occur through an overlap of the HOMO (diene) with the LUMO (dienophile).[8] The LUMO of species **4** is characterized by a larger orbital coefficient on the *N*-atom. This could be explained taking in consideration the difference of electronegativity between nitrogen and oxygen. On the contrary, the LUMO of acylnitroso species **2** presents a larger orbital coefficient on the oxygen. Here, conjugation with the acyl group renders the *O*-terminus of the nitroso electron deficient. A similar effect is

observed in α,β-unsaturated carbonyls **14** that display a high electrophilic character at their β position (Figure 2).



10 **4** **2** **14**

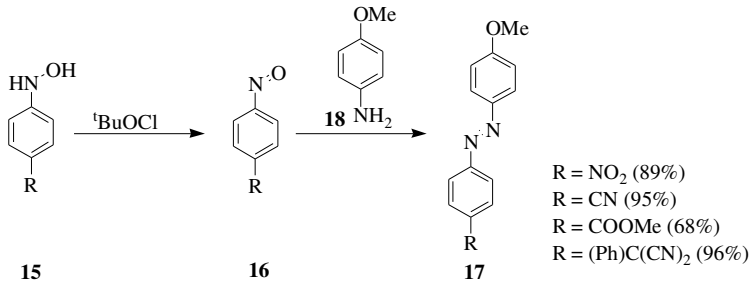
HOMO **LUMO** **LUMO** **LUMO**

Arylnitroso Acylnitroso

Figure 2

2. Arylnitroso dienophiles

Arylnitroso species **16** (Scheme 3) are stable compounds that could be isolated and stored for long time. Compounds **16** were firstly prepared from the corresponding arylhydroxylamine **15**, a reaction that runs under the catalysis of $Mo(O)-(O_2)_2(H_2O)(hmpa)$ and in the presence of H_2O_2.[9] Later, pyridinium chlorochromate was reported as an efficient reagent for the conversion of **15** to **16**.[10] Considering that heterogeneous oxidations frequently required long reaction times and often lead to formation of side products, newer oxidation methods have been developed running in homogeneous phase. Nowadays, the conversion of **15** to **16** is achieved by treatment of the reactant with *tert*-butyl hypochlorite.[11] This oxidation was particularly efficient and a full conversion of **15** was observed minutes after the addition of the oxidant. The yields calculated by means of a subsequent Mills coupling of **16** with amine **18** were generally high (Scheme 3).

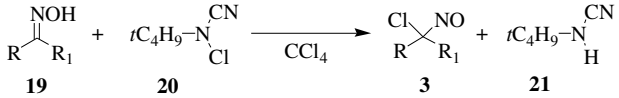


15 **16** **17**

Scheme 3

3. α-Chloronitroso dienophiles

α-Chloronitroso **3** (Scheme 4) are among the first nitroso dienophiles used.[12] Generally, these species were poorly stable and of consequence their use required low temperature and their generation realised *in situ*. However, specific kinds of α-chloronitroso species were described as stable compounds and were prepared in good yields.[12] The syntheses made use of chlorine,[13] aqueous hypochlorous acid,[14] *N*-halo-compounds[15] or an alkyl hypochlorite[16] as the oxidant. In recent past, a new method has been developed for the oxidation of ketoximes **19** that used *N*-*tert*-butyl-*N*-chlorocyanamide **20** as the oxidant (Scheme 4).[17]



19 **20** **3** (85-96%) **21**

Scheme 4

The use of oxidant **20** allowed isolating desired **3** in high yield and required shorter reaction times (< 1 min). In addition, the side product **21** could be recycled to **20** for further use.

Terent'ev *et al.* described the oxidation of ketoximes **22** and **24** using aqueous H_2O_2/HCl in dichloromethane (Scheme 5).[18] In this procedure, a dichloromethane solution of **22a–d** or **24a–c** was firstly treated with conc. HCl and then with 37% H_2O_2. The desired α-chloronitroso **23a–d** and **25a–c** were obtained in excellent yields (up to 94%) and in short reaction times (*ca.* 20 minutes).

22a, R = H, n = 7
22b, R = CH_3, n = 1
22c, R = *t*-Bu, n = 1
22d, R = H, n = 10

23a (94%)
23b (79%)
23c (84%)
23d (89%)

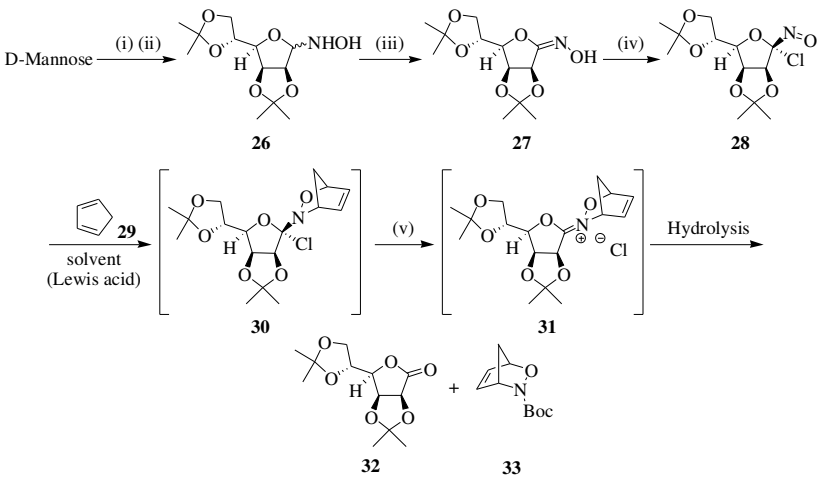
24a, R_1 = *i*Pr
24b, R_1 = Bu
24c, R_1 = C_5H_{11}

25a (78%)
25b (87%)
25c (88%)

Reagents: (i) aq. H_2O_2/HCl/DCM, 20 min., 40 °C.

Scheme 5

Miller *et al.* carried out extensive studies on the HDA reaction of chiral chloronitroso **28** that was prepared from D-mannose (Scheme 6).[19]



Reagents: (i) acetone, P_2O_5, $Ca(OH)_2$, carbon; (ii) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, reflux; (iii) MnO_2, MeOH (70%, three steps); (iv) *t*BuOCl, EtOH; (v) Boc_2O, $NaHCO_3$.

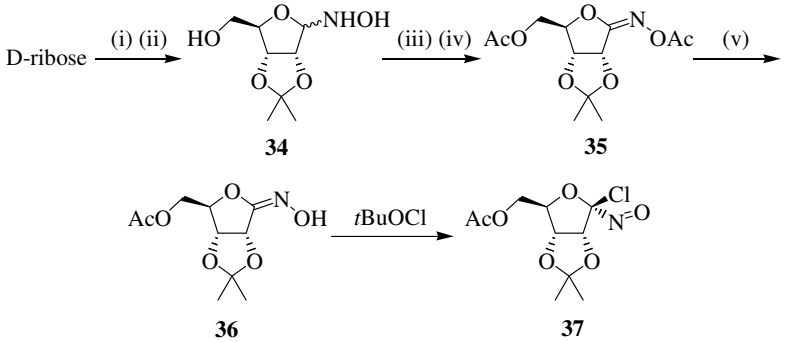
Scheme 6

D-Mannose was firstly reacted with acetone in the presence of acid and then treated with hydroxylamine to afford derivative **26**. Subsequent oxidation of **26** with MnO_2 furnished ketoxime **27** that in turn was converted to α-chloronitroso **28** by reaction with ^{t}BuOCl. The yields for the latter step were excellent (83% yield after recrystallization). Compound **28** was reacted with cyclopentadiene **29** to afford desired cycloadduct **30** under several reaction conditions. In particular, the effect of solvent polarity, amount and nature of the acid employed were studied. A set of optimised conditions was identified employing toluene as the solvent and titanium salts as the catalyst (Table 1). Treatment of **30** with $(Boc)_2O$ gave desired oxazine **33** in high yields and good enantioselectivity along with lactone **32** that could be recovered and used to regenerate **28**.

Table 1.

Solvent	Lewis acid (eq.)	Yield of **33** (%)	ee (%)
THF	Et_2AlCl (0.2)	25	73
Toluene	-	52	75
Toluene	Et_2AlCl (0.2)	61	84
Toluene	$Ti(O\textit{i}\text{-}Pr)_3Cl$ (0.3)	76	78
Toluene	$Ti(O\textit{i}\text{-}Pr)_4$/D-DET (1.0)	80	75

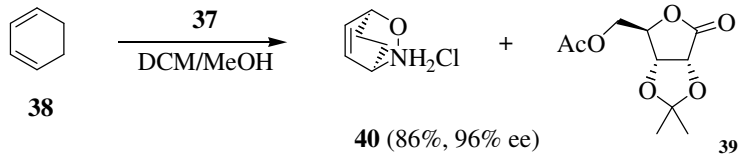
Defoin and co-workers prepared α-chloronitroso **37** in six steps from D-ribose (Scheme 7).[20] Initially, D-ribose was treated with acetone and P_2O_5 and then with hydroxylamine to furnish compound **34**. The hydroxylamine in **34** was oxidised and acetylated to give **35**. In turn, compound **35** was submitted to selective hydrolysis and the resulting ketoxime **36** converted to **37** by reaction with ^{t}BuOCl. Importantly, the stereochemistry of the α-chloronitroso moiety in **37** (Scheme 7) was opposite to the one in **28** (Scheme 6).

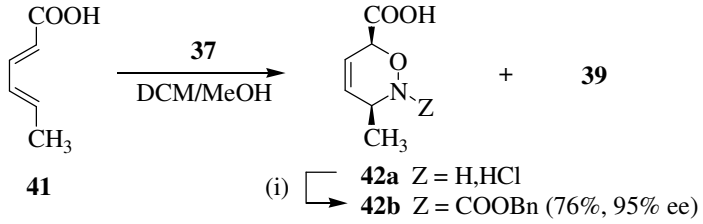


Reagents: (i) acetone, P_2O_5, $Ca(OH)_2$, carbon; (ii) $NH_2OH{\cdot}HCl$, $EtOH/H_2O$, reflux; (iii) $NaIO_4$, NaOAc, $EtOH/H_2O$, reflux; (iv) AcO_2, Py; (v) $NaHCO_3$, EtOH, reflux.

Scheme 7

Nitroso **37** was reacted with cyclic diene **38** and acyclic diene **41**. The reaction of **37** with cyclohexadiene **38** furnished adduct **40** in high yield and enantioselectivity. Acyclic diene **41** behaved similarly giving high yields of enantioenriched **42** (Scheme 8). Lactone **39** was recovered and used to prepare cyclic oxime **36**.

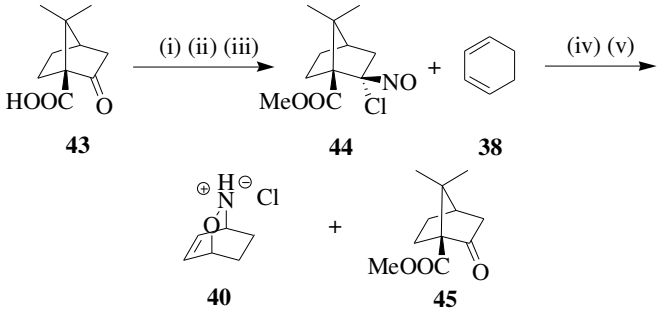




Reagents: (i) $ClCOOBn/NaHCO_3/H_2O$, then dry HCl/MeOH

Scheme 8

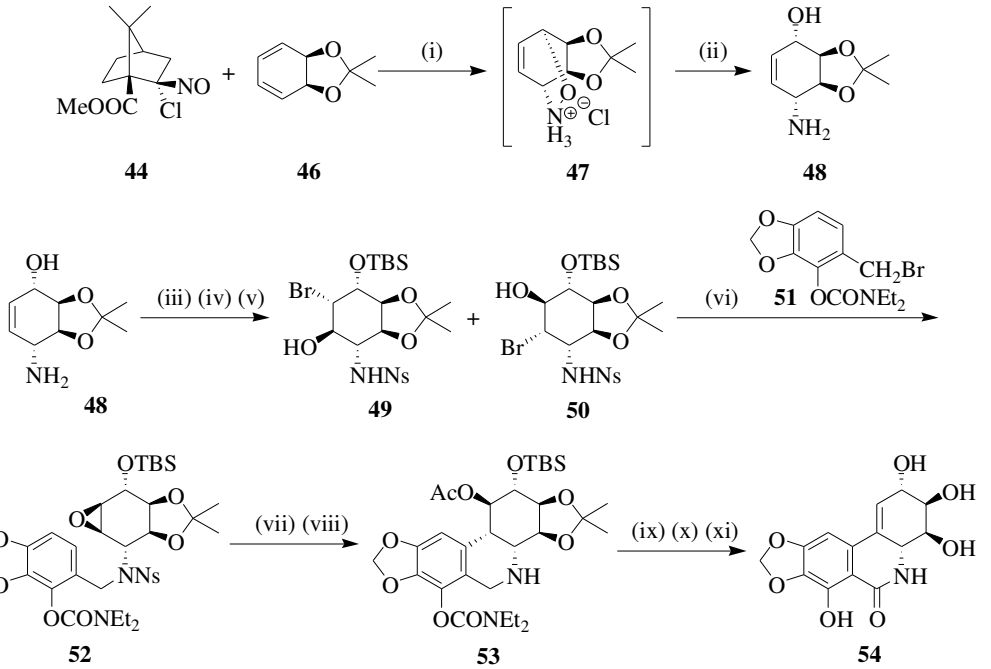
Yan and co-workers prepared α-chloronitroso **44** in three steps from ketopinic acid **43** (Scheme 9).[21] The synthesis entailed esterification of acid **43** using thyonil chloride in MeOH, followed by treatment with hydroxylamine and oxidation by ^{t}BuOCl. Compound **44** was obtained in 88% overall yield. Compound **44** reacted with 1,3-cyclohexadiene **38** efficiently to give **40** in good yield (88%) and enantioselectivity (>98% ee).



Reagents: (i) $SOCl_2$, MeOH; (ii) $NH_2OH{\cdot}HCl$, MeOH, NaOAc; (iii) *t*BuOCl, DCM; (iv) DCM, 0 °C; (v) *i*PrOH/H_2O.

Scheme 9

Compound **44** was employed to synthesise alkaloid (+)-Narciclasine **54** (Scheme 10).[22] Cycloaddition of **44** and diene **46** afforded chloride salt **47** which was converted to **48** using Al(Hg). Acetonide **48** was used to prepare (+)-Narciclasine **54**. Hence, compounds **49,50** were prepared by protecting the amino alcohol moiety, then reacting the alkene with NBS. Reaction of **49,50** with pyperonyl bromide **51** in the presence of K_2CO_3 led to compound **52**.



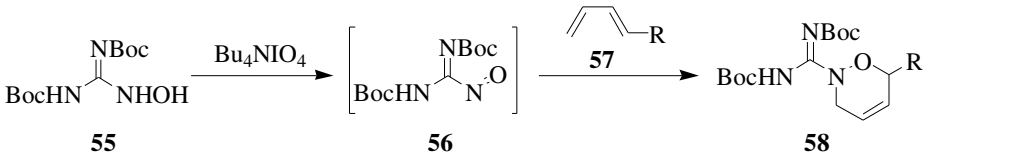
Reagents: (i) DCM, 0 to 25 °C; (ii) Al(Hg), MeCN, 86% (two steps); (iii) NsCl, Et_3N, CH_3CN; (iv) TBSCl, DBU (78%, two steps); (v) NBS, H_2O/acetone (98%); (vi) K_2CO_3, CH_3CN, 60 °C (88%); (vii) $SnCl_4$ (20mol %), DCM then Ac_2O, K_2CO_3 (98%); (viii) $HSCH_2COOH$, LiOH, DMF (78%); (ix) Boc_2O, CH_3CN then $RuCl_3$, $NaIO_4$, H_2O (67%); (x) DBU, benzene, 70 °C (96%); (xi) HCOOH, THF, 60 °C then concentration, $LiAlH_4$, THF (65%).

Scheme 10

Exposure of **52** to $SnCl_4$ followed by addition of Ac_2O and final treatment with mercaptoacetic acid in an alkaline ambient gave free amine **53**. Compound **53** was then reacted with $(Boc)_2O$ and $NaIO_4/RuCl_3$ to convert the secondary amine to a lactam. Final deprotection of the hydroxyl groups gave **54**.

4. Iminonitroso dienophiles

Iminonitroso derivates displayed a lower reactivity compared to acylnitroso species. The reactivity of iminonitroso species can be augmented by attaching an appropriated electron withdrawing group. This usually lowers the energy of the $LUMO_{(nitroso)}$ and renders the HDA reaction with a diene faster. Batey and Miller reported a high level of regioselectivity in HDA reactions of iminonitroso derivates **56** with dienes (Scheme 11).[23] Species **56** was obtained by oxidation of parent guanidine **55** using Bu_4NIO_4. Species **56** reacted with unsymmetrical dienes **57** to give preferentially compounds **58**. This regioselectivity is similar to the one observed for acylnitroso species and predicted by calculations of the energy of the possible transition states.[24]

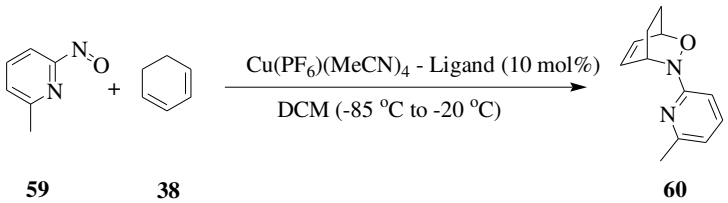


55 **56** **58**

R = OMe (86% yield; >98:2 ratio)
R = Et (75% yield; 85:15 ratio)

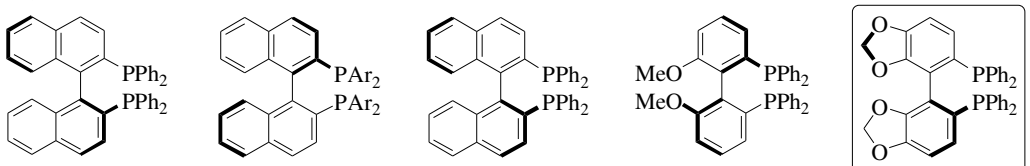
Scheme 11

Yamamoto studied the cycloaddition of nitrosopyridine **59** and cyclohexadiene **38** in the presence of Cu^I and chiral ligand **61–65** (Scheme 12).[25]



59 **38** **60**

Ligand:



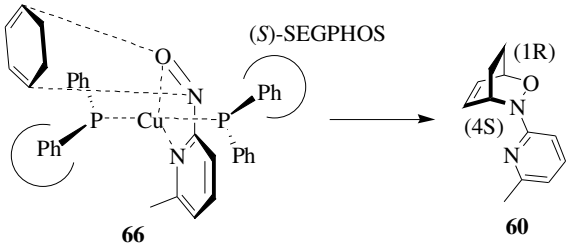
61 (*S*)-BINAP (87% ee) (**73.5**°)

62 (*R*)-BINAP (Ar = Ph) (87% ee) (R)-BINAP (Ar = 4-MeC_6H_4) (86% ee)

63 (*R*)-H_8-BINAP (67% ee)

64 (*R*)-MeO-BIPHEP (90% ee) (**68.9**°)

65 (*S*)-SEGPHOS (92% ee) (**65.0**°)

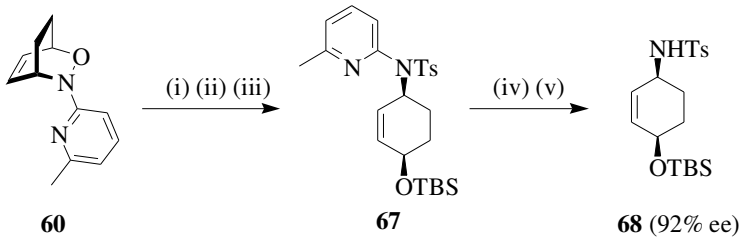


66 **60**

Scheme 12

Reaction of **59** with **38** run in the presence of 10 mol% of $Cu(PF_6)(MeCN)_4$ and chiral ligands **61–65** providing adduct **60** in quantitative yield and excellent enantioselectivity (67–92% ee). In this process, the dihedral angle of the phosphine ligand played a key role in determining the enantioselectivity: phosphines possessing a narrow dihedral angle gave a greater enantioselectivity.[26] The best result was obtained using (*S*)-SEGPHOS **65** (92% ee) that had the minimal dihedral angle of 65.0º. Yamamoto explained the preferential formation of stereoisomer **60** considering that in complex **66** one face of the nitroso **59** was selectively shielded.

Compound **60** was then converted to alcohol **68** in five steps (Scheme 13). The transformation of **60** to **67** entailed cleavage of the N-O bond using $Mo(CO)_6$ and $NaBH_4$, followed by TBSCl protection of the alcohol and tosylation of the amine. Intermediate **67** was then used to access desired **68** by pyridine *N*-methylation and alkaline hydrolysis. Importantly, the conversion of **60** to **68** occurred without loss of enantioselectivity.

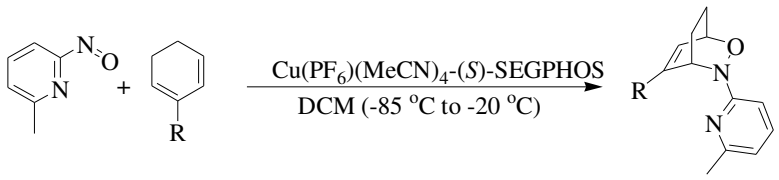


60 **67** **68** (92% ee)

Reagents: (i) $Mo(CO)_6$, $NaBH_4$, CH_3CN/H_2O; (ii) TBSCl, TEA, DMAP, CH_3CN; (iii) Ts_2O, TEA, DCM; (iv) MeOTf, DCM; (v) NaOH, $MeOH/H_2O$.

Scheme 13

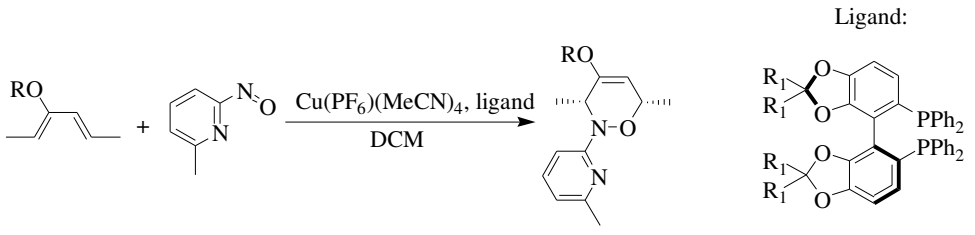
The same authors reported the reaction of **60** with cyclic unsymmetrical dienes **69a–c** using $Cu(PF_6)(MeCN)_4$-(*S*)-SEGPHOS as the catalyst (Scheme 14). These reactions proceeded with total control of regioselectivity giving adducts **70a–c** in excellent yields and enantioselectivity.



60 **69a** R = Me; **69b** R = Ph; **69c** R = OTBS

70a (>99%, 94% ee); **70b** (>99%, 97% ee); **70c** (95%, 92% ee)

Scheme 14



71a, R = TMS; **71b**, R = TBS; **71c,** R = TIPS **60** **72a-c** **73**, R_1= H; **74**, R_1 = F

Scheme 15

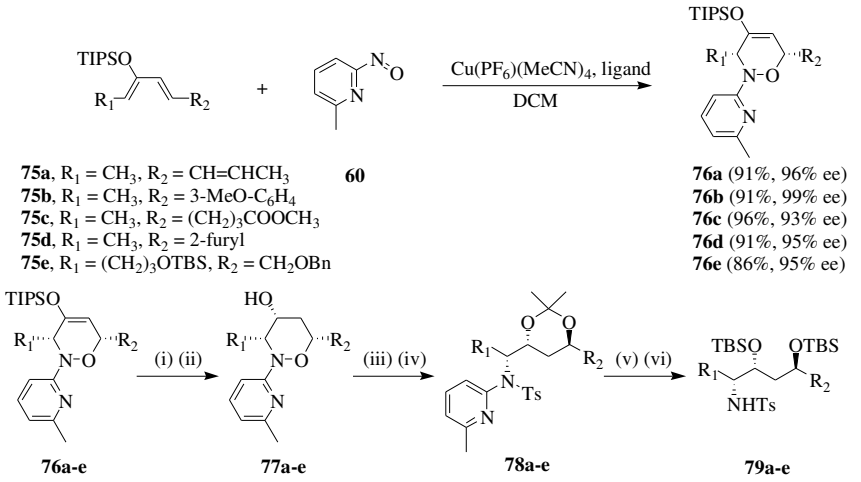
The reaction of iminonitroso **60** in the presence of Cu^{I} and (*S*)-SEGPHOS showed a remarkable versatility and could be applied to the synthesis of adducts **72a–c** (Scheme 15). Hence reaction of **60** with acyclic dienes **71a–c** afforded **72a–c** in high yields, regioselectivity and enantioselectivity.[27] When 6-methyl-2-nitroso-pyridine **60** was reacted with (2*Z*,4*E*)-3-substituted-silyloxy-2,4-hexadienes **71a–c** in the presence of $Cu(PF_6)(MeCN)_4$-(*S*)-SEGPHOS **73** or $Cu(PF_6)(MeCN)_4$-(*S*)-DIFLUOROPHOS **74** (10 mol%) the corresponding cycloadducts **71a–c** were obtained with variable enantioselectivity (16% to >99% ee).

The authors showed that the enantioselectivity is severely improved by increasing the size of the silyl group (R) present on the diene. Small (R) groups gave low enantioselectivity while larger (R) groups as TIPS ensured an optimal level of enantioselectivity (Table 2).

Table 2.

Diene	Ligand	Yield of **72a** (%)	ee (%)
60	**73**	86	16
60	**73**	88	84
60	**73**	93	98
60	**74**	95	>99

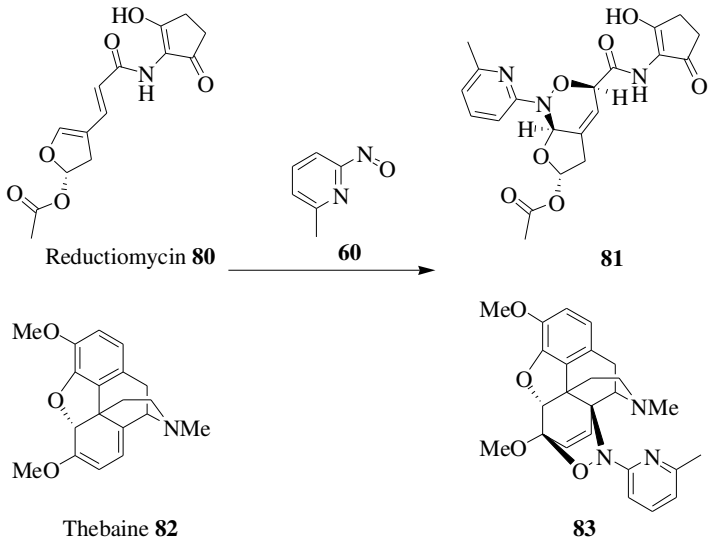
The scope of this reaction was finally shown by reacting several functionalized dienes **75a–e** (Scheme 16). Alkyl, aryl, heteroaryl substituted dienes and trienes gave the expected cycloadducts **76a–e** in high yields and enantioselectivity. Compounds **76a–e** were converted in six steps into the respective protected amino alcohols **79a–e** which are fragments present in many important natural products.[28] Hydrolysis of the silyl group in **76a–e** using TBAF/AcOH and reduction of ketone gave the corresponding alcohols **77a–e** as a single diastereoisomer. Reductive cleavage of N-O bond using H_2 with Pd/C followed by protection of the diol and tosylation with Ts_2O afforded ketals **78a–e**. Deprotection of the acetonide in **78a–e**, successive treatment with TBSOTf and final removal of pyridine ring using MeOTf and NaOH furnished the protected amino alcohols **79a–e**.



Reagents: (i) TBAF/AcOH; (ii) $NaBH_4$ (up to 98%, two steps); (iii) Pd/C, H_2, then 2,2-dimethoxypropane, TsOH; (iv) Ts_2O, diethylisopropyamine, 1,2-dichloroethane; (v) TsOH, MeOH, then TBSOTf, 2,6-lutidine, DCM; (vi) MeOTf, DCM, then 10 N KOH, MeOH.

Scheme 16

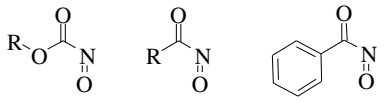
Iminonitroso Diels-Alder reactions were also used as an efficient method to obtain natural products derivatives.[29] Cyclic and acyclic dienes reacted efficiently with 6-methyl-2-nitrosopyridine **60** (Scheme 17). For example, Reductiomycin **80** reacted with **60** in THF at 0 °C to give cycloadduct **81** as a single isomer (yield >90%). Analgesic Thebaine **82** reacted similarly to give compound **83** in 99% yield and as a single isomer.



Scheme 17

5. Acylnitroso dienophiles

Acylnitroso dienophiles **1** and **2** (Figure 3) in which the nitroso moiety is bound to an electron withdrawing carbonyl are the least stable and therefore the most reactive nitroso dienophiles. For this reason, acylnitroso of general formula **1** and **2** could only be generated *in situ* and their presence revealed by trapping with a diene. Compounds **1** and **2** are usually short living. It has been observed, for example, that the lifetime of benzoylnitroso **84** is *ca.* 1ms.[30] Nevertheless, these compounds have been widely used as efficient hetero dienophiles for the synthesis of 1,2 oxazines.[31]



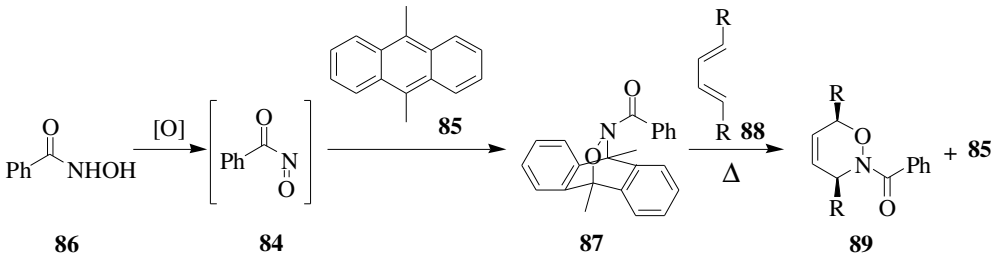
1 **2** **84**

Figure 3

5.1. Preparation of acylnitroso species

The study on the generation of acylnitroso species was pioneered by Kirby.[5] Acylnitroso species are obtained from the oxidation of the parent hydroxamic acid. This reaction employs organic oxidants such as periodate salts,[5,32] Dess-Martin periodinane,[32] NMO-nitrile oxides,[33] Swern-Moffat reagent,[34] and *t*-BuOOH[35] as well as inorganic reagents such as PCC[10] and hypochlorite.[36] These reagents are often not compatible with oxidant sensitive functionalities. In order to overcome this problem, a strategy was devised to obtain a masked form of nitroso **2** (Scheme 18). Hence, acylnitroso species **84** were generated from parent **86** and subsequently trapped by 9,10-dimethylanthracene **85**. The resulting adduct **87** was shown to release

84 by heating. Considering that adducts **87** could be isolated and stored and that generation of **84** from **87** does not require the use of an oxidant, this strategy increased dramatically the importance of the nitroso Diels Alder in organic synthesis, allowing the generation of acylnitroso in the presence of sensitive groups.

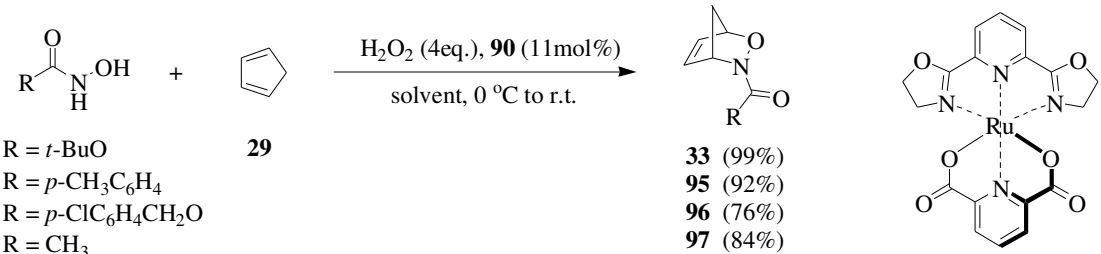


86 **84** **87** **89**

Scheme 18

The methodologies relying on oxidants suffered from the drawback of leaving considerable amounts of inorganic or organic side products. In order to obviate this, several groups have investigated the use of hydrogen peroxide as the terminal oxidant as water would be formed as the only side product.[37]

In this context, Iwasa *et al.* reported the oxidation of hydroxamic acids **86** and **91–94** using hydrogen peroxide (Scheme 19).[38] The process was catalysed by 11 mol% of Ru^{II}(pybox-dh)(pydic) **90**, used only small excesses of hydrogen peroxide and afforded desired adducts **33** and **95–98** in good isolated yields. Particularly reactive hydroximate **91** (R = ^{t}BuO) was efficiently oxidised at 1 mol% catalyst loading affording **33** in 99% yield. Considering that the reaction was carried out at minimal scale (*ca.* 24 mg of **91**) and involved extraction and chromatographic purification of **33**, this was a particularly remarkable result.



91 R = *t*-BuO
92 R = *p*-$CH_3C_6H_4$
93 R = *p*-$ClC_6H_4CH_2O$
94 R = CH_3
86 R = C_6H_5

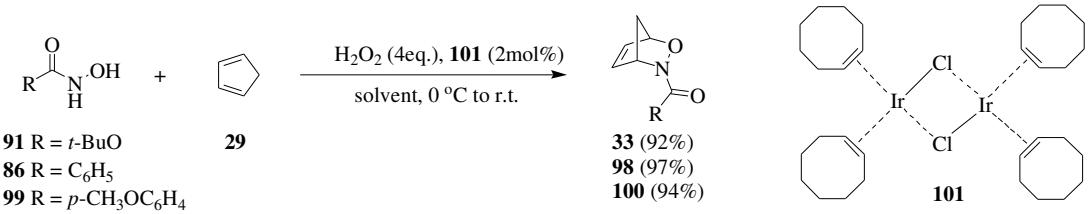
29

33 (99%)
95 (92%)
96 (76%)
97 (84%)
98 (90%)

90

Scheme 19

Complex $[Ir(coe)_2Cl]_2$ **101** has been described as an efficient catalyst for the oxidation of **86**, **91** and **99** using hydrogen peroxide as the terminal oxidant (Scheme 20).[39] This methodology allowed the preparation of 1,2-oxazines **33** and **98** and **100** in high isolated yields.



91 R = *t*-BuO
86 R = C_6H_5
99 R = *p*-$CH_3OC_6H_4$

29

33 (92%)
98 (97%)
100 (94%)

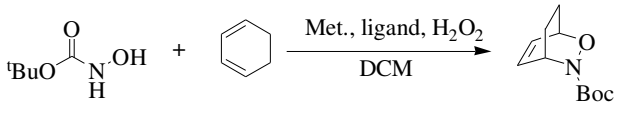
101

Scheme 20

Cu^I salts were also found to catalyse the oxidation of hydroxamic acids to acylnitroso species. Nicholas reported the oxidation of hydroxamic acid **91** occurring in the presence of 10 mol% of CuBr and

dimethyl sulphide.[40] This reaction required high temperatures and long reaction times and furnished the hetero Diels Alder adduct in moderate yields.

Adamo and Bruschi have recently reported a screening of metal catalysts for the oxidation of hydroxamic acid **91** using hydrogen peroxide as the oxidant[41] (Scheme 21). In this study, Ru^{III}, Cu^{I}, Cu^{II}, and Fe^{III} salts were found to be efficient catalysts. In particular, it was observed that the presence of organic ligands imparted a dramatic acceleration to the oxidation process. For this reason, the effect of simple amines, aminoalcohols and diamines on the oxidation rate was studied.



91 **38** **102**

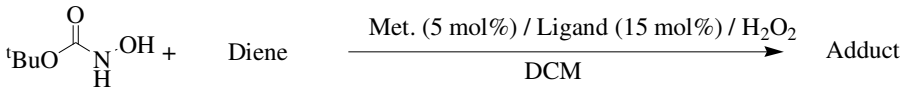
Scheme 21

Data collected identified a set of optimal conditions that employed 5 mol% of Ru^{III}, Cu^{I}, Cu^{II} and Fe^{III} and amines or aminoalcohols as the ligand. Typically, the oxidation of **91** was carried out in the presence of a metal and a ligand and hydrogen peroxide used as the terminal oxidant. The reaction was monitored measuring the yield of cycloadduct **102**. These oxidations were remarkably fast: typically full conversion of **91** was observed within 20–30 minutes when the reaction was carried out at room temperature (Table 3).

Table 3.

Metal (5 mol%)	Ligand (15 mol%)	Time (min.)	Yield of **102** (%)
Ru^{III}	Et_3N	30	76
Cu^{I}	$HOCH_2CH_2NH_2$	30	83
Cu^{II}	$HOCH_2CH_2NH_2$	20	84
Fe^{III}	$NH_2CH_2CH_2NH_2$	20	76

The scope of these reactions was briefly studied (Scheme 22). It was demonstrated that cyclic and acyclic dienes gave the corresponding adducts in similar good yields (Table 4). The reactions described were practical and executable from truly commercially starting materials and afforded synthetically useful products in good to excellent yields. Compared with existing methodologies, these procedures afforded cycloadducts in similar yields, but employing reagents in a 1:1 ratio and a reduced catalyst loading. Remarkably, the crude reaction mixture showed the hetero Diels-Alder adduct as the only compound present: this renders the reactions described ideal for the development of tandem processes.



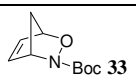
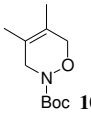
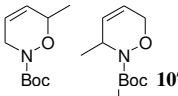
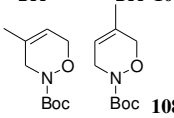
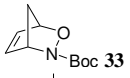
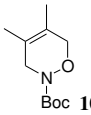
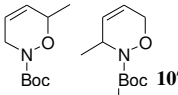
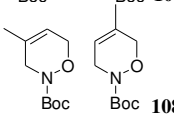
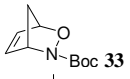
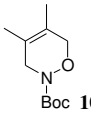
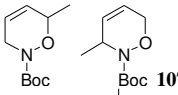
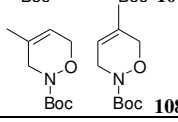
91 **29, 103-105** **33, 106-108**

Scheme 22

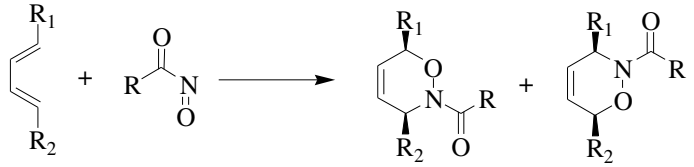
5.2. Applications in organic synthesis

The Diels Alder reaction of acyl nitroso species with dienophiles has provided entry into a number of important ring systems. The early Kirby's studies established that the use of acylnitroso dienophiles **2** offers an efficient route to access the 3,6-dyhydro-1,2-oxazines **109** and **110** (Scheme 23).[5]

Table 4.

Catalyst	Diene	Product	Yield %[a]	Time (m)
Cu^{I} / $HOCH_2CH_2NH_2$	 **29**	 **33**	63	20
Cu^{I} / $HOCH_2CH_2NH_2$	 **103**	 **106**	74	30
Cu^{I} / $HOCH_2CH_2NH_2$	 **104**	 **107a/b**	70[b]	30
Cu^{I} / $HOCH_2CH_2NH_2$	 **105**	 **108a/b**	58[d]	30
Cu^{II} / $HOCH_2CH_2NH_2$	 **29**	 **33**	64	20
Cu^{II} / $HOCH_2CH_2NH_2$	 **103**	 **106**	70	30
Cu^{II} / $HOCH_2CH_2NH_2$	 **104**	 **107a/b**	54[b]	30
Cu^{II} / $HOCH_2CH_2NH_2$	 **105**	 **108a/b**	65[d]	30
Fe^{III} / $H_2NCH_2CH_2NH_2$	 **29**	 **33**	78	20
Fe^{III} / $H_2NCH_2CH_2NH_2$	 **103**	 **106**	76	30
Fe^{III} / $H_2NCH_2CH_2NH_2$	 **104**	 **107a/b**	54[b]	30
Fe^{III} / $H_2NCH_2CH_2NH_2$	 **105**	 **108a/b**	64[d]	30

[a]Isolated yield after chromatography. [b]Obtained as a 1:1.6 mixture of regioisomers. [c]Obtained as a 1:3 mixture of diastereoisomers. [d]Obtained as 1:1 mixture of regioisomers.

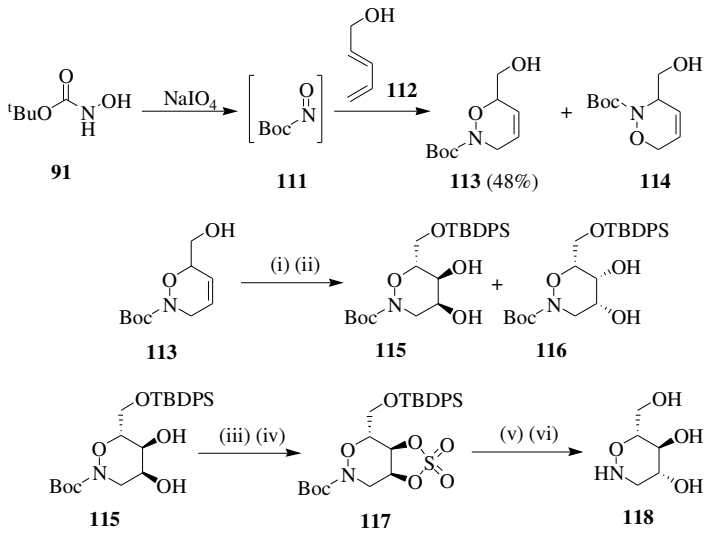


6 **2** **109** **110**

Scheme 23

Elaboration of **109** or **110** provided a means to prepare sugar analogues. Bach has shown that 3,6-dyhydro-1,2-oxazines **113,114** could be prepared by [4+2] cycloaddition of **91** and 2,4-pentadienol **112** (Scheme 24).[42] 3,6-Dyhydro-1,2-oxazines **113,114** were obtained as a mixture of diastereoisomers in a 2:1 ratio. Compound **113** was converted to 1-azaglucose analogue **118** in six steps. Initially, the alcohol in **113** was protected using TBDPSCl and then the alkene dihydroxylated to give diols **115,116** (**115**:**116** = 95:5).

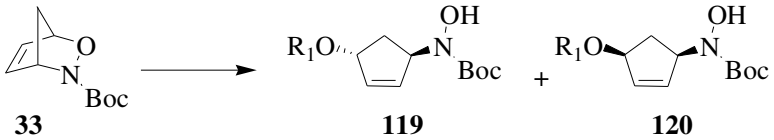
Diol **115** was subsequently converted to cyclic sulphate **117**. Compound **117** was finally deprotected to give 1-azaglucose analogue **118**. Compound **118** showed high affinity for β-glucosidases with a K_i of 60 μM.[42]



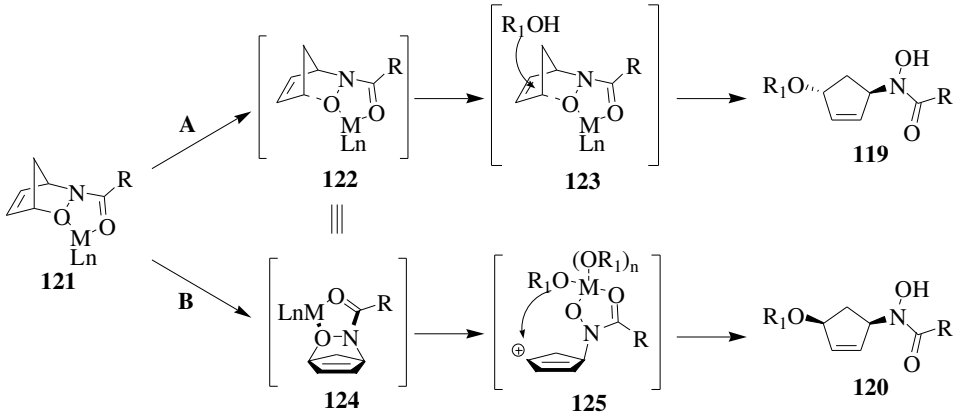
Reagents: (i) TBDPSCl, imidazol, DMF (90%); (ii) OsO_4, acetone/H_2O/*t*-BuOH; (iii) $SOCl_2$, Et_3N, DCM (67%); (iv) RuO_4, $NaIO_4$, $CHCl_3$/CH_3CN/H_2O (67%); (v) NaOBz, DMF; (vi) H_2SO_4, H_2O/dioxane, then Na_2CO_3, MeOH (50% two steps).

Scheme 24

Miller found that treatment of adducts **33** with an appropriated Lewis acids gave *anti*-1,4 and *syn*-1,4-hydroxamic acid **119** or **120** that differed for the stereochemistry of the 1,3 aminoalcohol moiety (Scheme 25).[43] Two protocols were established to obtain **119** or **120** in a selective fashion. It was found that the solvent had a major impact on the distribution of products. Treatment of cycloadducts **33** with Fe^{III} or Cu^{II} in alcohol induced ring opening to afford predominantly *anti*-1,4-hydroxamic acids **119**, while treatment of **33** with Cu^{II} in toluene afforded *syn*-1,4-hydroxamic acids **120**. Compounds **119** and **120** were obtained in yields up to 95%.



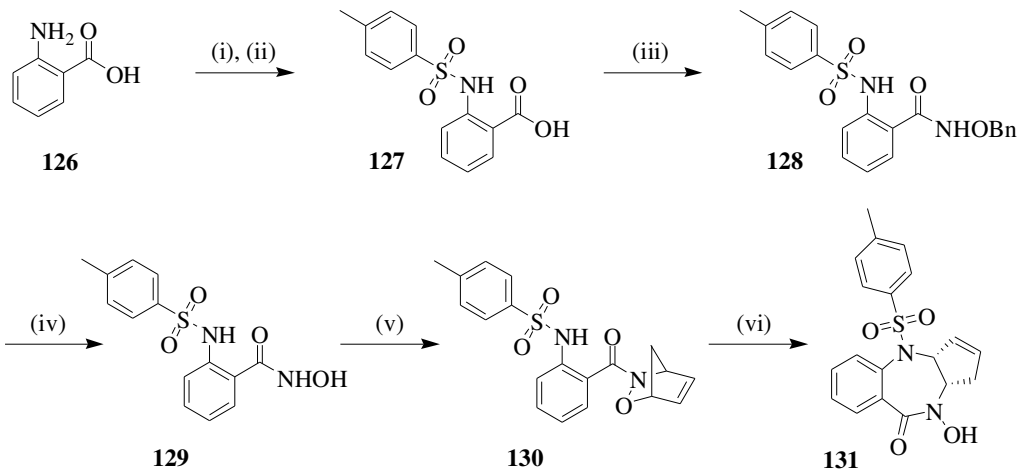
Scheme 25



Scheme 26

The switch in diastereoselection could be explained as follows. 1,2-Oxazines are good ligands that could efficiently form complex as **121** when reacted with Lewis acids (Scheme 26). The fate of complex **121** depended on the nature of the media. In small nucleophilic solvents (such as methanol) an S_n2 pathway prevailed and an inversion of configuration was observed in *anti* aminoalcohol **119** (Scheme 26, path A). When the nucleophile was large an S_n1 pathway dominated and the reaction produced carbocation **125**. The hydroxymate metal complex in **125** guided the nucleophile addition and the overall process occurred with retention of configuration (Scheme 26, path B).

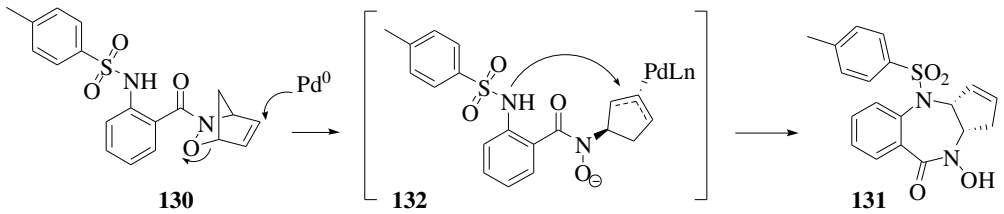
Miller reported a synthesis of the medicinally relevant 1,4-benzodiazepine core *via* nitroso Diels Alder (Scheme 27).[44] In this synthesis, an appropriate functionalized cycloadduct **130** was prepared starting from anthranilic acid **126** (Scheme 27). The synthesis of **130** started with a selective tosylation to obtain *N*-tosyl anthranilic acid **127** in two steps. Compound **127** was then reacted with EDC (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide) and coupled with *O*-benzyl hydroxylamine to provide *O*-benzyl hydroxamate **128**. Removal of benzyl group using hydrogenolysis gave hydroxamic acid **129** in quantitative yield. Oxidation of **129** in presence of cyclopentadiene gave desired *N*-tosyl cycloadduct **130**. Treatment of **130** with Pd^0 provided benzodiazepine **131** in modest yield (20%).



Reagents: **A** (i) TsCl, Na_2CO_3, H_2O, 60 °C; (ii) HCl (69% two steps); (iii) $BnONH_2$, EDC, DCM (81%); (iv) H_2, Pd/C, MeOH (99%); (v) cyclopentadiene, $NaIO_4$, MeOH, H_2O, 79%; (vi) $Pd(PPh_3)_4$, THF, reflux (20%). **B** (i) 3-nitrobenzenesulfonyl chloride, Na_2CO_3, H_2O, 60 °C; (ii) HCl (64% two steps); (iii) $TBSONH_2$, EDC, DCM; (iv) HCl, MeOH; (v) cyclopentadiene, $NaIO_4$, MeOH, H_2O, (81% three steps); (vi) $Pd(PPh_3)_4$, THF, reflux (38%).

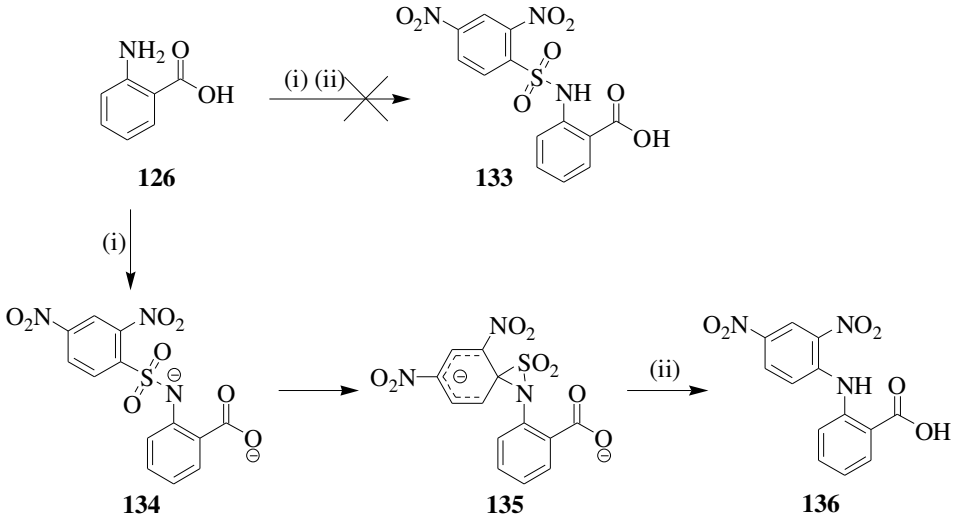
Scheme 27

The conversion of **130** to **131** proceeded *via* nucleophilic attack of Pd^0 to cycloadduct **130** (Scheme 28). The resulting π-allyl complex in **132** reacted intramolecularly with the sulfonamide nitrogen, resulting in the formation of **131**.



Scheme 28

It was observed that the pK_a of the sulphonamide group had an effect on the reaction yields. These increased with the decrease of nitrogen pK_a. Consequently, the presence of two nitro group on the sulphonamide ring ensured high yields. The inclusion of additional nitro groups imposed a revision of the synthetic strategy. Anthranilic acid **126** reacted with a 2,4-dinitrobenzenesulfonyl chloride and base to give the aniline derivative **136** (Scheme 29).



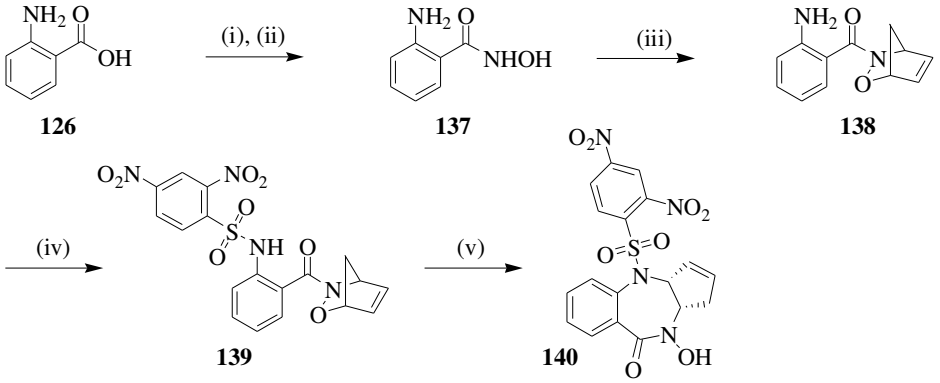
126 **133** **134** **135** **136**

Reagents: (i) 2,4-dinitrobenzenesulfonyl chloride, Na_2CO_3, H_2O, 60 ^oC; (ii) HCl.

Scheme 29

In this synthesis, the presence of two nitro groups favoured an intramolecular rearrangement of the sulphonamide moiety. Hence reaction of **126** with base generated anion **134** that underwent rearrangement to **136** through intermediate **135** (Scheme 29).

Hydroxamic acid **137** was prepared reacting antranilic acid **126** and $BnONH_2$ followed by hydrogenation (Scheme 30). Compound **137** was oxidised to its nitroso intermediate using $NaIO_4$ which was trapped by cyclopentadiene into cycloadduct **138**. Treatment of **138** with 2,4-dinitrobenzenesulfonyl chloride and pyridine afforded compound **139** in moderate yield. Exposure of **139** to Pd^0 furnished 1,4-benzo-diazepine **140** in 56% yield.

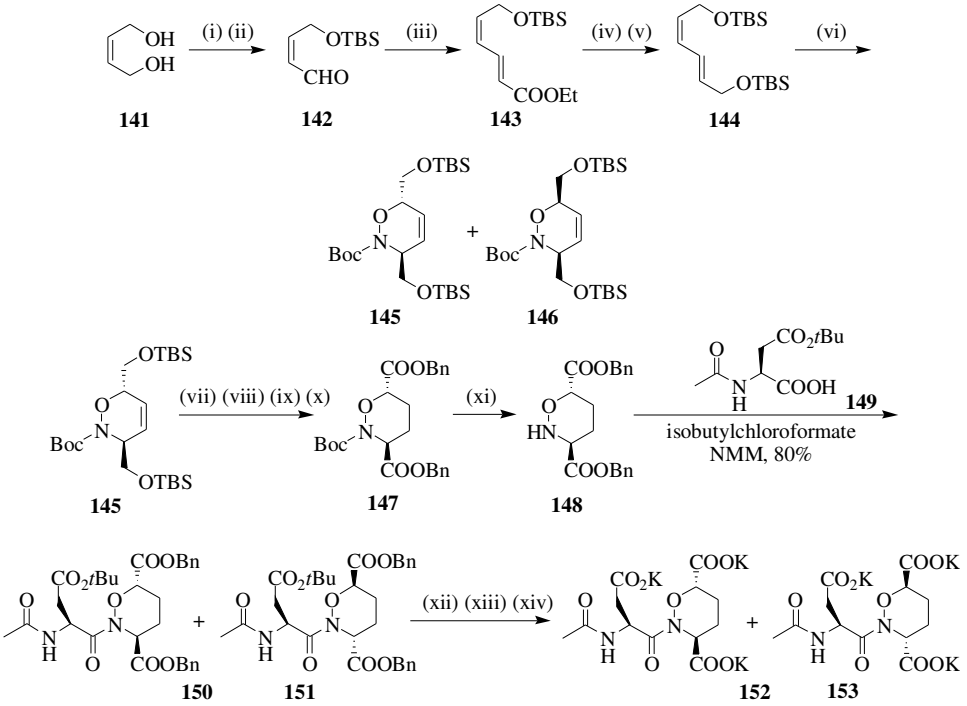


126 **137** **138** **139** **140**

Reagents: (i) $BnONH_2$, EDC, DCM (71%); (ii) H_2, Pd/C, MeOH (99%); (iii) cyclopentadiene, $NaIO_4$, MeOH, H_2O, (58%); (iv) 2,4-dinitrobenzesulfonyl chloride, pyridine, DCM (56%); (v) $Pd(PPh_3)_4$, THF, reflux (56%).

Scheme 30

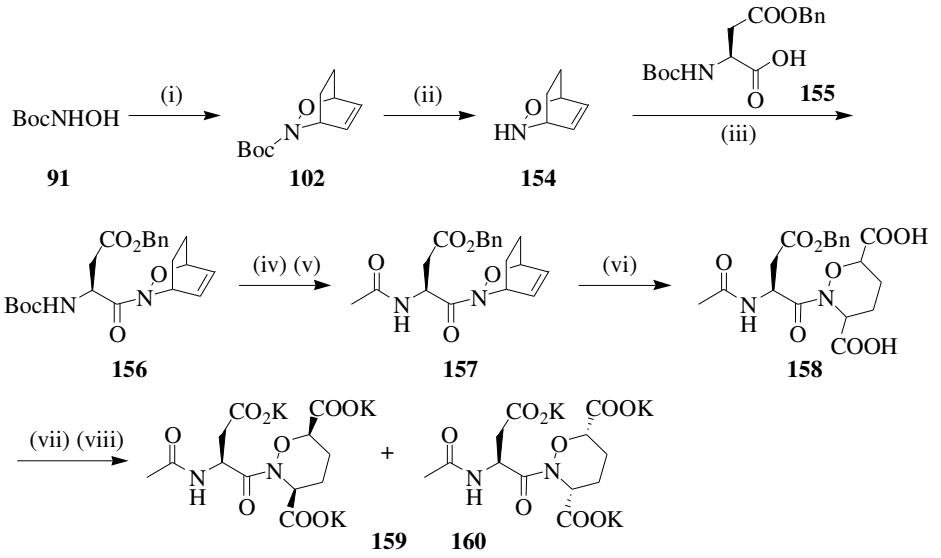
Peptidomimetic scaffolds **152,153** showed remarkable activity as inhibitors of *N*-acetylated-α-linked-acidic-dipeptidase (NAALADase).[45] Compounds **152,153** were obtained from a diastereomeric mixture of oxazines **145** and **146** (Scheme 31). Diene **144** was prepared in five steps from diol **141**. Thus, commercially available *cis*-diol **141** was protected as TBS ether and then oxidized to corresponding aldehyde **142** using Dess-Martin reagent. Compound **142** was transformed into ester **143** *via* a Wittig reaction. Subsequent reduction and protection provided the desired (*E*,*Z*)-diene **144**. Diene **144** reacted with Boc-nitroso **111** to provide a 1:1 mixture of *trans* and *cis* adducts **145** and **146**. The *trans* isomer **145** was separated and carried through the synthesis of **152,153**. This involved cleavage of the silyl ether by TBAF, hydrogenation of the alkene moiety, oxidation of the resulting alcohols to carboxylates and protection of the acid as benzyl esters. The Boc protection in **147** was cleaved by treatment with TFA to give the corresponding free amine **148**. The use of isobutyl chloroformate **149** and NMM as coupling reagent afforded **150,151** as an inseparable mixture of diastereomers. Removal of *tert*-butyl group, followed by hydrogenolysis of the benzyl protecting groups, gave the *trans*-potassium salts **152,153** as a diastereomeric mixture.



Reagents: (i) TBSCl, Et_3N, DCM (83%); (ii) Dess-Martin oxidation (85%); (iii) $Ph_3P{=}CHCO_2Et$, DCM (91%); (iv) DIBAL-H, THF (90%); (v) TBSCl, Et_3N, DCM (81%); (vi) BocNHOH, $NaIO_4$, MeOH:H_2O (4:1) (50%); (vii) TBAF, THF (89%); (viii) $ClRu(PPh_3)_3/H_2$, MeOH; (ix) $RuCl_3$-$NaIO_4$, EtOAc/CH_3CN/H_2O; (x) N,N'-dicyclohexyl-O-benzylisourea, toluene (46% three steps); (xi) TFA, then Na_2CO_3, DCM (quant.); (xii) TFA, DCM; (xiii) 10% Pd-C, H_2/MeOH; (xiv) ion exchange column (75% three steps).

Scheme 31

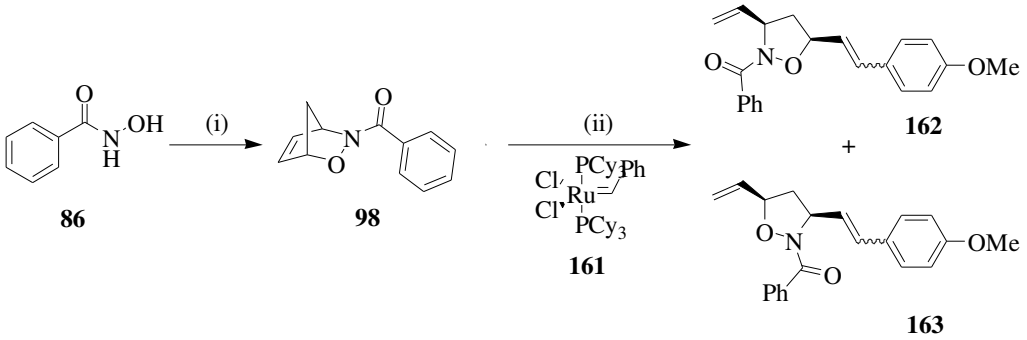
The *cis*-potassium salts **159,160** were obtained by a different synthesis (Scheme 32). Diels-Alder adduct **154** was coupled with protected aspartic acid **155**. This reaction afforded desired **156** in good yield. The Boc group in **156** was removed and the resulting free amine treated with acetic anhydride in the presence of piperidine to give **157**. Oxidative cleavage of the alkene in **157** using $KMnO_4$ in a basic media produced diacid **158**. Hydrogenolysis of benzyl ester in **158**, followed by ion exchange chromatography, provided the desired *cis*-potassium salts **159,160** as a mixture of diastereomers.



Reagents: (i) 1,3-cyclohexadiene, $NaIO_4$, $MeOH/H_2O$ (82%); (ii) TFA, DCM, then Na_2CO_3; (iii) EDC·HCl, AtOH, Na_2CO_3; (iv) TFA, Na_2CO_3; (v) Ac_2O, Py (92%); (vi) $KMnO_4$, K_2CO_3 (92%); (vii) H_2,Pd/C, MeOH; (viii) ion exchange column (80% two steps).

Scheme 32

King published recently a tandem process in which acyl nitroso species were reacted in a preliminary Diels Alder and the adduct obtained subjected to ring opening metathesis/cross metathesis (ROM/CM).[46,47] Cycloadduct **98** reacted with Grubbs catalyst **161** and *p*(OCH_3)-styrene to form a mixture of *E* and *Z* regioisomers **162** and **163** in moderate yield (Scheme 33).



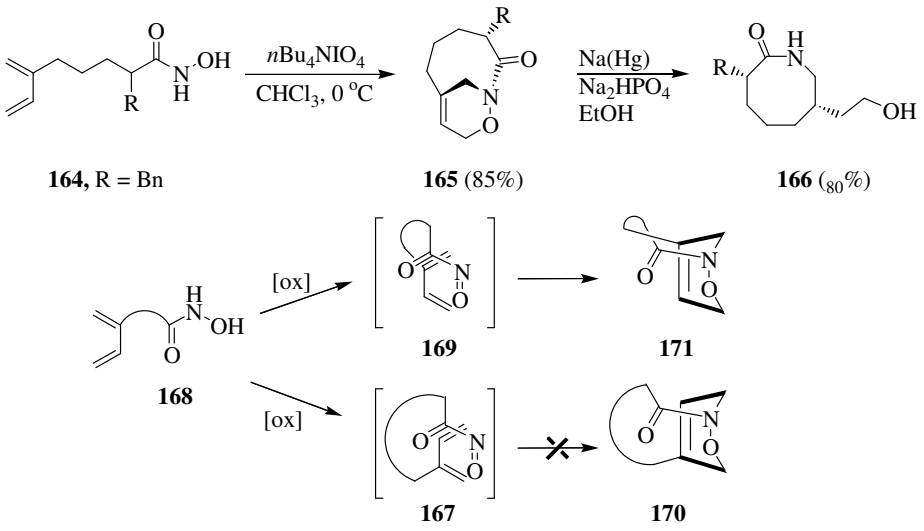
Reagents: (i) 1,3-cyclopentadiene, IO_4^-; (ii) benzohydroxamic acid, DCM, 57%.

Scheme 33

5.3. Intramolecular acyl nitroso reactions

The intramolecular HDA of nitroso species has often been used as a key step for the synthesis of nitrogen containing heterocycles. Medium-ring lactam **166** are present in a large number of natural and unnatural bioactive compounds. In particular, lactam **166** were shown sedative or anti-hypertensive properties.[48] The use of an intramolecular HDA cycloaddition provided a fruitful means to control the regio- and stereo- chemistry of desired lactam **166**. For example, Shea reported the synthesis of azocin-2-one **166** *via* HDA reaction (Scheme 34).[49] The synthetic plan involved the preparation of hydroxymate **164**, that in turn was converted to cyclic **165** by oxidation with periodate. Adduct **165** was obtained as a single regioisomer (Scheme 34): this result could be explained considering the difference in formation energy of the two regioisomers. The estimated energy of bicycle[5.3.1]alkene **170** was 8.5 kcal mol^{-1} lower than the

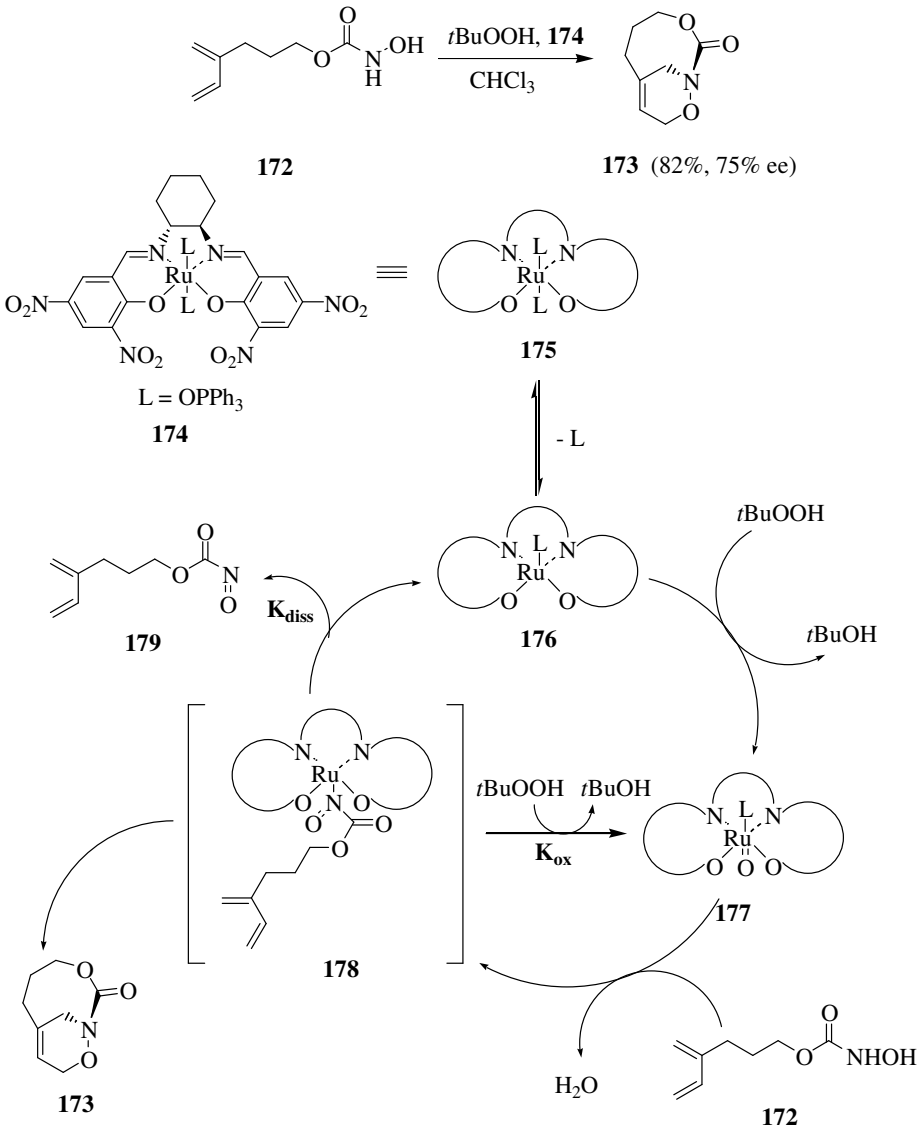
one of **171**. Cleavage of N-O bond using Na(Hg) amalgam provided *cis*-3,7-disubstituted azocin-2-one **166** in good yield.



164, R = Bn **165** (85%) **166** ($_{80}$%)

168 **169** **171** **167** **170**

Scheme 34



172 **173** (82%, 75% ee)

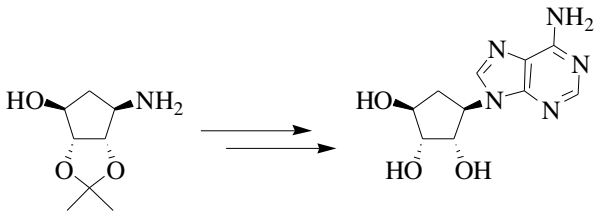
174 **175** **176** **177** **178** **179**

Scheme 35

A synthesis of oxazinolactam **173** *via* nitroso HDA was reported (Scheme 35).[50] Shea prepared the *N*-hydroxy formate ester **172** and treated this material with *t*-BuOOH in the presence of Ru^{II} SALEN complex **174**. This reaction furnished oxazinolactam **173** in good yield (up to 82%) and enantioselectivity (up to 75% ee). Importantly, in this reaction two factors affected the enantioselectivity: *(a)* the rate of reoxidation of Ru^{II} in chiral complex **178** to Ru-oxo species **177** (K_{ox}); *(b)* the dissociation of acylnitroso **179** from complex **178** (K_{diss}). The latter was particularly important as **179** could undergo cycloaddition without the chiral complex being involved, leading to loss of enantioselectivity.

5.4. Asymmetric acylnitroso Diels-Alder reactions

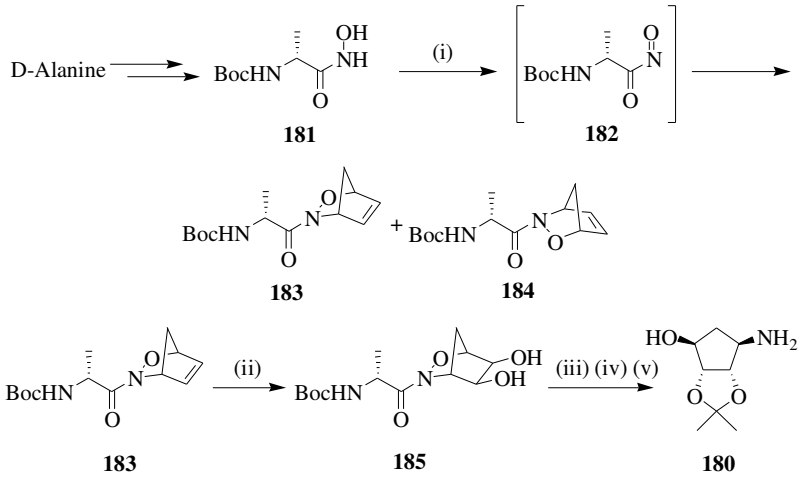
Considering what exposed so far the cycloaddition of acylnitroso compounds to cyclic and acyclic dienes represent a versatile and synthetically important reaction. The cleavage of N-O bond of HDA cycloadducts led to protected amino alcohols which were employed to prepare a large number of compounds. For example, enantiopure amino alcohol **180** has been used as in the synthesis of antiviral carbocyclic nucleosides **181** (Scheme 36).[51]



180 **181**

Scheme 36

Miller reported a simplified preparation of enantiomerically pure **180** (Scheme 37).[52] This synthesis started from hydroxamic acid **181**, which was obtained from D-alanine. The transient acylnitroso intermediate **182**, formed under Swern conditions, was trapped with cyclopentadiene to give cycloadducts **183** and **184** in a 5.9:1 mixture of diastereomers. Dihydroxylation of **183** provided diastereomer **184** that was formed by an *exo* approach of OsO_4 to the alkene. Protection of diol moiety in **185** as an acetonide, removal of the chiral auxiliary and cleavage of the N-O bond gave alcohol **180** was obtained in 36% overall yield.

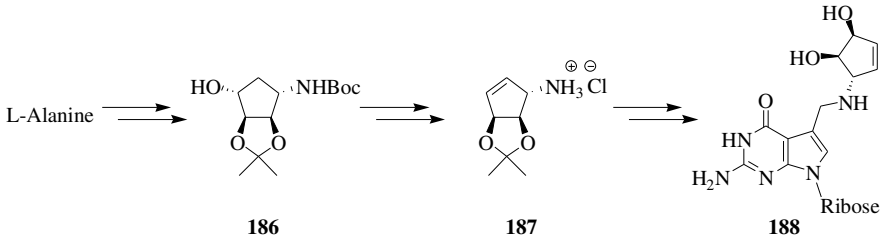


181 **182** **183** **184** **183** **185** **180**

Reagents: (i) $(COCl)_2$, DCM, cyclopentadiene, DCM, then piridine; (ii) OsO_4, NMO, $(CH_3)_2C(OCH_3)_2$, TsOH: (iii) $NaBH_4$; (iv) H_2, Pd/C.

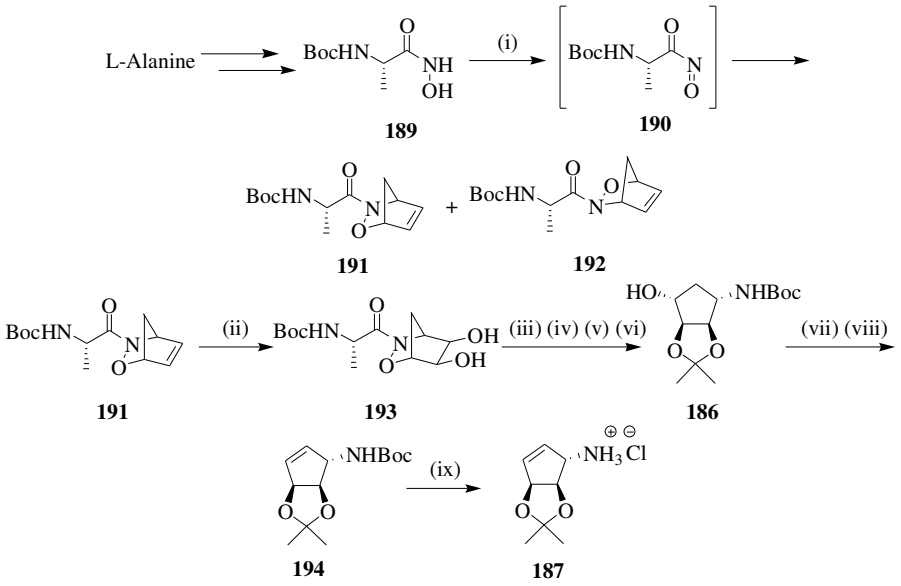
Scheme 37

Alcohol **186**, which possesses the opposite absolute stereochemistry compared to **180**, was obtained from L-alanine. Compound **186** was employed for the preparation of intermediate **187**, which is a fragment of *Nucleoside Q* **188** (Scheme 38).[53]



Scheme 38

Nucleoside Q, also known as *Queuosine*, is present in several tRNA of plants and animals. The interest in Nucleoside Q arose from its ability to affect the rate of tumor growth.[54] The synthetic route to amino cyclopentene **187** is shown below (Scheme 39). Hydroxamic acid **189**, readily accessible from L-alanine, was oxidized to acylnitroso species **190**, which in turn was trapped with cyclopentadiene to give cycloadducts **191** and **192** as a 5:1 mixture of separable diastereomers. The major diastereomer **191** was transformed to enantiopure diol **193**. Compound **193** was protected as acetonide, the chiral auxiliary removed using mild condictions ($NaBH_4$ in MeOH), the N-O bond cleaved by hydrogenation and finally the amino group reacted with $(Boc)_2O$ to provide aminoalcohol **186**. Compound **186** was converted into the corresponding mesyl derivative and then dehydrated to **194**. Desired compound **187** was finally prepared from **194** by treatment with diluted aqueous HCl.

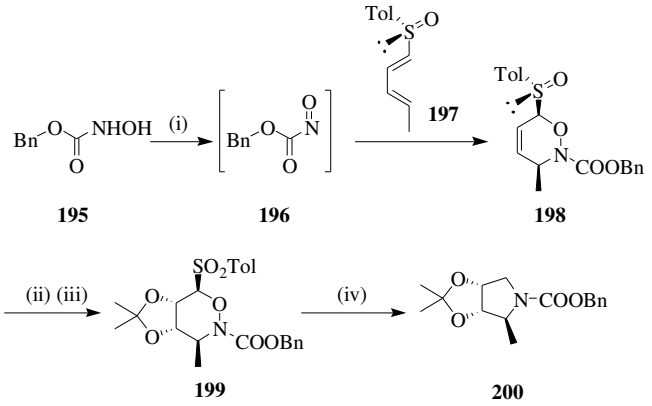


Reagents: (i) $(COCl)_2$, DMSO, DCM, Py, cyclopentadiene, 70%; (ii) OsO_4, NMO, THF/H_2O; (iii) $(CH_3)_2C(OMe)_2$, TsOH; (iv) $NaBH_4$, MeOH; (v) H_2, Pd/C, MeOH; (vi) Boc_2O, Na_2CO_3, THF/H_2O, 64% five steps; (vii) MsCl, Et_3N, DCM, 95%; (viii) DBU, toluene, reflux, 76%; (ix) 3M HCl, Et_2O.

Scheme 39

Asymmetric HDA reactions could also be carried out using optically pure 1,3-dienes as chiral auxiliaries, for instance chiral 1-sulfinyl-1,3-butadiene **197**.[55] These reactions often displayed a high level of stereoselectivity, additionally the ease of conversion of the adducts through highly stereo controlled

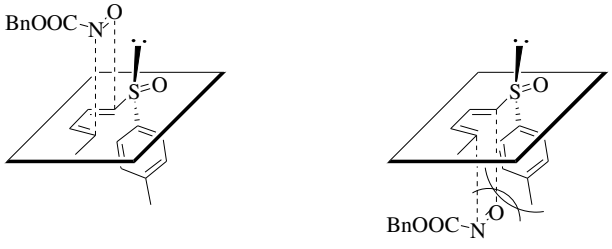
rearrangements made these reaction a valuable tool for the construction of stereo defined molecules.[56] The first asymmetric HDA reaction involving [(*S*)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene **197** and benzyl nitrosoformate **196** was reported by Garcia Ruano *et al.* (Scheme 40).[57] In this report, dienophile **196** was generated *in situ* by oxidation of *N*-benzyloxycarbonyl hydroxamic acid **195** with Bu_4NIO_4. Acylnitroso **196** was then trapped by diene **197** and the corresponding cycloadduct **198** isolated in 54% yield. This reaction proceeded with a complete regioselectivity and high stereoselectivity. Dihydroxylation of **198** and subsequent treatment of the resulting diol with DMP and PTSA furnished acetonide **199**. The sulfinyl group was oxidized to sulfone in this process. The hydrogenolysis of **199** and its successive treatment with benzyl chloroformate in aqueous $NaHCO_3$.gave enantiopure dihydroxypyrrolidine **200**.



Reagents: (i) Bu_4NIO_4, DCM (54%); (ii) OsO_4, NMO, acetone/H_2O (42)%; (iii) DMP, PTAS, acetone (89%); (iv) H_2, Pd/C, then ClCOOBn, $NaHCO_3$, H_2O (96%,two steps).

Scheme 40

The stereochemical course of HDA reaction could be explained considering that the heterodienophile approached the less hindered face of diene with the S=O bond laying in a *s-trans* conformation respect to C(1)=C(2) (Figure 4). Electrostatic repulsion between the carbonyl and sulfinyl oxygens in the transition state was invoked to justify the high reactivity of the *s-trans* conformation of sulfinyl oxygen. The nitroso species could either approach the diene from the face containing the lone pair (Figure 4, **201**) or the one containing the tosyl group (Figure 4, **202**). In the first case the nitroso did not experience a great steric hindrance being the lone pair selectively small. In the second case, the steric hindrance of the tosyl group prevented the approach of the nitroso to the diene.

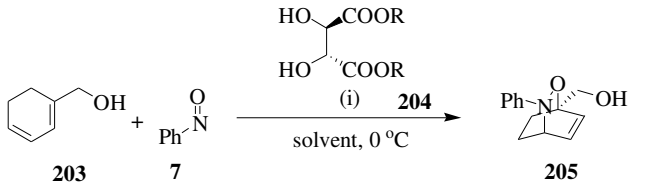


201 ***Favoured*** **202** ***Disfavoured***

Figure 4

Recently, Ukaji and Inomata have elaborated the first example of nitroso HDA reaction utilizing tartatic acid ester as chiral ligand.[58] In the experiment described, (cyclohex-1,3-dienyl)methanol **203** was

reacted with nitrosobenzene **7**, in the presence of (*R*,*R*)-tartrate ester **204** and an alkyl zinc. This reaction proceeded to give cycloadduct **205** with a complete regioselectivity, excellent yield and high enantioselectivity (Scheme 41). In this process the enantioselectivity was profoundly influenced by the nature of solvent and the tartrate ester: *tert*-butyl methyl ether and di-*tert*-butyl tartrate gave the best results (94% yield, 92% ee). The role of alkyl zinc derivates was not clarified, but it was proposed this reagent was involved in the formation of a chiral complex together the diene, the tartaric ester and the nitroso species.



203 **7** **205**

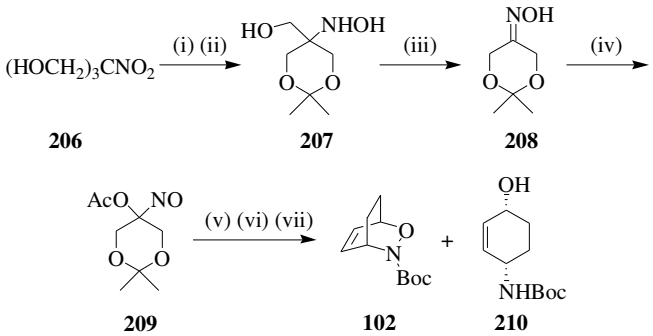
(18-94%, 11-92% ee)

Reagents: (i) *n*PrZnBr, *i*Pr$_2$Zn; (R = *i*Pr, Et, Bn, *t*Bu)

Scheme 41

6. α-Acetoxynitroso dienophiles

Kouklovsky *et al*. have reported the first example of HDA reaction using α-acetoxynitroso species **209** as dienophile (Scheme 42).[59] Compound **209** was obtained in four steps from commercially available *tris*-hydroxy-methylnitromethane **206**.[60] Condensation of **206** with acetone in presence of TsOH followed by reduction with Al(Hg) furnished corresponding hydroxylamine **207**. In turn, product **207** was converted into oxime **208** by $NaIO_4$ oxidation. Nitroso species **209** was finally synthesized by further oxidation employing $PhI(OAc)_2$ as the oxidant.



206 **207** **208** **209** **102** **210**

Reagents: (i) acetone, p-TsOH, benzene, reflux; (ii) Al/Hg; (iii) $NaIO_4$, KH_2PO_4, MeOH/H_2O, (37%, three steps); (iv) $PhI(OAc)_2$, DCM (67%); (v) 1,3-cyclohexadiene, Lewis acid (20 mol%), toluene, 0 °C; (vi) HCl (1N); (vii) NaOH, Boc_2O.

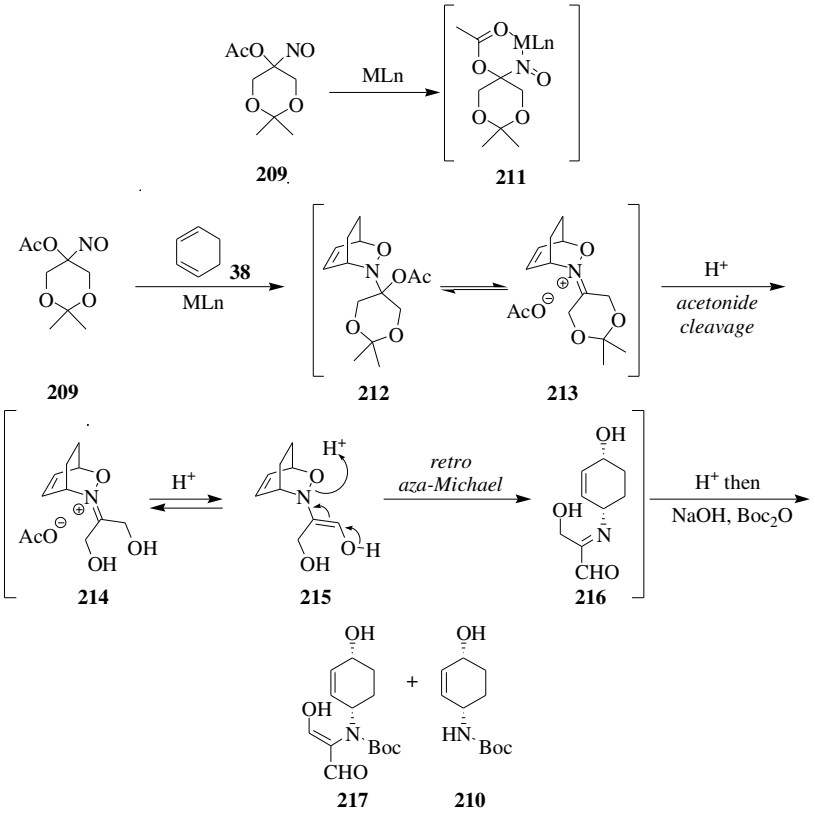
Scheme 42

Table 5.

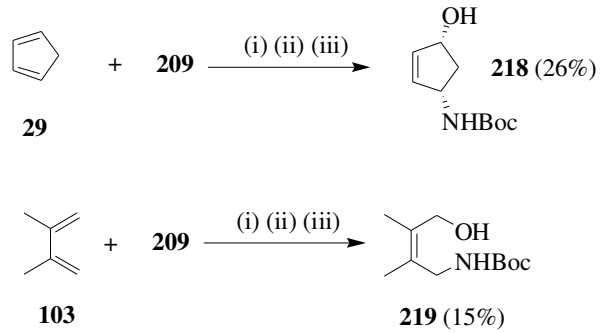
Lewis acid	Yields of **210** (% three steps)
-	14
$Mg(OTf)_2$	41
$CrCl_3$	41
$Cu(OTf)_2$	41

Initial studies showed that reaction of **209** with Lewis acid followed by acidic hydrolysis, neutralization and treatment with $(Boc)_2O$ afforded the expected oxazine **102** and the hydroxycarbamate **210** (ratio **102**:**210** = 2:98). A screening of the Lewis acid revealed that $Mg(OTf)_2$, $Cu(OTf)_2$ and $CrCl_3$ were the best enhancers for this reaction (Table 5).

The effect of the Lewis acid on the reaction could be explained with the presence of metal complex **211** (Scheme 43). Reaction of **209** and 1,3-cyclohexadiene **38** gave mixture of compounds **212** and **213**. Hydrolysis of the acetonide lead to 1,3-diol **214**, which equilibrated to the corresponding enaminol **215**. Retro *aza*-Michael reaction of **215** followed by hydrolysis of the resulting imine and protection of the amino group as a *tert*-butyl-carbamate gave product **210**. Support for this mechanism was obtained by isolating traces of **217** in the reaction mixture.



Scheme 43

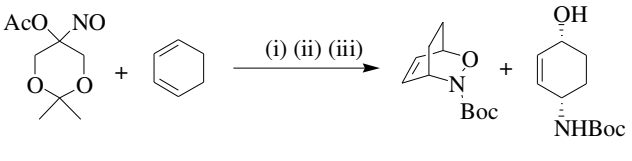


Reagents: (i) $Cu(OTf)_2$ (20 mol%), toluene; (ii) HCl (1N);
(iii) NaOH, Boc_2O; (iv) $CrCl_3$ (20 mol %).

Scheme 44

Reaction of **209** with dienes **29** and **103** in the presence of $Cu(OTf)_2$ or $CrCl_3$ gave hydroxycarbamates **218,219** in low yields (Scheme 44). This procedure offered the advantage of obtaining directly amino alcohols **218,219** without using $Mo(CO)_6$ or Na(Hg) amalgam, that were conventionally used to cleave the N-O bond.

Traces of water led to dramatic reversal of oxazine/hydroxycarbamate ratio **102/210** (Scheme 45). The pioneering studies of Breslow established that reaction rates, the regio- and stereo chemistry of Diels-Alder reactions were influenced by the presence of water.[61] In this case, the addition of just 2 equiv of water inverted the product ratio **102/210**.[62] Therefore **209** reacted efficiently with **38** in presence of 20 mol% of $Zn(OTf)_2$ in pure water as the solvent, to give high yields of **102** or **210** (Table 6).



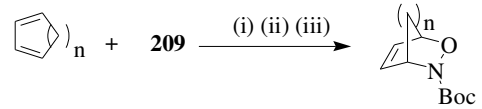
209 **38** **102** **210**

Reagents: (i) $Zn(OTf)_2$, H_2O, Toluene; (ii) HCl; (iii) NaOH, Boc_2O.

Scheme 45

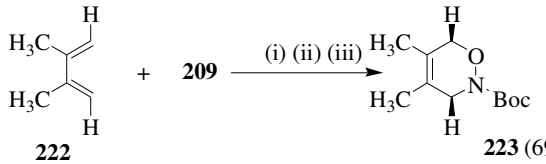
Table 6.

$Zn(OTf)_2$ (mol%)	Water (eq.)	Yield (%)	**102/210**
20	-	40	8/92
20	2	39	60/40
20	10	53	85/15
20	H_2O only	78	90/10
-	H_2O only	74	>98/2



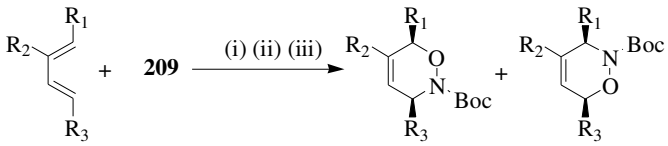
29, n = 1
220, n = 3

102 (65%)
221 (56%)



222

223 (69%)



224a, $R_1 = R_3 = H$, $R_2 = Me$
224b, $R_1 = CH_2OH$, $R_2 = H$, $R_3 = Me$
224c, $R_1 = CH_2OTBS$, $R_2 = H$, $R_3 = Me$
224d, $R_1 = CH_2OTBS$, $R_2 = H$, $R_3 = Ph$

226

225a (48%), (75:25)
225b (80%), (80:20)
225c (44%), (63:37)
225d (69%), (2:98)

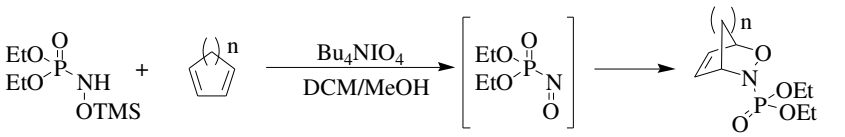
Reagents: (i) H_2O; (ii) HCl; (iii) NaOH, Boc_2O

Scheme 46

Cyclic dienes **29** and **220** reacted similarly affording the corresponding **102** and **221** in 65% and 56% yield respectively (Scheme 46). The use of dissymmetric acyclic dienes **222** or **224** furnished adducts **223** and **225**. Importantly in these experiments no hydroxycarbamate **226** was observed. Therefore it was demonstrated that α-acetoxynitroso species **209** could be employed to access either 1,2-oxazines or hydroxycarbamate simply operating in different conditions.

7. *P*-Nitroso dienophiles

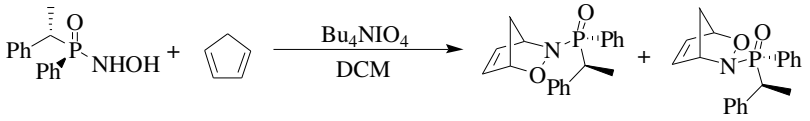
N-Nitrosophosphates such as **228** represent an alternative class of nitroso intermediates that can be used as efficient dienophiles in HDA cycloadditions. Periodate oxidation of *N*-(diethylphosphoryl)-*O*-(trimethylsilyl) hydroxylamine **227** in the presence of 1,3-cyclopentadiene **29** or 1,3-cyclohexadiene **38** produced cycloadduct **229** and **230** in good yield (Scheme 47).[63]



227 **26**, n = 1; **38**, n = 2 **228** **229**, n = 1 (67%); **230**, n = 2 (70%)

Scheme 47

Reaction of chiral phosphine oxide **231** with 1,3-cyclopentadiene **29** in the presence of Lewis acid resulted in a 7:1 ratio of diastereomers **232**:**233** (Scheme 48).[64]



231 **29** **232** **233**

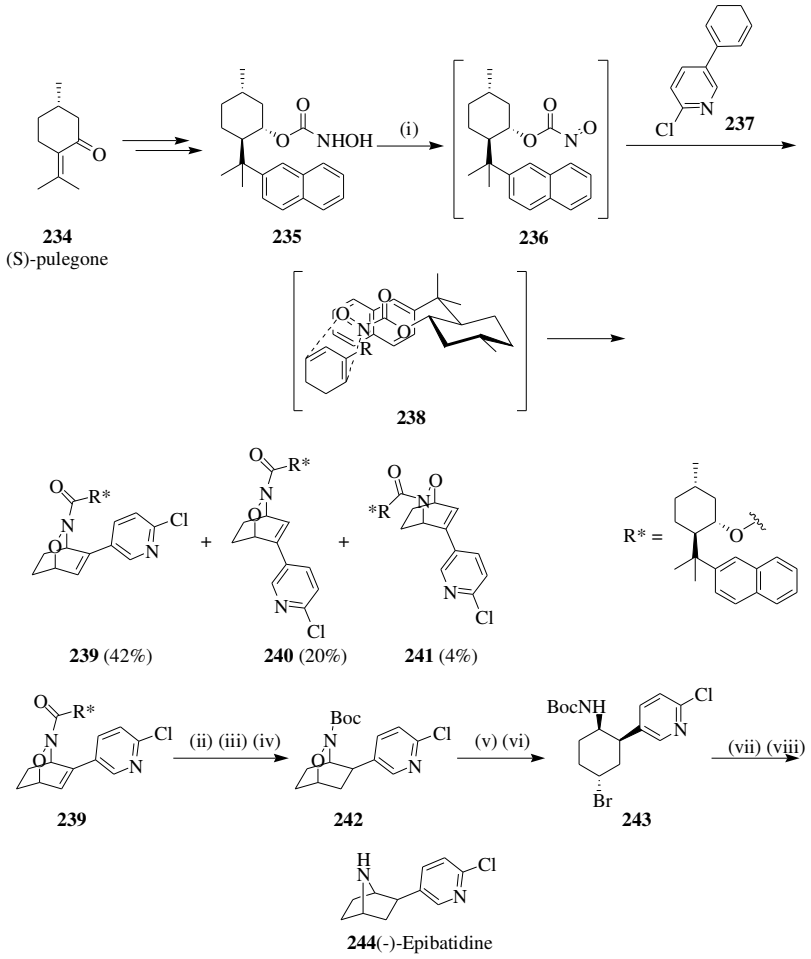
Scheme 48

8. Synthesis of natural products

Several natural products were synthesized using HDA cycloadducts as key intermediates. This includes the synthesis of (-)-Epibatidine, (+)-Azimine, (+)-Carpaine, (-)-Lepadin A, B and C, (+)-Loline, (-)-Kainic acid and (+)-Streptazoline.

Kibayashi and co-workers described a total synthesis of (-)-Epibatidine **244** that employed an asymmetric HDA reaction as a key step (Scheme 49).[65] Hence, chiral acylnitroso dienophile **236** derived from (*S*)-Pulegone **234** was obtained by oxidising the parent hydroxymate **235** under Swern conditions and trapped with 2-chloro-5-(1,5-cyclohexadienyl)pyridine **237**. This reaction afforded three stereoisomes **239–241**. Data collected indicated that the *meta-aza* regioisomer was favoured over the *para-aza* regioisomer, an effect due to the presence of an electron-withdrawing substituent at position 2 of the diene moiety. The facial diastereoselectivity observed can be explained examining transition state **238**. In this model, the acylnitroso group rest in its s-*cis* conformation with respect to the C-N bond and the naphthyl group shielded selectively one face of the nitroso group. This forced the diene to an *endo* approach. Thus, the desired cycloadduct **239** was obtained as the major one. Compound **239** was isolated by chromatography, then submitted to hydrogenation, the chiral auxiliary was removed and the free amine obtained protected by means of

treatment with $(Boc)_2O$. The N-O bond in compound **242** was reductively cleaved, then the hydroxyl replaced by an halogen to **243**. Removal of Boc group using TFA and prolonged heating provided desired (-)-Epibatidine **244**.

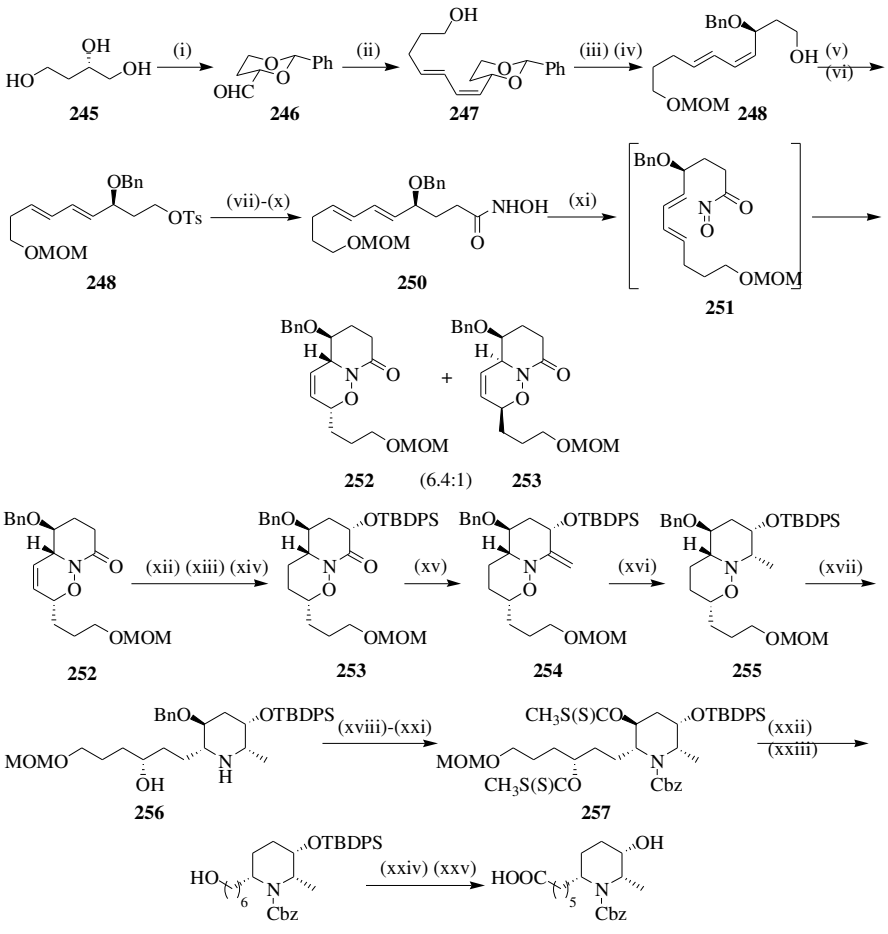


Reagents: (i) $(COCl)_2$, DMSO, Et_3N, DCM; (ii) H_2, PtO_2, dioxane (81%); (iii) $LiNH_2{\cdot}BH_3$, THF; (iv) Boc_2O, Na_2CO_3 (58% two steps); (v) $Mo(CO)_6$, CH_3CN/H_2O, reflux (85%); (vi) PPh_3, CBr_4, CH_3CN (42%); (vii) TFA, DCM, reflux (96%); (viii) reflux, CH_3Cl, three days (97%).

Scheme 49

(+)-Azimine **260** and (+)-Carpaine **266**, two macrocyclic dilactones containing a 2,3,6-trisubstituted piperidine skeleton, were recently obtained using bicyclic compound **252** as a key intermediate[66] (Schemes 50 and 51). These syntheses occurred *via* an intramolecular HDA reaction of nitroso intermediate **251**. The synthesis began with (*S*)-1,2,4-butanetriol **245** as a single source of chirality. Compound **245** was converted to 2,4-dihydroxybutanal and then protected as benzylidene acetal **246**. Wittig reaction of aldehyde **246** produced derivative **247** as a 6 : 1 inseparable mixture of 6-(*Z*,*E*) isomers. Protection of the hydroxyl group as MOM ether, followed by DIBAL-H reduction, gave alcohol **248** which was protected as tosyl ester and photolysed in the presence of I_2 to give pure (*E*,*E*) isomer **249**. Conversion to hydroxamic acid **250** was accomplished by a sequence of reactions involving nucleophilic displacement of the tosylate by cyanide ion, alkaline hydrolysis, esterification with diazometane and treatment with hydroxylamine. Oxidation of hydroxamic acid **250** with $NaIO_4$ generated nitroso **251** that underwent intramolecular Diels-Alder reaction to afford a 6.4:1 mixture of *trans* and *cis* adducts **252** and **253**. Olefin **252** was then hydrogenated and

submitted to α-keto hydroxylation using Davis' reagent.[67] The lactam formed by treatment with LiHMDS was oxidized using (+)-[(8,8-dichlorocamphoryl)-sulfonyl]oxaziridine to furnish exclusively the secondary alcohol which was protected as silyl ether **253**. Compound **253** was treated with methylmagnesium bromide to give the enamine **254**, which was reduced with $NaBH_3CN$ to yield the desired methylated product **255** in 76% overall yield and as the only stereoisomer. Reductive cleavage of the N-O bond in **255** provided amino alcohol **256**, which was converted into thionocarbonate **257** *via* hydrogenolytic removal of the benzyl protecting group, benzylcarbonilation of free amine and treatment with CS_2 and MeI. Transformation of **257** to **258** was accomplished using the Barton-McCombie deoxigenation reaction followed by deprotection of the MOM group. PDC oxidation, followed by removal of the silyl protecting group, transformed **258** into acid **259**.

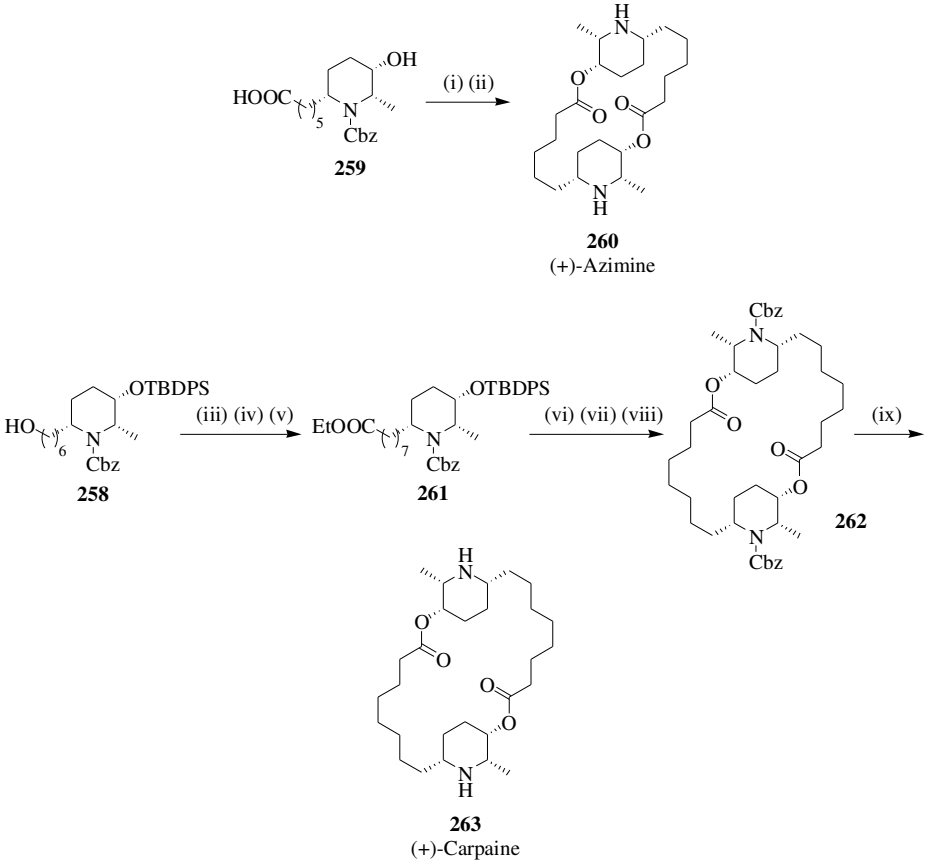


Reagents: (i) PhCHO, TsOH, then Swern oxidation; (ii) $Br^-Ph_3P^+CH_2CH{=}CH(CH_2)_3OH$, LiHMDS, HMPA, THF (66%); (iii) MOMOCl, iPr_2NEt_3, DCM, 60 °C (93%); (iv) DIBAL-H, DCM (84%); (v) TsCl, Et_3N, DMAP, DCM (91%); (vi) irradiation, I_2, benzene (94%); (vii) NaCN, DMSO, 50 °C (95%); (viii) NaOH, $MeOH/H_2O$, reflux; (ix) CH_2N_2, Et_2O, 0 °C (94% two steps); (x) $NH_2OH{\cdot}HCl$, KOH, MeOH, 0 °C (88%); (xi) $NaIO_4$, H_2O/DMF (50:1), 0 °C (69%); (xii) H_2, Pd/C (97%); (xiii) LiHMDS, (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine, THF (99%); (xiv)TBDPSCl, imidazole, DMF (73%); (xv) MeMgBr, THF; (xvi) $NaBH_3CN$, AcOH, THF (76% two steps); (xvii) Zn, AcOH, 60 °C (93%); (xviii) H_2, $Pd(OH)_2$, MeOH; (xix) CbzCl, Na_2CO_3; (xx) 1M NaOH, MeOH (45% three steps); (xxi) CS_2, NaH, imidazole, THF, reflux then MeI, reflux (93%); (xxii) Bu_3SnH, AIBN, bnzene, reflux (99%); (xxiii) PPTS, *t*BuOH, reflux (73%); (xxiv) PDC, DMF; (xxv) Bu_4NF, THF (82% two steps).

Scheme 50

Compounds **258** and **259** were used for the synthesis of (+)-Azimine **260** and (+)-Carpaine **263** (Scheme 51). Cyclization of **259** was carried out using the method developed by Yamaguchi.[68]

Hydrogenolysis of the Cbz group provided desired (+)-Azimine **260**. (+)-Carpaine **263** was obtained from piperidine **258**. Compound **258** was submitted to Swern oxidation, the resulting aldehyde subjected to Horner-Wadsworth-Emmons homologation and the olefin obtained hydrogenated to give compound **261**. Deprotection of the silyl group, hydrolysis of the ester and lactonization of resulting *N*-Cbz acid under Yamaguchi macrocyclization conditions provided intermediate **262**. Finally, deprotection of Cbz group led to target (+)-Carpaine **263**.

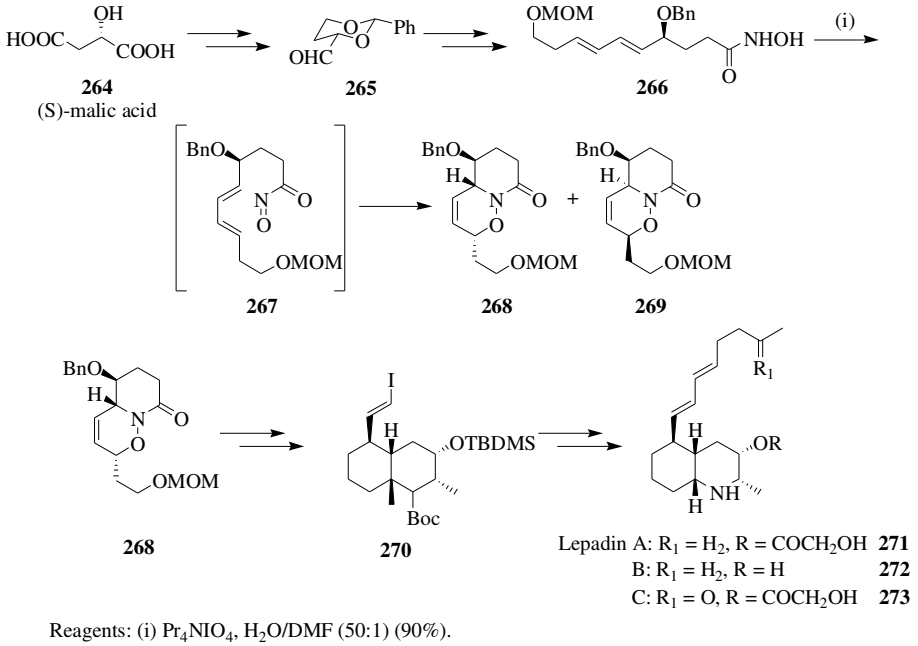


Reagents: (i) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF then DMAP, toluene, reflux (71%); (ii) H_2, $Pd(OH)_2$, MeOH (76%). (iii) $(COCl)_2$, DMSO, Et_3N, DCM; (iv) $(EtO)_2P(O)CH_2COOEt$, NaH, THF (91% two steps); (v) H_2, PrO_2, AcOEt (76%); (vi) Bu_4NF, THF (97%); (vii) $Ba(OH)_2{\cdot}8H_2O$, MeOH (97%); (viii) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF then DMAP, toluene, reflux (71%); H_2, $Pd(OH)_2$, MeOH (87%).

Scheme 51

Kibayashi reported the synthesis of (-)-Lepadin A, B and C **271–273** (Scheme 52).[69] These compounds possess a decahydroquinoline core and have shown a significant cytotoxicity against some human cancer cell lines.[70] (-)-Lepadin A, B and C were obtained through an intramolecular HDA reaction. The chiral hydroxymate **266** was employed to prepare desired bicycle-[4.4.0]-1,2-oxazine **268** in good yield and diastereoselectivity. Compound **266** was prepared from aldehyde **237** that was obtained from (*S*)-malic acid **264**. Conversion of **265** to **266** required ten steps.

Oxidation of **266** by Pr_4NIO_4 generated nitroso **267**, which in turn underwent an intramolecular HDA reaction to furnish cycloadducts **268** and **269**. Optimal conditions involved carrying out the reaction in a mixture H_2O/DMF at 0 °C (Table 7). The major isomer **268** was then converted to intermediate **270** which in turn was used to generate (-)-Lepadin A, B and C **271–273**.



Reagents: (i) Pr_4NIO_4, H_2O/DMF (50:1) (90%).

Scheme 52

Table 7.

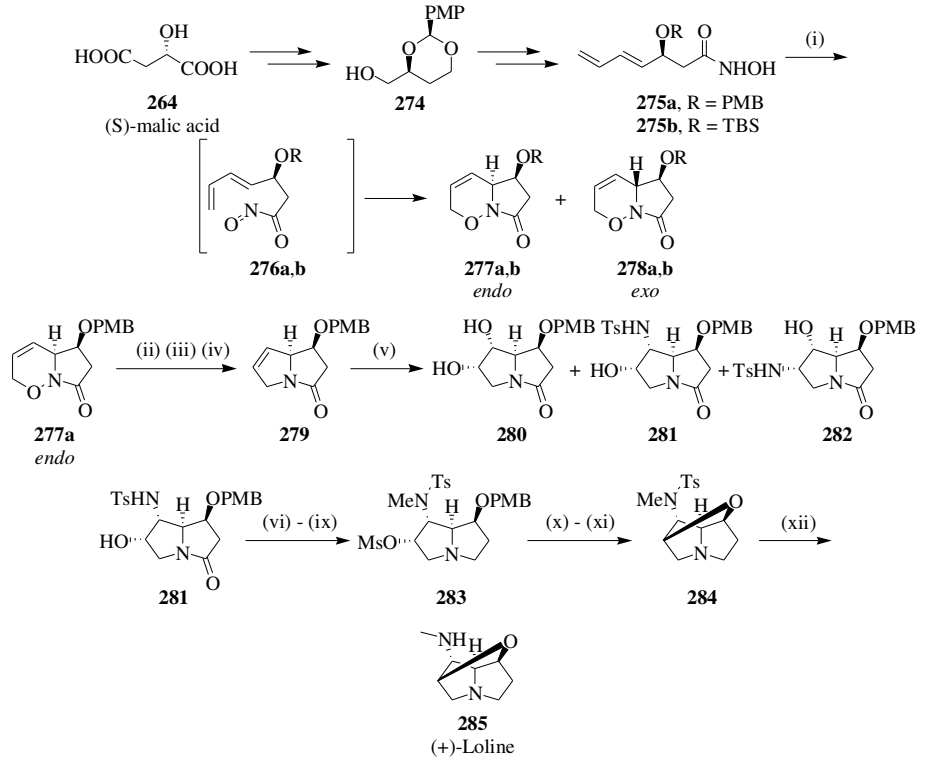
Solvent	**268** : **269**	Yield (%)
$CHCl_3$	1.7 : 1	81
MeOH	2.6 : 1	96
H_2O/THF (50:1)	4.3 : 1	88
H_2O/DMF (50:1)	6.6 : 1	90

White reported the synthesis of (+)-Loline **285** (Scheme 53).[71] The precursor chiral hydroxamic acids **275a**,**b** were synthesized from commercially available (*S*)-malic acid **264** in ten steps. Oxidation of **275a**,**b** was carried out with Bu_4NIO_4 under a variety of conditions.

The resulting nitrosodiene **276a**,**b** underwent spontaneous intramolecular cycloaddition to give bicyclic dihydrooxazines **277a**,**b** and **278a**,**b** with poor diastereoselectivity. It was found that in benzene or toluene **275a**,**b** gave predominantly the *endo* isomer **277a**,**b**. The yield increased with increasing the temperature, however at 80 °C the overall selectivity was diminished (Table 8). A reversal of selectivity was observed when the oxidation was carried out in aqueous THF. In this case, the *exo* cycloadduct was the major product. The *endo* **277a** was reduced with Na(Hg), mesylated and treated with LDA to furnish bicyclic **279**. Osmylation of **279** using excess of chloramine-T[72] yielded principally the diol **280** together with small amounts of amino alcohols **281** and **282**. Screening of reaction conditions established that $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$ in *t*-BuOH/H_2O mixture gave the best result (47% total yield **281**+**282**, **281**:**282** = 80:20). Compound **281** was then treated with MeI, MsCl in presence of Et_3N, $BH_3{\cdot}SMe_2$ and Pearlman catalyst to afford protected bicyclic **283**. Removal of PMB ether from **283** with DDQ followed by thermal cyclization at 180 °C in presence of 1,2-di-chlorobenzene furnished **284**. Removal of the tosyl group with sodium naphthalenide afforded desired (+)-Loline **285**.

Ogasawara reported the synthesis of (-)-Kainic acid **298** *via* formation of (+)-*cis*-4-carbobenzoxyamino-2-cyclopentenol (+)-**291** from *N*-carbobenzoxyhydroxylamine **286** (Scheme 54).[73] The

oxidation of **286** generated the correspondent nitroso species which was trapped with cyclopentadiene to give cycloadduct **287**. This was subsequently converted to recemic aminoalcohol (±)-**288** by reductive cleavage of N-O bond.



Reagents: (i) periodate salt, solvent; (ii) Na(Hg), Na_2HPO_4, EtOH; (iii) MsCl, Et_3N, DCM; (iv) LDA, THF; (v) TsNClNa, Os. cat., solvent; (vi)MeI, *t*BuOK, *t*BuOH, 50 °C (76%); (vii) MsCl, Et_3N, DCM, 0 °C (99%); (viii) $BH_3{\cdot}SMe_2$, THF; (ix) $Pd(OH)_2/C$, MeOH (73% two steps); (x) DDQ, DCM/H_2O (20/1) (70%); (xi) 1,2-di-ClC_6H_4, 180 °C (75%); (xii) sodium naphthalenide, DME, -60 °C (48%).

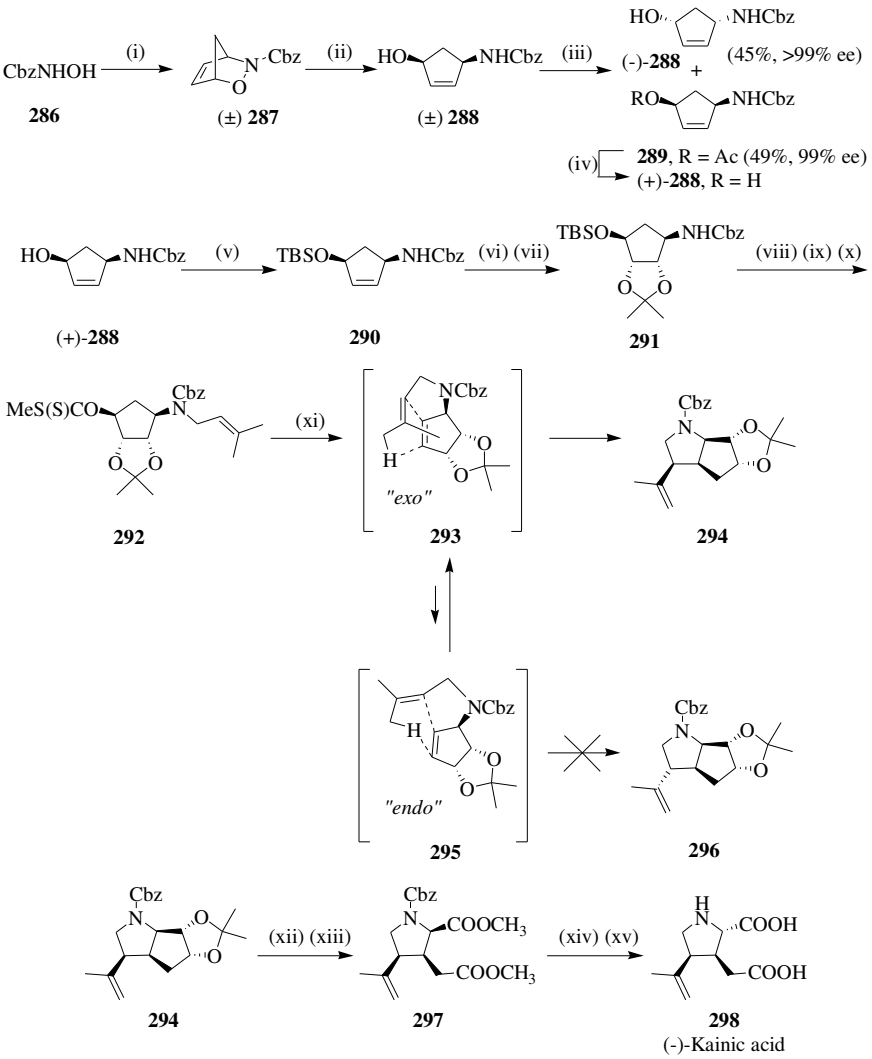
Scheme 53

Table 8.

Hydroxamic adic	Oxidant	Solvent	Temp. (°C)	**281** : **282**	Yield (%)
234b	Bu_4NIO_4	Toluene	–20	70/30	49
234b	Bu_4NIO_4	Benzene	0	71/29	60
234b	Bu_4NIO_4	Benzene	80	60/40	80
234b	Bu_4NIO_4	DCM	–78	50/50	86
234b	Bu_4NIO_4	$CHCl_3$	22	55/45	91
234a	Bu_4NIO_4	$CHCl_3$	22	57/43	87
234b	$NaIO_4$	H_2O/THF (1:1)	0	27/73	97

The enzymatic resolution with lipase AK afforded compound **289** in high yield and excellent enantioselectivity (49%, 99% ee). Deacetylation of **289** afforded (+)-*cis*-4-carbobenzoxyamino-2-cyclopentenol (+)-**288** in excellent yield. Subsequent treatment with TBSCl gave the corresponding protected aminoalcohol **290** which was dihydroxylated and protected as an acetonide to furnish **291**. The secondary carbamate of **291** was alkylated to give the tertiary prenyl carbamate. The subsequent Chugaev elimination and intramolecular ene reaction afforded compound **294** as a single diastereomer presumably

through an 1,6-diene intermediate **293**. The complete control of the stereochemistry was due to the preference of the *exo* transition state **293** over the *endo* transition state **295**. The acetonide group of **294** was removed under acid hydrolysis, the resulting diol cleaved with sodium periodate, oxidized with Jones' reagent and treated with diazomethane to form the trisubstituted pyrrolidine ester **297**. Compound **297** was epimerized at C-2 with base to give the *trans* C2/C3 and the *cis* C3/C4 diastereomer, which on alkaline hydrolysis afforded (-)-Kainic acid **298** in 13% overall yield from enantiopure compound (+)-**288**.

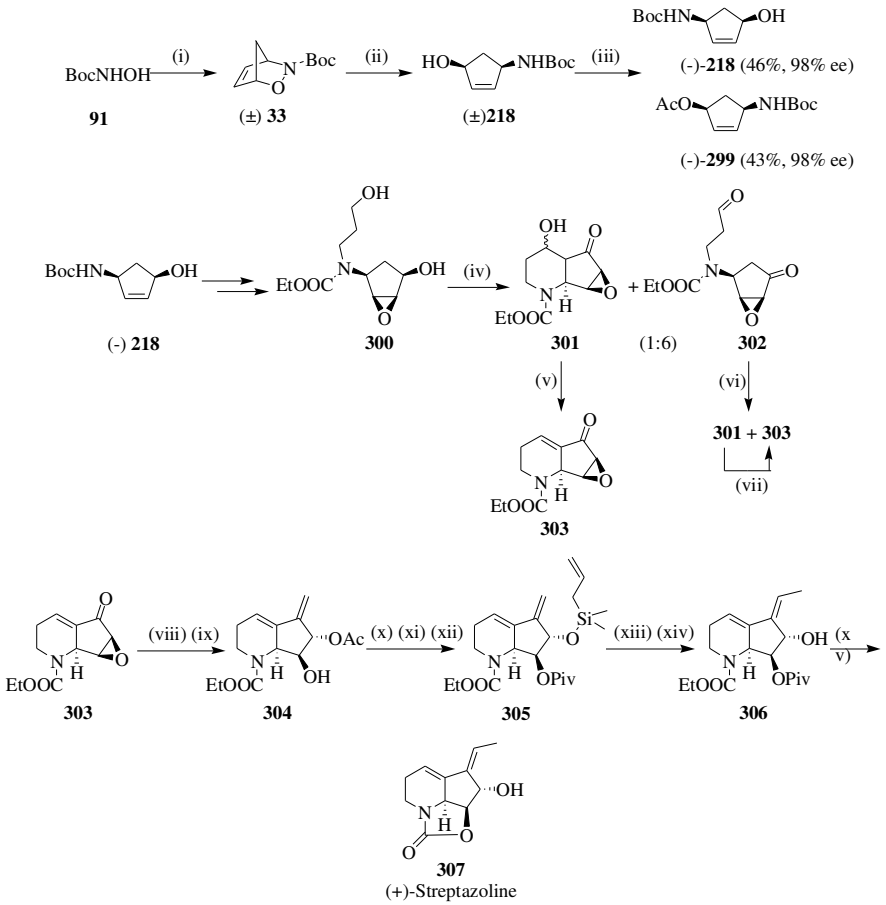


Reagents: (i) cyclopentadiene, $NaIO_4$, MeOH/H_2O (3:1); (ii) $Mo(CO)_6$, MeCN/H_2O (15:1) (52% two steps); (iii) Lipase AK, vinyl acetate, DCM; (iv) K_2CO_3, MeOH (98%); (v) TBSCl, imidazole, DMF (91%); (vi) OsO_4, NMO, THF/H_2O (2:1); (vii) $Me_2C(OMe)_2$, PPTS, DMF (87%); (viii) prenyl-Cl, NaI, NaH, THF; (ix) TBAF, THF (80%); (x) CS_2, MeI, NaH, THF (92%); (xi) $NaHCO_3$, Ph_2O, reflux (72%); (xii) 1N HCl/THF (3:2), reflux; (xiii) $NaIO_4$, THF/H_2O (2:1) then Jones oxidation then CH_2N_2 (48%); (xiv) NaH, DBU, benzene; (xv) 40% NaOH/MeOH (1:1) (63% two steps).

Scheme 54

Miller *et al.* obtained the antibiotic (+)-Streptazoline **307** using an enantiopure aminoalcohol as key intermediate (Scheme 55).[74,75] Racemic aminocyclopentenol **218** was obtained from cycloadduct **33**, which was synthesized by oxidation of BocNHOH **91** in presence of cyclopentadiene. The subsequent N-O reductive cleavage using $Mo(CO)_6$ afforded **218**. Kinetic resolution of racemic alcohol **218** was achieved using commercially available immobilized *Candida antartica* B lipase. With this enzyme, the enantiopure acetate (-)-**299** and alcohol (-)-**218** were obtained in 43% and 46% yield, respectively, with 98% ee after

recrystallization. Enantiopure (-)-**218** was subsequently transformed into epoxide **300** in eight steps. Swern oxidation carried out on **300** gave bicyclic **301** and aldehyde **302** as 1:6 mixture. Compound **301** was then transformed into compound **303** by dehydration of water using MsCl in basic media. Aldehyde **302** was converted to **303** in two steps using Al_2O_3 followed by MsCl in the presence of Et_3N and DMAP. Wittig reaction carried out on **303** and treatment with NaOAc in AcOH afforded the mono protected diol **304** in good yield. Protection of free alcohol as pivaloyl derivate, deacetylation and treatment with chlorosilyl derivate, afforded the corresponding silyl ether **305**. Derivative **305** reacted with Grubbs' second generation catalyst to give a RCM reaction followed by treatment with KF to remove a silyl group to obtain the allylic alcohol **306**. Compound **306** was then converted to (+)-Streptazoline **307** by cyclization in basic conditions.



Reagents: (i) cyclopentadiene, $NaIO_4$, $MeOH/H_2O$; (ii) $Mo(CO)_6$, $NaBH_4$, $MeCN/H_2O$; (iii) *C. Antartica B*, vinyl acetate, DCM, eptane; (iv) $(COCl)_2$, DMSO, DCM (82%); (v) Et_3N, MsCl, DMAP (86%); (vi) Al_2O_3 (83%); (vii) Et_3N, MsCl, DMAP (86%); (viii) NaH, Ph_3PCH_3Br, THF (71%); (ix) AcOH, NaOAc (87%); (x) $O(CO(CH_3)_3)_2$, TMSOTf, 0 °C (80%); (xi) K_2CO_3, MeOH; (xii) $Me_2ClSiCH_2CH{=}CH_2$ (74% two steps); (xiii) Grubbs II (2 mol%), DCM, reflux (100%); (xiv) KF, $KHCO_3$, MeOH/THF 1:1 (50%); (xv) NaOMe, MeOH, reflux, (76%).

Scheme 55

Acknowledgments

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CYCLOPHANES AND BICYCLOPHANES: FASCINATING MOLECULES IN ORGANIC CHEMISTRY

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Abstract. *The syntheses and biological activities of a series of four novel bispyridinium cyclophanes as Choline Kinase (ChoK) inhibitors are presented. Their synthetic methodology has been optimized according to dilution, temperature and reaction time and provides pure bispyridinium cyclophanes in high yields very easily. One of these cyclophanes, 4,8-diaza-3(1,4),9(4,1)-dipyridina-1(1,4),6(1,3)-dibenzenacyclodecaphan-3^1,9^1-bis(ilium) dibromide showed an $(IC_{50})_{ChoK}$ of 0.3 μM and is the most potent human ChoK inhibitor described to date. The syntheses of triply-bridged triscationic bicyclophanes are presented. Variable temperature ^{1}H NMR on the triquinolina triscationic derivative, 4,8,13-triaza-3,12(1,4),9(4,1)triquinolina-1,6(1,3,5)dibenzena-bicyclo[4.4.4]-tetradecaphane-$3^1$$9^1$$12^1$-tris(ylium) tribromide, showed the presence of two sets of conformers below –40 ºC separated by an activation barrier having a $\Delta G_c^{\neq}$ = 11.4 kcal mol^{-1}. The conformers arose from partial rotation around the $N_{exocyclic}$-4-CH_2 and CH_2-N^+ bonds, with the C_3 conformation assigned to the unique conformer at 25 ºC. Theoretical studies conform to the experimental results.*

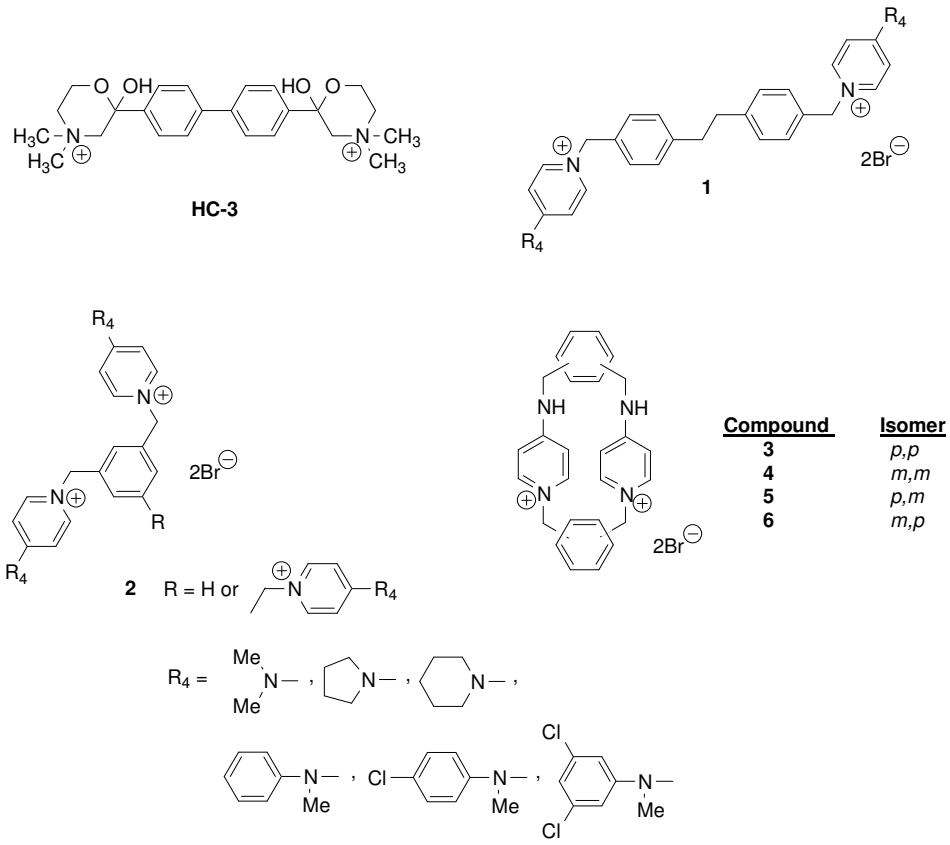
Contents

1. Introduction

Cancer cells differ from their normal counterparts in their mode of communication with their neighbouring due to aberrations in their signal network. The realization of aberrant signal transduction as the source of the transformed phenotype of cancer cells has generated mounting interest towards developing therapies targeting these aberrations.[1,2] Cancer cells develop as a result of a series of mutations in their

signalling pathways: (1) cells divide inappropriately with respect to their environmental context, (2) cells develop robust anti-apoptotic signals, avoiding stresses, and (3) cells develop molecular mechanisms to escape the immune system.

These cancer-specific signalling networks can, in principle, become their "Achilles' heel". Identification of these signaling pathways has become the basis of the "signal transduction therapy".[2] Cancer treatment is in need of selective drugs that can interfere specifically with signalling pathways affected during the carcinogenic process. Identification of new potential molecular targets is the key aim in the design of new anticancer strategies. Once identified, attempts for the generation of specific molecules to regulate their function can be achieved. Choline Kinase (ChoK) is responsible for the generation of phosphorylcholine (*P*Cho), a proposed second messenger required for DNA synthesis induced by growth factors. ChoK levels are increased in different tumour-derived cell lines and in several human tumours when compared with their corresponding normal tissues.[3] Moreover, ChoK inhibition has drastic inhibitory effects on cell proliferation and prevents tumour growth in mice.[4] It has been demonstrated that ChoK inhibitors lead tumour cells to apoptosis, whilst normal cells remain unaffected.[5]



Scheme 1

The synthesis of several derivatives was based on structural modifications of HC-3 that improve the ChoK inhibitory activity and omit the toxic effect. We have correlated the inhibitory effect on proliferation of symmetrical bisquaternary compounds[6] with their ability to inhibit the production of *P*Cho in whole cells. When the 1,2-ethylene-*p*-(bisbenzyldimethyl-diyl) (**1**, Scheme 1) moiety was used as a linker between the two 4-substituted pyridinium cationic heads, the structures were screened for their activity inhibiting isolated

ChoK. R_4 group which is a tertiary amine made a substantial contribution and it was suggested[7] that its role was electronic, *via* delocalisation of the positive charge. The importance of frontier orbital energies (LUMO) of model compounds was emphasised and interpreted.[8] Fifty-six biscationic dibromides with distinct heads [bis(4-substituted)pyridinium, bis(4-aminoquinolinium), bisquinolinium, and bisisoquinolinium moieties] and several spacers between the two charged nitrogen atoms were synthesized. The electron characteristic of the substituent at position 4 of the heterocycle and the theoretical lipophilic character of the whole molecule were found to significantly affect the antitumour activity.[9] We have studied the role played by a third positive charge on both ChoK inhibitory and antiproliferative activities. A benzene ring was used as a linker in order to carry out such a study because it allows us to obtain symmetrical bis- and tris-cationic compounds (general structure **2**, Scheme 1).

Trispyridinium compounds are more potent than the bispyridinium ones as inhibitors of human ChoK. The triscationic compound with the general structure **2**, R_4 being = 4-chloro-*N*-methylanilino (Scheme 1) showed a very good ChoK inhibitory activity (IC_{50} = 1.4 μM).[10] Nevertheless, the trispyridinium compounds are less active than the bispyridinium ones as antiproliferative agents because the latter show better lipophilicity to cross the cytosolic membranes. We have reviewed the relevance of the deregulation of ChoK (E.C. 2.7.1.32) in oncogene-driven cell transformation.[11]

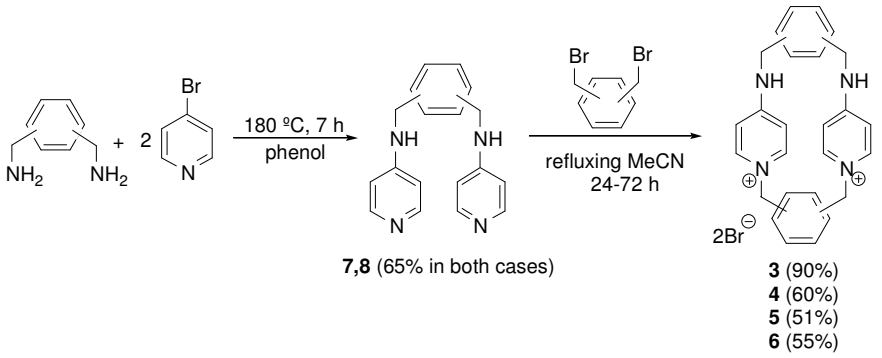
2. Bispyridinium cyclophanes: novel templates for human ChoK inhibitors

Up to here all the structures synthesized by our research group were open compounds and accordingly highly flexible molecules. However, rigidification has been a habitual tactic used to increase the activity of a drug or to reduce its side-effects. Incorporating the skeleton of a flexible drug into a ring is the usual way of "locking" a conformation that, moreover, can give information on the active conformation of the compound. As a first stage in the design of this new class of ChoK inhibitors, we embarked upon the synthesis of the simplest model of cyclic compounds that have only one benzene ring as a linker. The purpose is to study how the rigidity increases affects the ChoK inhibitory and/or antiproliferative activities and the following bispyridinium cyclophane family (**3–6**, Scheme **1**) was therefore prepared.[12] These cyclophanes differ from each other by the substitution pattern shown by the benzene rings. The first prefix takes into account the upper linker that connects the amino groups, whereas the second one is related to the disubstitution pattern of the lower benzene ring that links the N^+ atoms.

As can be seen in Scheme 1, compounds derived from both the *ortho*-benzenes have not been obtained due to the lack of solubility of the intermediates that makes the final cyclization reaction impossible.

2.1. Synthesis

The cyclophanes were synthesized according to Scheme 2. The dipyridines **7** and **8** (*para* and *meta* isomers, respectively) are novel and were prepared from the commercially available diamines and 4-bromopyridine in the presence of phenol, which is known to catalyze the reaction in the case of 2- and 4-haloquinolines.[13] As a reaction medium, phenol reduces both the reaction time and temperature of halogen-replacement reactions. Dipyridines **7** and **8** were characterized as the bishydrobromide compounds after recrystallization from methanol. The conversion of **7** and **8** to the desired cyclophanes was carried out under high-dilution conditions in acetonitrile at the reflux temperature of the mixture.



Scheme 2

To start with, the initial concentration was 0.04 M and the reaction was carried out by adding a solution of the dibromide drop by drop to the dipyridine structure; in this way the preparation of the cyclophanes is favoured and, accordingly polymer formation is kept to a minimum. Nevertheless, the ^{1}H NMR spectra of the structures obtained show the presence of a second compound very similar to the desired compounds. High resolution liquid secondary ion mass spectrometry (LSIMS) data and elemental analyses were correct demonstrating that impurity should have the same molecular formula as our targets. This led us to think that the substance obtained was the open monocationic compound as a consequence of an incomplete cyclization process.

Thus, a 50% mixture was obtained, which made the separation by recrystallization impossible due to the similarity of their physicochemical properties, and forced us to improve the synthesis method in order to oblige the monocationic salt to cyclize. The monoquaternized salt has to be dissolved to undergo the cyclization step with the participation of the other pyridine nitrogen atom. Therefore, increment of dilution, the use of a solvent more polar than acetonitrile and/or extending the reaction time facilitated the macrocycle formation (Table 1).

Table 1. Conditions used for the preparation of cyclophanes **3–6**.

Compound	Solvent	Dilution (M)	Time	Purification	Yield (%)
3	Acetonitrile	0.04	24 h	Impossible	50% Mixt.
4	Acetonitrile	0.02	24 h	Recrystallitation	60
5	Acetonitrile	0.02	24 h	Recrystallitation	51
6	Acetonitrile	0.01	24 h	Recrystallitation	55
3	Acetonitrile	0.004	3 d	Not necessary	90
3	Ethanol	0.004	12 d	Not necessary	N.D.[a]

[a]N.D.: Not Determined

Similar bisquinolinium cyclophanes[14,15] needed to be purified by tedious reverse-phase preparative HPLC since conventional purification methods failed to give analytically pure samples for biological testing, in spite of having been obtained under high-dilution conditions (0.001–0.002 M). In our case, this represents a great advantage for the accessibility of such an interesting class of compounds.

2.2. Biological activity

Compounds **3–6** were tested in an *ex vivo* system using human ChoK as a target. This assay allowed us to evaluate the affinity of the compounds for ChoK, without considering the possible passage through membranes. The effects on cell proliferation by the ChoK inhibitors in *ras*-transformed cells were next investigated on the HT-29 cell line (*in vitro* assay). This cell line was established from a colon adenocarcinoma, one of the most frequent solid cancers in humans that are mainly resistant to chemotherapy,[16] making these cells appropriate for the search for new antitumour drugs. The biological results of the four bispyridinium cyclophanes are shown in Table 2. Compound **6** is approximately 5-fold more potent than the most effective inhibitor of human ChoK previously reported [see ref. 10 and the triscationic compound with the general structure **2**, R_4 being = 4-chloro-*N*-methylanilino (Scheme 1)].

Table 2. ChoK inhibitory, antiproliferative activities and distance (Å) between the N^+ atoms for the most stable conformations of cyclophanes **3–6**. Compounds have been arranged according to decreasing ChoK inhibitory activity.

Compound	Isomer*	$(IC_{50})_{ChoK}$ (μM)	$(IC_{50})_{HT\text{-}29}$ (μM)	Distance N^+-N^+ (Å)
6	*m,p*	0.3	28.8	6.21
3	*p,p*	2.1	36.9	6.41
4	*m,m*	13.2	>100	5.14
5	*p,m*	24.8	58.6	5.25

*The first prefix takes into account the upper linker that connects the amino groups, whereas the second one is related to the disubstitution pattern of the lower benzene ring that links the N^+ atoms.

The first thing that draws attention is the fact that four structurally isomeric compounds present biological activities that are so different. This indicates that the substitution model of the cyclophane linkers is very significant for biological activity.

On one hand, regarding the ChoK inhibitory activity, it can be accepted that the lower benzene ring must be *para* because the two most active compounds (**6** and **3**) correspond to this pattern. If the $(IC_{50})_{ChoK}$ values of the two compounds with the *meta* pattern for the lower linker (**4** and **5**) are compared, and the two compounds with the *para* pattern for the lower one (**6** and **3**) are compared too, it can be inferred that the inhibitory activity notably increases when the upper benzene ring is *meta*.

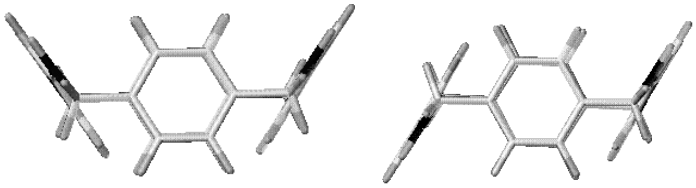
On the other hand, the influence of the isomerism of the lower linker on the antiproliferative activity follows the same trends shown in the ChoK activity. The fact that the enzymatic inhibition and the antiproliferative activity do not display an exact relationship may be explained on the basis that $(IC_{50})_{ChoK}$ assesses only the affinity of the ligand by the enzyme whereas in the $(IC_{50})_{HT\text{-}29}$, other biological factors intervene such as the passage through the cellular membranes. Although the anticancer activities of the cyclophanes are modest, the increase in lipophilicity should favorably affect the passage through the cytoplasmic membrane.

2.3. A model for the inhibition of ChoK by a new type of inhibitor

The study of the possible conformations of the cyclophane derivatives has been carried out by the Sybyl[17] programme on a Silicon Graphics Workstation. The different molecules have been constructed from

standard fragments of the libraries of the programme, necessitating the definition of a new type of atom (N.ar4) for the quaternary nitrogen of the pyridinium fragments. The force field Amber 4.1,[18] implemented in the Sybyl programme, has been used in the energy calculations. For the pyridine nitrogen the atomic N* has been used, corresponding to a nitrogen with sp^2 hybridization, needing the definition of new parameters,[19] which were generated by *ab initio* calculations on model molecules. Once the initial geometries were generated, we proceeded to their optimization using the Powell[20] method. The atomic charges were calculated by means of the AM1[21] Hamiltonian implemented in the MOPAC 6.0[22] programme. A distance-dependent dielectric constant with a value of $\varepsilon = 1$ was used and the optimization was continued until the energy gradient was less than 0.01 kcal/mol·Å^2. Conformational searches were carried out by means of molecular dynamics, using the "simulated annealing" technique, heating the molecule up to 1000 K for 1000 ps and cooling it down later exponentially to 200 K, maintaining it for another 1000 ps. 500 heating-cooling cycles were carried out on each molecule and the geometries obtained at the end of each cooling period were kept. These 500 conformations were optimized under the same conditions described before and were compared with each other to identify those conformations that were energetically and geometrically different. Finally, all unique conformations identified for each compound were optimised using *ab initio* (3–21 G) calculations performed by means of the Gaussian98[23] programme and used in the subsequent study.

Compound **3** has shown the simplest and very interesting conformational behaviour of all of them.[14] To summarize, four different conformations that are two-by-two isoenergetic were found for this molecule forming a conformational equilibrium. Transition states for the interconversion between them have been characterized and related to its spectroscopical properties. Scheme 3 shows the two different conformations for such a compound.



I

Amber4.1: 0.00
ab initio: 0.00

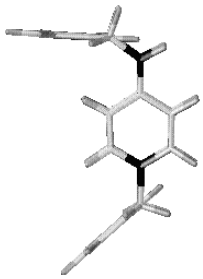
II

Amber4.1: 0.00
ab initio: 0.00

Scheme 3. Representation of the two energetically different conformations of compound **3** showing the way the two pyridinium rings are arranged. Relative energies are given in kcal·mol^{-1}.

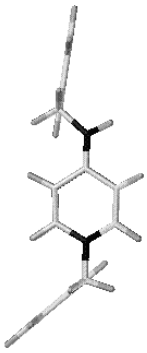
In both conformations the benzene rings are located in a practically parallel and fixed position, the main difference between them being the relative orientation of the two pyridine rings. In the most stable conformer (I) the pyridinium moieties are located in planes that form an angle of approximately 120º, while in the other conformer (II) both rings are parallel to each other. Both Amber and *ab initio* calculations agree in the values of the relative energies of both conformers and identify the first one as the most stable conformation for this molecule, unless the energy difference between them is small.

Compound **4** shows the existence of a more complex conformational equilibrium with 10 different conformations, of which 6 have different energies.[24] Scheme 4 represents the four most stable conformers of these molecules that also show the highest degree of symmetry.



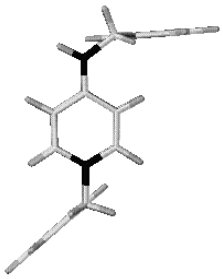
I

Rel. E: Amber 4.1: 0.00
ab initio: 0.00



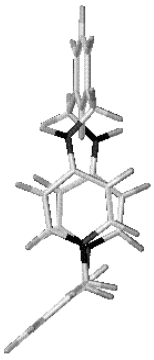
II

Rel. E: Amber 4.1: 0.31
ab initio: 0.69



III

Rel. E.: Amber 4.1: 1.91
ab initio: 3.29



IV

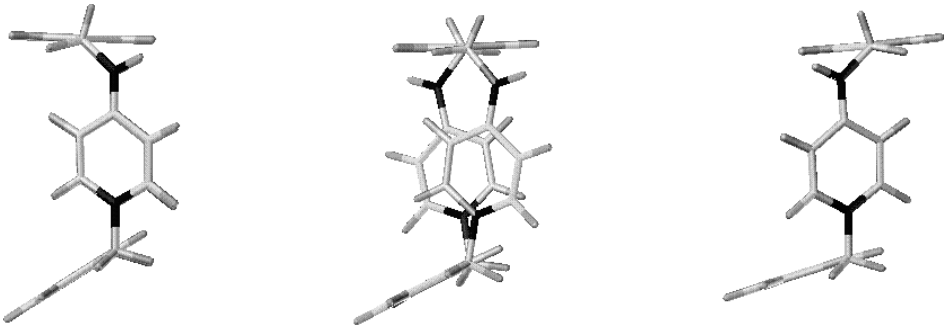
Rel. E.: Amber 4.1: 2.79
ab initio: 3.52

Scheme 4. Representation of the four different conformations for compounds **4**, showing the parallel layout of both pyridinium rings in all conformers and the high mobility of the upper benzene ring. Relative energies are given in kcal·mol^{-1}.

In all these conformations the pyridinium rings are located parallel to each other, whereas the benzene rings occupy more variable positions in the molecule, especially the upper ring that links the two amino groups. In the three first conformers (I–III), both amine NH bonds are parallel to each other whereas in the fourth one (IV), NH bonds are orientated in opposite directions. The other conformations found for compound **4** have smaller symmetry degrees, showing non-parallel pyridinium rings. Such conformations are intermediate conformers in the pseudorotation between the more stable conformers, and since their relative energies are elevated (more than 4 kcal/mol), their conformational populations are small. In fact, calculation of the conformational population using a Boltzman distribution indicates that the two most stable conformers account for more than 85% of the conformational population of this molecule. The main difference between all conformers of compound **4** is the position of the upper benzene ring that shows a high mobility and can adopt several different dispositions.

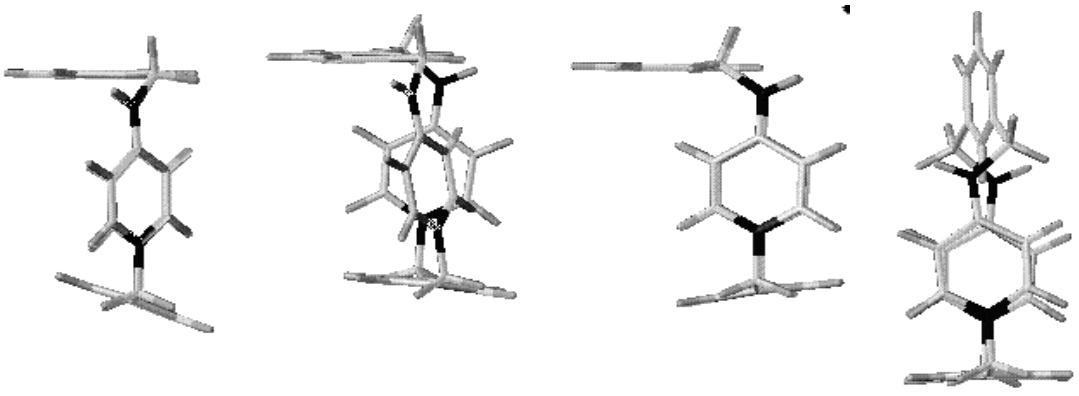
Four conformers are identified for **5**, although only three of them are of different energy (Scheme 5).[24] The order of energy of the two most stable conformations (I and II) depends on the method used in the calculation. Nevertheless, since the new parameters we have developed for Amber are not extensively

checked and the *ab initio* calculation is more accurate, we accept Gaussian results as being more reliable than those achieved by Amber. In any case, the energy differences between conformers are not very high and each of them is very suitable as a possible active conformation. The fourth conformation found for this molecule is symmetrical and isoenergetic to conformation II, and both conformations can be considered as intermediate conformers in the pseudorotation from I to III. Considering the *ab initio* values for the relative energy, the Boltzman distribution of the conformation of this molecule indicates that conformation I is the most populated one, representing 93% of the total conformational population. In this molecule, the upper benzene ring also shows higher mobility than the lower one, but the mobility is smaller than that corresponding to compound **4**.



I	II	III
Amber4.1: 0.21	Amber4.1: 0.00	Amber4.1: 1.91
ab initio: 0.00	*ab initio*: 1.53	*ab initio*: 3.29

Scheme 5. Representation of the energetically different conformations of compound **5**. Pyridinium rings adopt a non-parallel arrangement in this compound while the benzene rings can adopt spatial orientations that are equivalent to those of **3** (upper ring) and of **4** (lower ring). Relative energies are given in kcal·mol^{-1}.



I	II	III	IV
Amber4.1: 0.00	Amber4.1: 0.10	Amber4.1: 0.39	Amber4.1: 2.74
ab initio: 0.00	*ab initio*: 0.38	*ab initio*: 1.00	*ab initio*: 2.76

Scheme 6. The four energetically different conformations of **6**. Upper benzene rings adopt spatial arrangements equivalent to those of compound **3** while the lower one is equivalent to those of **2**. Relative energies are given in kcal·mol^{-1}.

Compound **6** presents the more complex conformational behaviour of all the above-mentioned molecules.[24] The total number of conformations found has been 14, from which only 4 are energetically different (Scheme 6). The three most stable conformations (I–III) of this compound have very similar energy. Conformations I and III show the NH bond parallel to each other while in conformations II and IV they are orientated in the opposite direction. Conformation II is an intermediate conformer in the pseudorotation from I to III while conformation IV is an intermediate in the transformation between III and its symmetrical conformation (not shown). Pyridinium rings are parallel to each other in conformations I, III and IV, while the benzene rings show a higher mobility, specially the upper benzene ring that occupies several spatial arrangements equivalent to those adopted by the same ring in **4**.

2.4. Structure-activity relationships

Cyclophanes, being rigid derivatives, could serve as templates for the definition of a model of the interaction with ChoK since all of them show distances between N^+ atoms that are practically constant. The distance between both atoms in the most stable conformation of each compound has been measured in order to compare it with the biological activity.

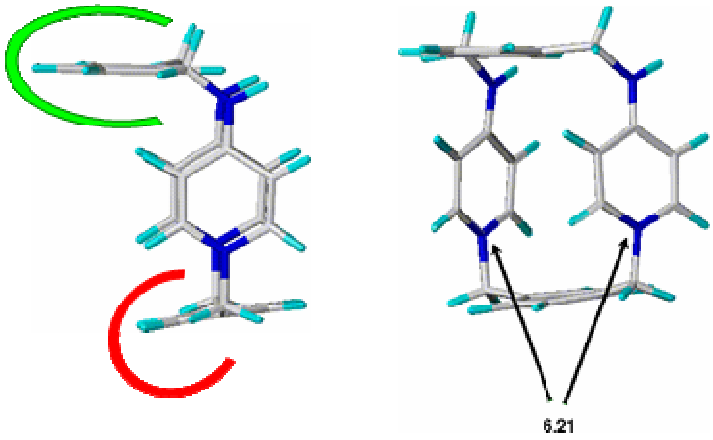
Table 1 also shows the distance (Å) between the N^+ atoms for the most stable conformation of cyclophanes **3–6**. It can be observed that in the most active compound, the distance between the N^+ atoms is 6.21 Å and that any deviation from this value involves a decrease in the ChoK inhibition potency. If the enzyme inhibition depended only on this structural factor, we could state that with more deviation, less inhibition is reached. The order of activity should have been the following: **6** (6.21 Å) > **3** (6.41 Å) > **5** (5.25 Å) > **4** (5.14 Å). Nevertheless, the order of ChoK inhibition of compounds **4** and **5** seems to be interchanged contrary to what could be expected on the basis of the above reasoning. Moreover, the differences in the distances between the quaternary nitrogen atoms are not so large as to explain such differences in their inhibitory potencies. Consequently, other factors must control the biological activity of these compounds.

Since cyclophanes are very rigid, their conformational flexibilities are very low and the differences observed in the activity must be due to the global shape of the molecule more than to any other factor. Hence, a comparison between the four compounds can explain the experimental inhibition activity:

a) The quaternary nitrogen atoms of **6** and **3** can be superimposed very tightly and nearly coincide in space. Both compounds show a similar substitution pattern in the lower benzene ring (*para*) and hence this moiety is completely equivalent in both molecules. The pattern substitutions for the upper ring are different and this feature defines the main difference between both molecules: compound **3** (*para* substitution) is more rigid than **6** (*meta* substitution) and the upper benzene ring in **6** can occupy more variable dispositions. Nevertheless, since **6** is the most potent compound, its higher flexibility is not detrimental to the interaction with ChoK. It can also be affirmed that the higher rigidity of **3** does not increase the binding to the enzyme.

b) Compounds **6** and **4** coincide in the type of substitution (*meta*) in the upper benzene ring and both compounds show a similar shape in this part of the molecule. The upper benzene rings of **6** and **2** can be superimposed almost perfectly in all the conformations of these molecules. On the other hand, the substitution in the lower benzene is different and the quaternary nitrogen atoms occupy more differentiated positions than in the previous couple of compounds. In **4**, the *meta* substitution in the lower benzene draws both nitrogen atoms near to each other (5.14 Å) and forces this benzene to be located further outwards than in **6**.

c) Comparing **6** and **5**, it can be seen that the pattern substitution in the upper and in the lower benzene rings is different. Hence, neither the quaternary nitrogen atoms nor the benzene rings coincide.



Scheme 7. Compound **6** showing a putative binding model for its interaction with ChoK. The optimal distance between the two quaternary nitrogen atoms is about 6.21 Å. The top zone indicates a wide hydrophobic region that must be filled by the upper benzene ring, whereas the lower zone indicates a region of very low steric tolerance, in which an increase in the size of the substituents would cause a decrease in the enzyme affinity.

All these features allow us to rationalize the behaviour of these molecules in the interaction with ChoK, and propose a model for the interaction with three anchorage zones (Scheme 7, green zone). One of these would be a wide hydrophobic pocket to allocate the upper benzene ring and allow that **6** and **4** completely fulfill it since only these compounds possess the appropriate geometry and flexibility in this zone of the molecule. The second anchorage point (probably two negatively charged acidic amino acids in the active site of the enzyme) would serve to interact strongly with the two quaternary nitrogen atoms and would be located at a distance of about 6.2 Å (Scheme 7, red zone). Compounds **6** and **3** are those that interact more strongly with this point since their distance between the N^+ atoms is very appropriate.

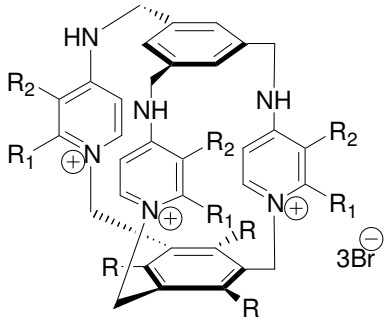
Finally, a small steric tolerance must exist in the interaction site in which the lower benzene ring (that links the two benzilic carbon) is located, and this gives rise to a lesser affinity for the enzyme in compounds **4** and **5**.

In short, **6** shows the best characteristics for the interaction, that is, the N^+ atom distance, geometry and flexibility in the upper benzene and appropriate geometry in the lower one. Compound **3** shows an appropriate N^+ distance and also the substitution in the lower benzene but not an appropriate geometry in the upper benzene, the second being a more potent compound. Structure **4** shows a poor N^+ distance but the *meta* substitution in the upper benzene gives place to a better interaction with the enzyme than **5** and is consequently the third compound in activity. Finally, **5** does not possess any of these conditions and will therefore give the worst interactions and the least activity.[24]

3. A C_3-symmetrical triquinolina triscationic bicyclophane: a highlight of a molecular architecture

Bicyclophanes are compounds in which two aromatic rings are joined by three bridges, all containing aromatic rings, and which are seldom referred to in bibliography. The exception that proves the rule was

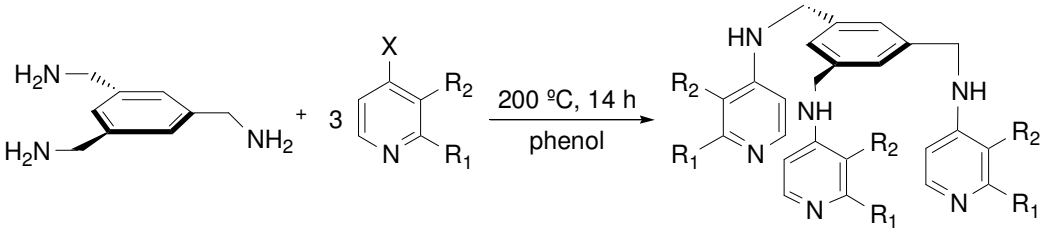
represented by Högberg and Wennerström,[25] and by Olsson *et al*.[26] more than twenty years ago. As part of the programme leading to the synthesis and biological evaluation of ChoK inhibitors we were interested in fulfilling the need for bicyclophane analogues in this unexplored area, and also interested in new triscationic ChoK inhibitors.



9 $R_1 = R_2$: H; R : H
10 $R_1 = R_2$: H; R : Me
11 $R_1 + R_2$: $(CH{=}CH)_2$; R : H

Scheme 8

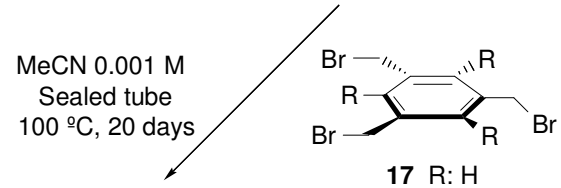
Bicyclophanes **9–11** (Scheme 8) were synthesized according to Scheme 9.[27] Tripyridine **15** and triquinoline **16** are novel and were prepared from the triamine **12**[28] and 4-bromopyridine **13** or 4-chloroquinoline **14**, respectively, in the presence of phenol.



12

13 $R_1 = R_2$: H, X : Br
14 $R_1 + R_2$: $(CH{=}CH)_2$; X : Cl

15 $R_1 = R_2$: H (66%)
16 $R_1 + R_2$: $(CH{=}CH)_2$ (57%)



17 R: H
18 R: Me

9 (87%), **10** (65%), **11** (8%)

Scheme 9

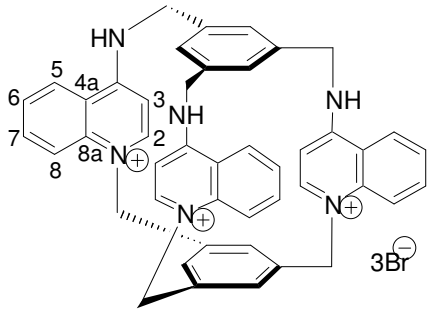
Tripyridine **15** and triquinoline **16** were characterized as tris-hydrobromide compounds. The conversion of **15** and **16** to the desired tricyclophanes was carried out in acetonitrile under high-dilution conditions (0.001 M) at the reflux temperature of the mixture in a sealed tube. A solution of the tribromide **17**[29] or **18** was added drop by drop to the trispyridine or trisquinoline structures. In this way the preparation of the tricyclophanes is favoured and polymer formation is accordingly kept to a minimum. The products **9** (87%) and **10** (56%) were isolated by vacuum filtration and purified by washing with ethyl acetate and

diethyl ether. When the same procedure was applied for the preparation of **11**, the product obtained proved to be impure and was then purified by repeated recrystallizations from ethanol which resulted in a low yield (8%). The structures of all the compounds were characterized by elemental analyses (C, H, N), HRMS, ^{1}H and ^{13}C NMR spectroscopies.

3.1. ^{1}H and ^{13}C NMR assignments

The first thing that drew our attention was the high symmetry of **9–11**, expressed by the number of proton and carbon signals corresponding to one third of the molecules. In the ^{1}H NMR spectra of **9–11**, H-3 shows the largest heterocycle shift (upfield), and H-2 behaves in a similar manner to the α-proton of pyridinium ions[30] (largest downfield). In the case of **9** and **10** the assignment of all the proton and carbon resonances is straightforward. In compounds **9** and **10** the symmetrical hydrogen atoms of the pyridinium rings show important differences in their chemical shifts. Protons H-2 and H-3 give rise to two sets of signals (δ 8.34 ppm, d, J = 7.4 Hz and δ 7.81 ppm, d, J = 7.7 Hz for **9**, and δ 8.42 ppm, d, J = 7.1 Hz and δ 6.97 ppm, d, J = 7.1 Hz for **10**, in DMSO-d_6 in both cases). Similarly, two sets of resonances are observed for the protons H-3 and H-5 (δ 6.85 ppm, dd, J = 2.7 and 7.4 Hz and δ 6.41 ppm, dd, J = 2.7 and 7.7 Hz for **9**, and δ 6.81 ppm, dd, J = 2.9 and 7.1 Hz and δ 6.33 ppm, dd, J = 2.7 and Hz for **10**, in DMSO-d_6 in both cases). Such a process was studied in depth in **3·PF$_6^-$** and the process observed by which the different chemical shifts of the pyridinium protons showed coalescence at a high-temperature ^{1}H NMR was the rotation around the C-4$_{pyridinium}$-NH$_{exocyclid}$ bond.[31] We did not consider it necessary to undertake a similar study on **9** and **10**, that would have provided only a different free energy activation, and decided to focus our efforts on the triquinolina triscationic bicyclophane **11**.

The ^{1}H and ^{13}C NMR unequivocal assignments are more complicated for bicyclophane **11**. Together with the ^{1}H and ^{13}C NMR spectra (in CD_3OD), a variety of 2D NMR experiments was performed to allow the assignment of proton and carbon chemical shifts and to elucidate unambiguously the structure of compound **11** at room temperature. The strategy followed provided for the concerted application of several gradient-enhanced experiments such as ^{1}H/^{13}C 2D HSQC[32] and HMBC.[33] A diagram is provided to show the numbering of both proton and carbon atoms for **11** (Figure 1).



11

Figure 1

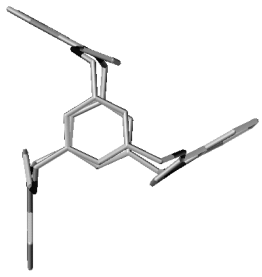
The unequivocal assignment of the benzene hydrogen atoms of the quinolinium moiety of **11** was the following step. The coupling pattern for H-5 and H-8 was the same (doublets), whilst the same held true for H-6 and H-7 (double doublets). The chemical shifts attributed to C-4, C-4a and C-8a were distinguished on

the basis of their HMBC connectivities. Cross correlations were observed between H-3 (δ 6.57 ppm, d, *J* = 7.6 Hz), and C-4a (δ 119.03 ppm), between H-2 (δ 7.92 ppm, d, *J* = 7.6 Hz), C-4 (δ 155.70 ppm) and C-8a (δ 138.62 ppm), between C-4a (δ 119.03 ppm), H-6 (δ 7.75 ppm, dd, *J* = 8.8 and 1.4 Hz), and H-8 (δ 8.46 ppm, d, *J* = 8.8 Hz). Additionally, H-7 (δ 8.05 ppm, dd, *J* = 8.8 and 1.4 Hz) exhibited a two-bond correlation to C-8a (138.62 ppm).

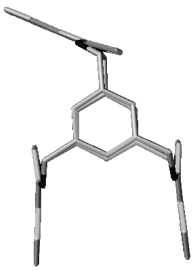
3.2. Conformational behaviour of bicyclophane 11

In order to determine the conformational behaviour of **11** in a CD_3OD solution, the structure of the conformers and the interconversion pathway between them warrant consideration. We have tried to record the ^1H NMR spectra at low temperatures in order to analyze the conformational behaviour of **11** in a CD_3OD solution but all the attempts were fruitless, because no coalescence phenomenon was observed. We have looked at the methylene protons and tried to exchange environments *via* a dynamic process over a range of temperatures, and no coalescence of these two proton signals was observed in the range 25 ºC to –60 ºC. Moreover, we were unable to obtain a crystalline sample suitable for molecular structure determination by X-ray crystallography. To overcome all these problems molecular modelling has been carried out as reported previously,[19] but optimizing the different conformations by means of *ab initio* calculations at the 6–31G* level.

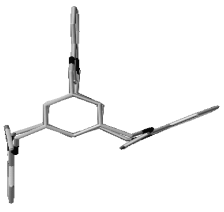
At the molecular level, helical chirality[34] is usually a consequence of strong conformational preferences around covalent bonds. This is the case in molecular propellers, chiral molecules possessing two or more subunits which can be considered as "blades" (*e.g.*, aryl or spirocyclic rings), which radiate from an axis of rotation (propeller axis).[35] Triarylmethanes are the most extensively studied structures of this class.[34a,36]



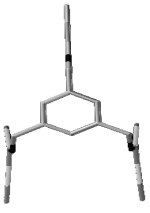
11a



11b



T1



T2

T3

Scheme 10. Top view of conformers (**11a** and **11b**) and transition states (**T1**, **T2** and **T3**) (*ab initio*) for **11**.

A careful study of the conformational behaviour of this molecule based on symmetry considerations allows us to identify a total of eight conformations. These conformations make up two diastereomeric sets of enantiomers. One set of enantiomers is of C_3 symmetry and consequently each enantiomer has three equivalent (homotopic) quinolinium rings (**11a** in Scheme 9). The other six have C_1 symmetry and each enantiomer has three nonequivalent quinolinium rings, differing from each other in the orientation sense (clockwise or counterclockwise) of the quinolinium rings. The other six conformations show two quinolinium rings in almost parallel dispositions as it is shown in Scheme 10 for the **11b** conformation.

The computational method indicates that conformation **11a** is the most stable conformer of the molecule. The C_3-symmetrical derivative **11a** was found to be 2.58 kcal mol^{-1} more stable than the C_1-symmetrical conformation **11b**. This energy difference is sufficient to consider **11a** and its enantiomeric one the only two conformations existing in solution at 25 ºC, the conformational population being calculated at 97.4 % (48.7 % for each one), considering a Boltzman distribution. The other six conformations account for only 2.5 % (0.4 % each one) of the conformational distribution.

When the ^{1}H NMR chemical shifts of the quinolinium moieties of the open derivatives **19** (Scheme 1, structure **1** with R_4: NH_2, R_5 + R_6: $(CH{=}CH)_2$, Z: $(CH_2)_n$, where n: 1–4, $(CH{=}CH)_c$ and –C≡C-, space isomers: 4',4'', X: N^+, Y: CH)[37] and bicyclophane **11** are compared (Table 3), it is observed that H-2 and H-3 are more shielded in the latter than in the former (δ 7.92 ppm and δ 6.57 ppm for H-2 and H-3 for **7**, against δ 8.57 ppm and δ 6.92 ppm, respectively, for **19**), whereas H-8 in **11** (δ 8.46 ppm) is more deshielded in relation to the same proton in **19** (δ 7.95 ppm). Obviously, the reason for this behavior lies in the different mobility of the quinolinium fragments which is more restricted in **7** than in **19**. Both **11a** and **11b** conformations can correctly explain the H-2 shielding observed in relation to compounds **19** since this hydrogen atom is located between both benzene rings in **11**.

Table 3. ^{1}H NMR chemical shifts for compounds **11** and **19** in CD_3OD solutions.

Proton	11	19[a]
H-2	7.92	8.57 ± 0.01[b]
H-3	6.57	6.92 ± 0.01[b]
H-5	8.33	8.40 ± 0.01[b]
H-6	7.75	7.69 ± 0.01[b]
H-7	8.05	7.89 ± 0.02[b]
H-8	8.46	7.95 ± 0.03[b]

[a]Taken from ref. 37. [b]Standard deviation for six values.

Similarly, H-8 suffers deshielding when compared to **19**. This fact is due to the higher rigidity of compound **11** that forces H-8 to a disposition in the shielding zone of the lower benzene ring. Although both **11a** and **11b** conformations may explain these findings, the higher conformational population calculated for **11a** and the simplicity of the NMR spectra in which only one third of the theoretical signals are observed, allow us to consider **11a** as the only conformation existing in solution for compound **11**.

Assuming that in solution the ground state of **11** is a propeller (helical) conformation, the possibilities for its interconversion may be analyzed systematically. The interconversion of diasteromers can be

considered in terms of "flip mechanisms", a "flip" being defined as a passage of one quinolinium ring through the plane perpendicular to that of the upper and lower benzene rings, which are parallel each other. In order to calculate the energy barrier for the interconversion between both types of conformations, transition states have been optimized by means of an *ab initio* calculation (HF and B3LYP, 6–31G** level). Three possible types of transition state have been found, all of which show a quinolinium ring orientated in a radial manner in relation to both benzene rings, differing in the orientation of the two remaining heterocycles. The calculated energies for these transition states depend on the theory level employed in the calculation method, and slightly smaller values are found with B3LYP method: 5.52, 6.32 and 6.63 kcal/mol, respectively (Table 4).

Table 4. Energy and number of occurrences for conformers and transition states of **11**. In parenthesis, conformational population calculated using a Boltzman distribution.

Conformation	No. occurrences	Amber	HF 6–31G**	B3LYP 6–31G**
11a	2	0.00	0.00 (48.1)	0.00 (46.1)
11b	6	1.29	2.58 (0.62)	1.94 (1.29)
T1	6	7.89	8.11	5.52
T2	3	9.30	9.51	6.32
T3	3	8.03	9.51	6.63

The smaller values of transition states energy obtained with B3LYP method are consistent with the fact that no decoalescence processes have been observed even at a temperature as low as –60 ºC. Probably such a dynamic process could be observed at lower temperatures, but the low solubility of this molecule does not permit the use of another solvent (different from CD_3OD) able to be cooled to an even lower temperature.

Although both **11a** and **11b** conformations may explain these findings, the higher conformational population calculated for **11a** and the simplicity of the NMR spectra in which only one third of the theoretical signals are observed, allow us to consider **11a** as the only one conformation existing in solution for compound **11**.

Table 5. Energy and number of occurrences for conformers and transition states of **11**.

Conformation	No. occurrences	Amber	6–31G*
11a	2	0.00	0.00
11b	6	1.29	2.58
T1	6	7.89	8.11
T2	3	9.30	9.51
T3	3	8.03	9.51

Assuming that in solution the ground state of **11** is a propeller (helical) conformation, the possibilities for its interconversion may be analyzed systematically. The interconversion of diastereoisomers can be

considered in terms of "flip mechanisms", a "flip" being defined as a passage of one quinolinium ring through the plane perpendicular to that of the upper and lower benzene rings, which are parallel each other. In order to calculate the energy barrier for the interconversion between both types of conformations, transition states have been optimised by means of an *ab initio* calculation (level 6–31G*). Three possible types of transition state have been found, all of them showing a quinolinium orientated in a radial manner in relation to both benzene rings, the difference between them being the orientation of the two remaining heterocycles. The calculated energies for these transition states are 8.11 and 9.51 kcal·mol^{-1}, respectively (Table 5).

3.3. Biological activity

Compounds **9–11** proved to be inactive as ChoK inhibitors. The inactivity of bicyclophanes **9–11** as ChoK inhibitors probably could be due to their large size, which prevents them to interact with the active site of the enzyme. Nevertheless, they are fairly active as antiproliferative agents against the MCF-7 human breast cancer cell line (*in vitro* assay): **9**, IC_{50} = 18.24 ± 2.38 μM; **10**, IC_{50} = 11.88 ± 3.92 μM; **11**, IC_{50} = 14.39 ± 2.06 μM. The fact that the bicyclophanes have shown antiproliferative effects but no inhibition of ChoK, indicate that cyclophanes and bicyclophanes act as antitumoural agents by different mechanisms.

Breast cancer represents the most common tumour of females in many industrialized countries.[38] The MCF-7 human breast cancer cell line had been used as an excellent experimental model to improve the efficacy of different therapies before its use in patients.[39,40]

4. Conclusions

The synthesis and biological activities of novel bispyridinium cyclophanes as ChoK inhibitors have been described. The ChoK inhibition activities of the cyclophanes (**3–6**) strongly depend on the disubstitution model of the upper and lower benzene rings. Compound **6** is the most potent human ChoK inhibitory agent reported to date, showing activity in the low micromolar range. Clearly the bispyridinium cyclophane derivatives that we have described here are useful pharmacological tools for the further investigation of ChoK inhibitors as antiproliferative agents.

To our knowledge, **9–11** are the first examples of triscationic tripyridina bicyclophanes, a subclass of the propeller-like cages. Compound **11** exists as two diastereomeric sets of enantiomers, one with C_3 symmetry and one with C_1. The NMR spectrum at room temperature showed the signals corresponding to a single conformer with helical asymmetry. Compound **11** showed an IC_{50} = 14.39 ± 2.06 μM as an antiproliferative agent against the MCF-7 human breast cancer cell line. ChoK inhibitors provide evidence that the blockade of *P*Cho is a valid strategy for the development of new anticancer agents, opening a new avenue for the development of antitumour drugs with a novel mechanism of action. Nevertheless, further studies are needed to better understand the mechanism(s) of ChoK regulation that might help us to improve the design of antitumour drugs against this enzyme. Obviously, solving the 3D-structure of the human ChoK with an inhibitor will certainly trigger the design and discovery efforts towards novel and more potent ChoK inhibitors with antiproliferative properties.

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