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Preface

Heterocyclic derivatives are important in organic chemistry as products (including natural) and/or useful tools in the construction of more complicated molecular entities. Their utilization in polymeric, medicinal and agricultural chemistry is widely documented. Both dyestuff structures and life molecules frequently involve heterocyclic rings that play an important role in several biochemical processes.

Volume 14 (2010) keeps the international standard of THS series and contains eleven chapters, covering the synthesis, reactivity, and activity (including medicinal) of different heterorings. Authors from Belgium, France, Italy, Poland, Portugal, Russia and Spain are present in this book.

As yet, THS Volumes 1-14 published 197 reviews by 552 authors from 25 different countries for a total of about 6.000 pages.

Comprehensive Reviews reporting the overall state of the art on wide fields as well as personal Accounts highlighting significative advances by research groups dealing with their specific themes have been solicited from leading Authors. The submission of articles having the above-mentioned aims and concerning highly specialistic topics is strongly urged. The publication of Chapters in THS is free of charge. Firstly a brief layout of the contribution proposed, and then the subsequent manuscript, may be forwarded either to a Member of the Editorial Board or to one of the Editors.

The Authors, who contributed most competently to the realization of this Volume, and the Referees, who cooperated unselfishly (often with great patience) spending valuable attention and time in the review of the manuscripts, are gratefully acknowledged.

The Editors thank very much Dr. Lucia De Crescentini for her precious help in the editorial revision of the book.

Orazio A. Attanasi and Domenico Spinelli

Editors

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CYCLOADDITION REACTIONS OF CONJUGATED AZOALKENES

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Abstract: *Cycloaddition reactions of conjugated azoalkenes, also named 1,2-diaza-1,3-butadienes, leading to the synthesis of six-, five-, four- and three-membered heterocycles, are overviewed. Main emphasis on [4+2] cycloadditions is given, but [3+2], [4+1], [2+2] and [2+1] cycloadditions are also discussed.*

Contents

1. Introduction

Over the past decades, conjugated azoalkenes have emerged as powerful intermediates for the preparation of an impressive number of new heterocyclic systems, when used either as Michael-type acceptors in conjugate 1,4-additions or in cycloaddition reactions, with a wide range of olefinic and heterocyclic partners. The adducts and cycloadducts so formed have proved to be of great value and importance, not only due to their pharmacological properties and/or biological activity, but also as building blocks or key intermediates in organic synthesis.

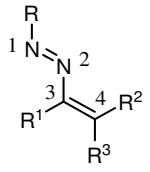


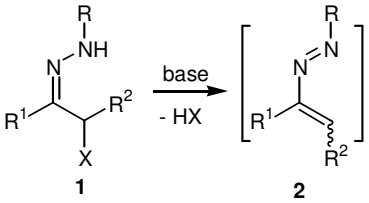
Figure 1. Numbering and possible substitution pattern on azoalkenes.

Despite their considerable interest and numerous synthetic applications, conjugate additions of azoalkenes, which have been recently reviewed,[1] fall beyond of the scope of this overview. General methods

for the synthesis or generation of azoalkenes are described briefly but most of the review is devoted to their use in cycloaddition reactions.

2. Synthesis or generation of azoalkenes

Conjugated azoalkenes are usually very reactive species. Their properties are profoundly modulated by the electron-withdrawing or releasing ability of substituents. Their stability is also directly associated with the substitution pattern. Electron-deficient 4-unsubstituted azoalkenes are very unstable species that are usually generated and intercepted *in situ*. Depending on the nature of their substituents, 1,3,4-substituted-azoalkenes are very often stable enough to be isolated or even to be purified by column chromatography. Whether they are isolated or generated *in situ*, by far the most common and general method for the preparation of azoalkenes is a base induced 1,4-dehydrohalogenation of α-halo-hydrazones[1–7] carrying a wide variety of substituents, the most representative of which are carboxyl, carbonyl, phosphonyl, phosphinyl, heterocyclic, aryl and alkyl groups (Scheme 1).

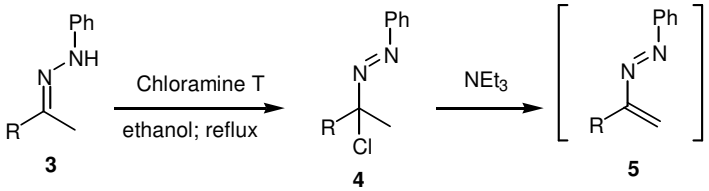


1 **2**

R = CO_2R^3; $SO_2C_6H_4Me$-4; COR^4; Aryl
R^1 = CO_2R^5; $P(O)(OR^6)_2$; Alkyl; Aryl
R^2 = H; Br; Cl; $P(O)(OR^7)_2$; $P(O)Ph_2$; CO_2R^8; COR^9
X = Br; Cl

Scheme 1

Recently, dehydrohalogenation has also been used to promote the generation of azoalkenes. This was not the habitual 1,4- but an 1,2-dehydrochlorination, mediated by triethylamine, of chloro-azo compounds such **4** derived from Chloramine T oxidized aromatic or alkyl *N*-phenylhydrazones **3** possessing an α-methyl group[8] (Scheme 2). Other methods with less relevancy or impact like oxidation with I_2[9] or HgO[9,10] MnO_2[10] or Cu(I)[11] and thermolysis[12] of hydrazones have also been occasionally used.



3 **4** **5**

R = Et; Ph; Furyl; C_6H_4-(NO_2)-4; C_6H_4-Cl-4

Scheme 2

3. Cycloaddition reactions of azoalkenes

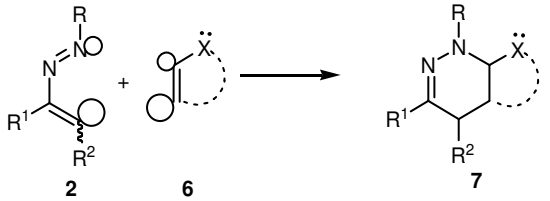
3.1. [4+2] Cycloadditions

Cycloadditions in which azoalkenes behave as conjugated heterodienes are the most representative and significant reactions and have been the basis of much of the new chemistry of these compounds in recent decades.

3.1.1. With electron-rich C=C bonds and heterocycles

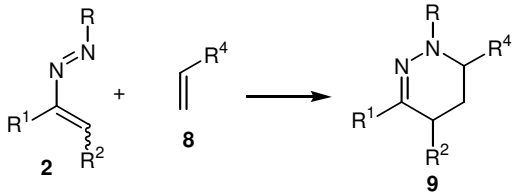
Due to the presence of the two nitrogen atoms, more electronegative than carbon, combined with one or, more often, with two electron-withdrawing substituents, these azoalkenes possess strong electrophilic character and therefore their cycloadditions are predominantly with electron-rich double bonds and heterocycles in a Diels-Alder process with 'inverse electron demand'.

The cycloadducts are usually obtained with a high degree of regio- and stereo-selectivity, as predicted by frontier molecular orbital interactions in which the dienophile is the donor component - HOMO controlled- and the diene is the acceptor - LUMO controlled. Consequently, the major regioisomer is the result of the interaction of the terminal atom of the electron-rich alkene or heterocycle bearing the higher HOMO coefficient with the terminal carbon atom of the azoalkene, which in the LUMO bears the higher orbital coefficient (Scheme 3).

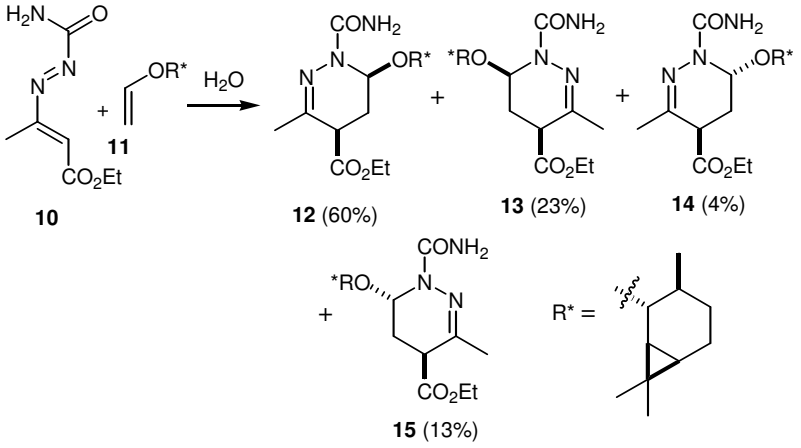


Scheme 3

The reaction with carbon dienophiles[12b,13,14] produces 2,3,4,5-tetrahydropyridazines (Scheme 4) and follows the pattern of the donor-acceptor relationship, *i.e.*, as more electron-rich or donor is the 2π partner and the more electron-deficient or acceptor is the azoalkene, the efficiency and selectivity of the reaction increase. Thus, for example, vinyl ethers are much more efficient reaction partners than simple alkenes. In some cases, and especially with 4-unsubstitued azoalkenes (R^2=H), a proper balance between electrophilicity/reactivity and stability must be attained in order to obtain better yields and clean reactions.



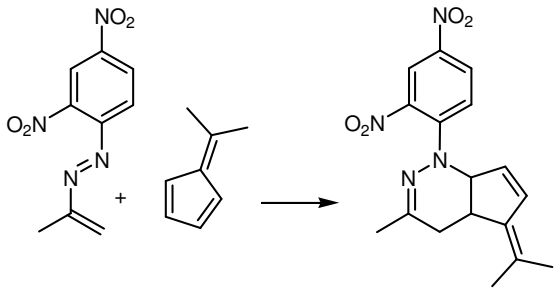
Scheme 4



Scheme 5

The vast majority of these reactions have been carried in a great variety of organic solvents, but often water is a better solvent and has been proved to be particularly suitable for asymmetric inverse-electron demand Diels-Alder reaction of azoalkenes[15] (Scheme 5).

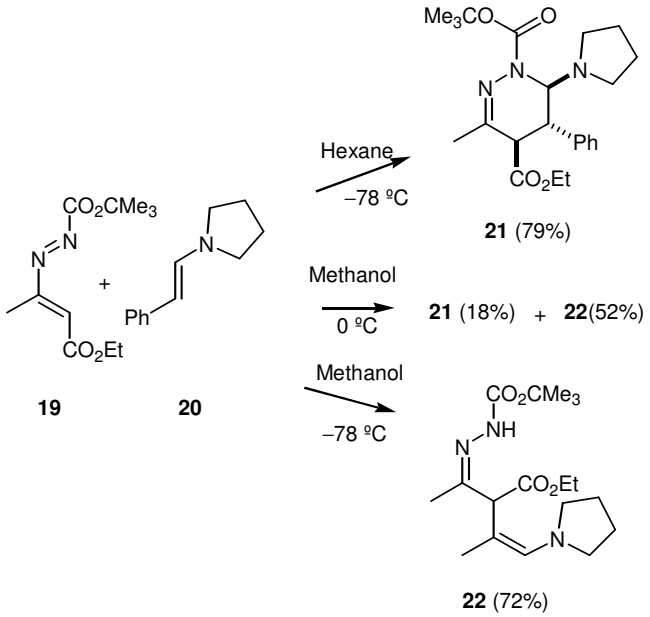
Cyclic and acyclic carbodienes such cyclopentadiene, 6,6-dimethylfulvene and 1,3-dimethyl-1,3-butadiene also participate, as dienophiles, in cycloaddition reactions with azoalkenes,[10,13h,j,16] although occasionally diverse reactivity has been observed[17](Scheme 6).



16 **17** **18** (68%)

Scheme 6

When compared with other alkenes, reactions with highly activated dienophiles, such as enol ethers carrying extra donor substituents or enamines, are sometimes less straightforward. For example, reactions with enamines have been shown to be solvent and temperature dependent[18] (Scheme 7).



19 **20**

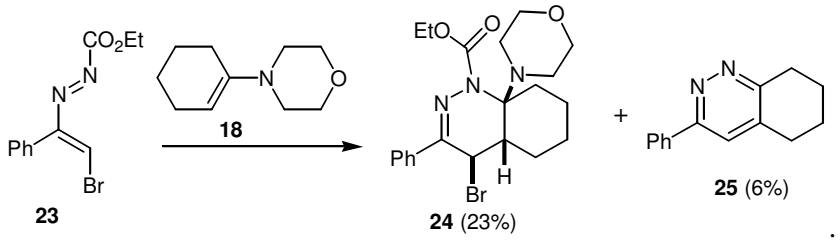
21 (79%)

21 (18%) + **22**(52%)

22 (72%)

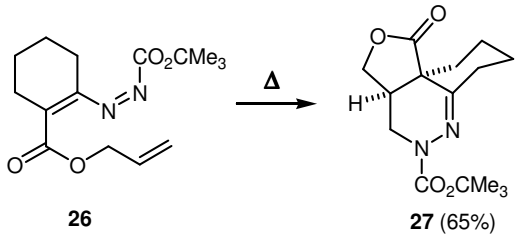
Scheme 7

In an investigation searching for possible anti-influenza virus, tetrahydropyridazines have been obtained as the sole reaction products in reactions of azoalkenes with enamines[19] but 4-chloro- or 4-bromo-azodienes[20] produced tetrahydropyridazines and aromatized pyridazines (Scheme 8). Quite often the reactions of azoalkenes with enamines are on the borderline between [4+2] and [3+2] cycloadditions or between these and conjugate addition,[18,20,21] and small structural or reaction conditions changes can drive the reactions to follow different mechanisms or even different mechanisms operating in the same reaction.



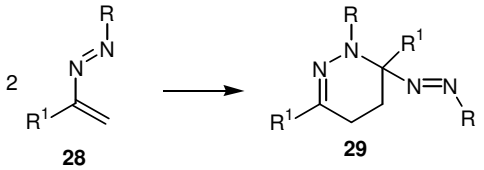
Scheme 8

Intramolecular [4+2] cycloadditions of azoalkenes have also been successfully reported as reliable synthetic strategies to diverse fused polyheterocycles.[22] An illustrative example is shown in Scheme 9.



Scheme 9

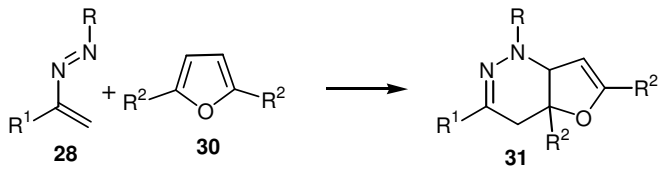
In the absence, or in the presence of a very inefficient dienophile, azoalkenes bearing no substituent at the 4-position show the tendency to self-condense giving cyclic dimers[16,23] (Scheme 10).



Scheme 10

3.1.2. With electron-rich aromatic heterocycles

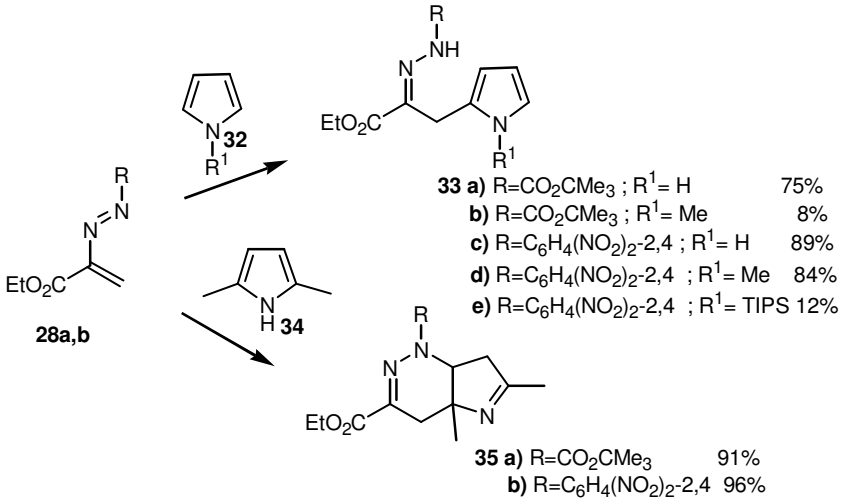
The most commonly reported cycloadditions with this class of compounds are with 5-membered rings, π-excessive heteroaromatics such furans, pyrroles and indoles. Furan and 2,5-dimethylfuran have proved to be particularly good dienophiles in reactions with highly electrophilic azoalkenes bearing no substituent at C-4[13b,h,16] (Scheme 11). However, when azoalkenes carrying 1- and/or 3-substituents possessing lower electron-withdrawing capacity were used, the reaction efficiency was lower and the yields inferior. No adducts were isolated when an ethoxycarbonyl group was present at the C-4 position.[16]



a) R = CO_2CMe_3; R^1 = CO_2Et; R^2 = H 100%
b) R = $C_6H_4(NO)_2$-2,4; R^1 = CO_2Et; R^2 = H 73%
c) R = $C_6H_4(NO)_2$-2,4; R^1 = Ph; R^2 = H 89%
d) R = $C_6H_4(NO)_2$-2,4; R^1 = Me; R^2 = H 22%
e) R = $C_6H_4(NO)_2$-2,4; R^1 = Ph; R^2 = Me 87%

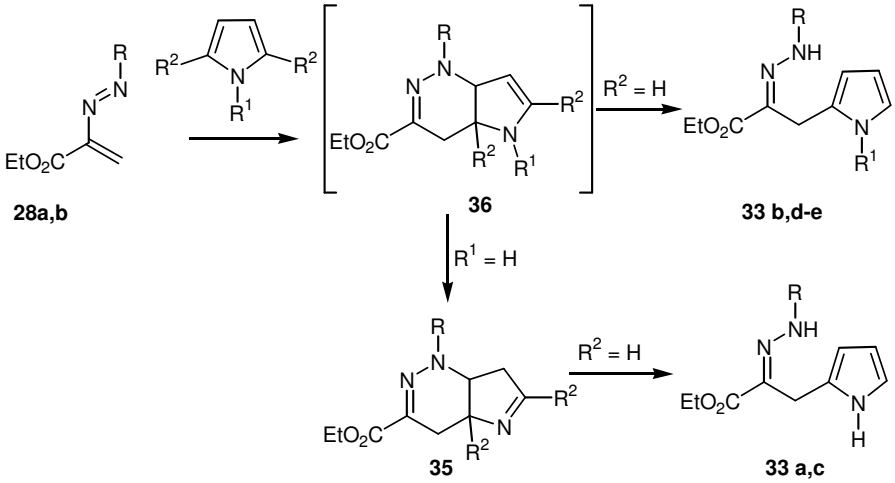
Scheme 11

With pyrrole[13a,c,24] and *N*-methyl pyrrole[24] the open chain hydrazones **33** were isolated as single *anti* stereoisomers, but with 2,5-dimethylpyrrole **34** bicyclic pyridazines **35** were obtained[24] (Scheme 12).



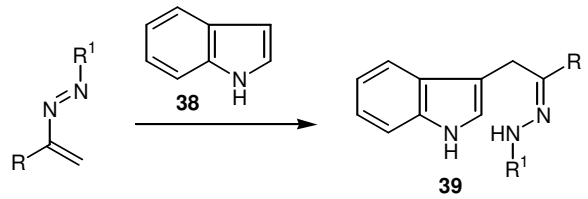
Scheme 12

With 1,2,5-trisubstituted pyrroles no adducts or cycloadducts were isolated, but only degradation products were detected. Taking into account all the above observations, the authors postulate that these reactions are all Diels-Alder cycloadditions with inverse electron demand. Cycloadducts **36** are proposed as the primary products of the reactions, but if no 2,5-substituents are present (R^2=H), the six-membered heterocycles open to the corresponding hydrazones with the concomitant rearomatization to the thermodynamically more favorable pyrrole ring. With 2,5-disubstituted pyrroles, the primary cycloadducts **36** tautomerize to the imines such **35**; with 1,2,3-trisubstituted pyrroles this enamine-imine tautomerization is blocked and likely further additions (with the very reactive enamine double bond of **36**) can occur producing complicated mixtures of products[24] (Scheme 13).



Scheme 13

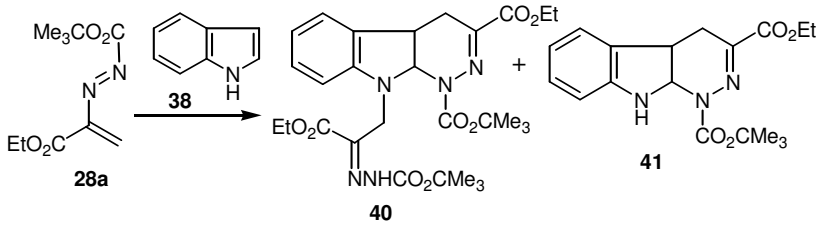
Generally, for the reaction of azoalkenes with indole, the open chain hydrazones **39** are isolated as result of the rearrangement of primarily formed cycloadducts[13c] (Scheme 14).



a) R = CO_2Et ; $R^1 = C_6H_3(NO_2)_2$ -2,4 93%
b) R = CO_2Et ; $R^1 = SO_2C_6H_4Me$-4 23%
c) R = $P(O)(O^iPr)_2$; $R^1 = CO_2CMe_3$ 36%

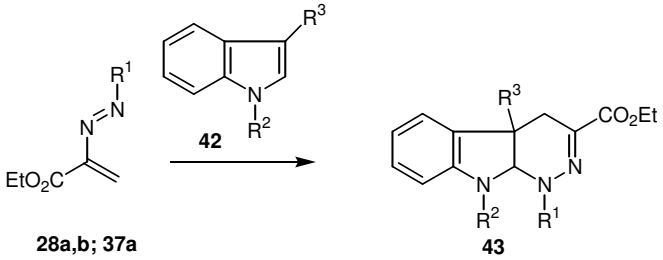
Scheme 14

The reaction of a large excess of indole with azoalkene **28a**[13g] was more complicated. Two products were isolated, but neither of them was the expected open chain hydrazone. One, **40** (47%) was formed from one molecule of indole and two of the azoalkene; the other one was the 1:1 cycloadduct **41** (41%). If one equivalent of indole was used, only the 2:1 adduct **40** was isolated in 78% yield (Scheme 15).



Scheme 15

When an *N*-substituted indole such as 1-benzylindole was reacted with azoalkenes **28a** and **37a**, the 1:1 adducts **43a,b** were isolated. In contrast, this strategy was not necessary in the reactions of 3-methylindole and this latter proved to be a good heterodienophile. The cycloadducts **43c–d** were the sole isolated products[13h] (Scheme 16).



a) $R^1 = CO_2CMe_3$; R^2 = Bn; R^3 = H 63%
b) $R^1 = C_6H_3(NO_2)_2$ -2,4; R^2 = Bn; R^3 = H 81%
c) $R^1 = C_6H_3(NO_2)_2$ -2,4; R^2 = H; R^3 = Me 50%
d) $R^1 = SO_2C_6H_4Me$-4; R^2 = H; R^3 = Me 54%

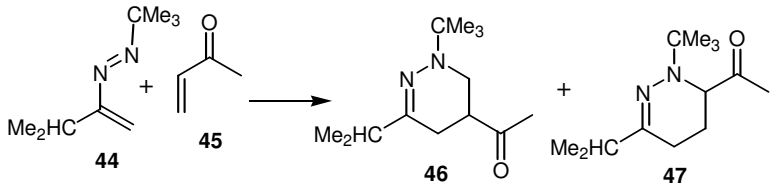
Scheme 16

Reactions between 1,3-dimethylindole and 1,3,4-trisusbtituted azoalkenes were troublesome,[21b] leading to complicate mixture of products arising from [4+2] or [3+2] cycloadditions.

3.1.3. With electron-deficient dienophiles

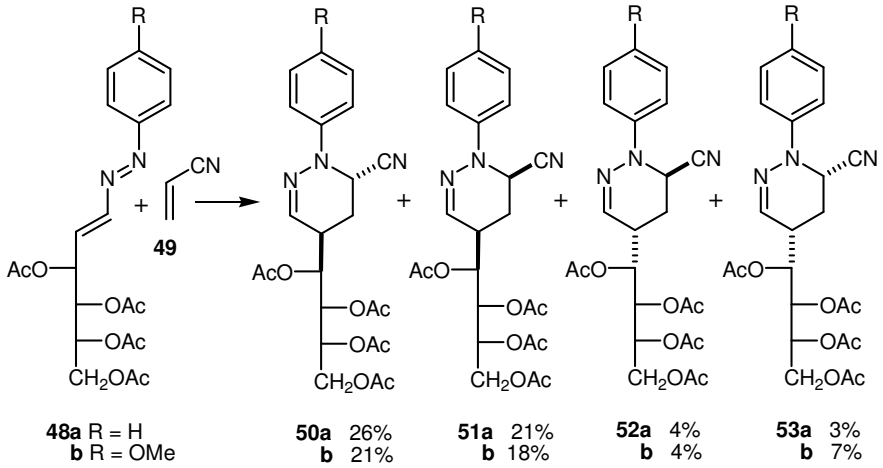
Although fewer examples are found, conjugated azoalkenes carrying no electron-withdrawing substituents, *i.e.*, possessing neutral or electron-releasing properties, can also efficiently participate, as

heterodienes, in normal electron demand Diels-Alder reactions with a large variety of electron-deficient 2π partners. Symmetrical dienophiles, such as tetracyanoethylene,[25] *N*-phenylmaleimide,[25] 4-phenyl-4*H*-1,2,4-triazole-3,5-dione,[12a] maleic anhydride,[26] maleimide,[26] dimethyl fumarate[26] and diethyl azodicarboxylate (DEAD)[27] have been satisfactorily used. Methyl vinyl ketone[23c,26] proved to be a very efficient dienophile for azoalkene **44**, since a quantitative yield was obtained, but the reaction lacked in regioselectivity since a 39/61 mixture of structural isomers of 5- and 6-acetyltetrahydropyridazines **46** and **47** were obtained, respectively (Scheme 17). Reactions of chiral carbohydrate-derived azoalkenes with 1,4-benzoquinone, 1,4-naphtoquinone and also diethyl azodicarboxylate[28] occurred with high facial stereoselectivity. The reaction with DEAD was greatly improved by the use of microwave induction.[29]



Scheme 17

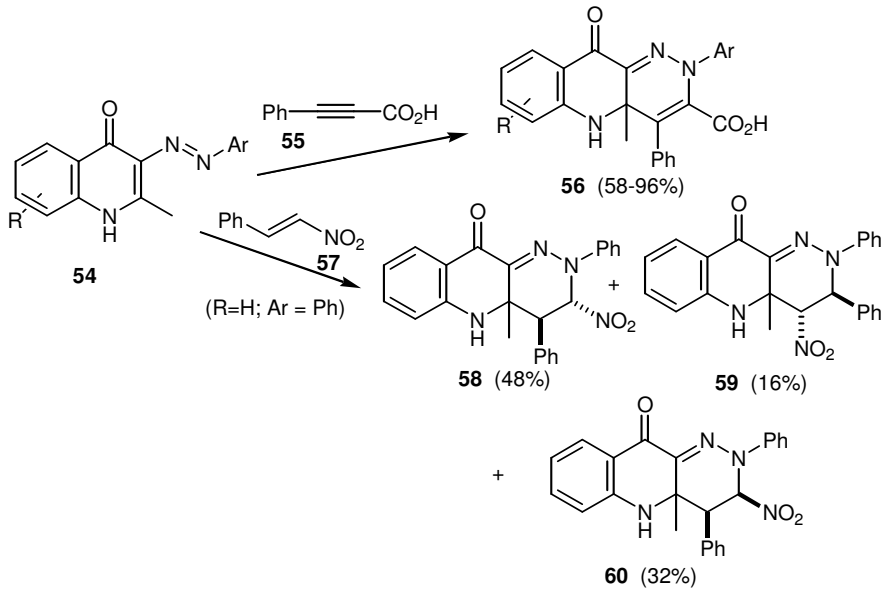
In order to shed some light on the regio- and diastereo-selectivity, the behaviour of chiral azoalkenes **48** with the unsymmetrical dienophile acrylonitrile **49** was experimentally and theoretically investigated[30] (Scheme 18).



Scheme 18

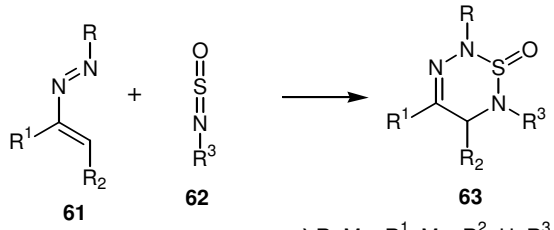
Reactions were found to be completely regiospecific and the observed diastereoselection was consistent with a preferred attack to the *Re* face of the heterodiene unit. The stereochemistry of the major cycloadduct **50a** has been definitely established by X-ray crystallography, revealing in addition a conformation in which the cyano group was in axial position. The theoretical calculations, on a reduced model, correctly predicted the regiochemistry experimentally observed and also indicated that the axial orientation of the cyano group can be rationalized in terms of a stabilizing anomeric effect.

Quinolone based azoalkenes have been reported[31] to produce pyridazines regioselectively when intercepted by phenylpropiolic acid; β-nitrostyrene was also an efficient dienophile, but in this case, tetra-hydropyridazinequinolone cycloadducts were obtained with lower selectivity (Scheme 19).



Scheme 19

In addition to electron-deficient C=C and N=N bonds, also N=S bonds of sulphinylamines[32] (Scheme 20) and C=S bonds of fluorenethione and fluorenethione *S*-oxide (sulphine) have been used as hetero-dienophiles in reactions with azoalkenes (Scheme 21).[33] However, diarylsulphines and diarylthiones failed to react.

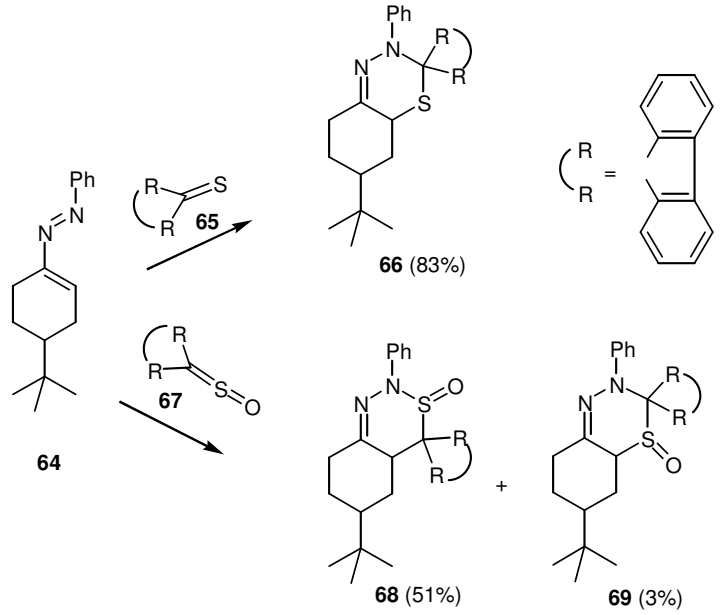


a) R=Me; R^1=Me; R^2=H; R^3=COPh 56%
b) R=Me; R^1=Me; R^2=H; R^3=Ts 75%
c) R=Me; R^1=Me; R^2=Me; R^3=Ts 59%
d) R=Ph; R^1=Me; R^2=CONPh; R^3=Ts 43%
e) R=Ph; R^1=R^2= -$(CH_2)_4$-; R^3=Ts 56%
f) R=Ph; R^1=R^2= -$(CH_2)_4$-; R^3=CO_2Et 56%
g) R=Me; R^1=R^2= -$(CH_2)_4$-; R^3=Ts 90%
h) R=Me; R^1=R^2= -$(CH_2)_4$-; R^3=Ms 86%

Scheme 20

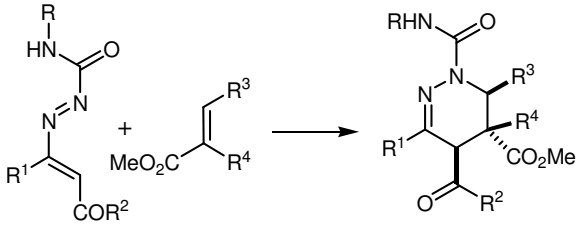
Thus, cycloadditions of azoalkene **64** with thione **65** were found to be completely regioselective, leading to the corresponding 6*H*-1,3,4-thiadiazine **66** but with sulphine **67**, smaller selectivity was observed, with the formation of regioisomeric mixtures of 2*H*-1,2,3- and 6*H*-1,3,4-thiadiazine-1-oxides **68** and **69**, even though the latter in a much smaller amount.

Diels-Alder cycloaddition reactions between electron-rich dienes and electron-rich dienophiles or *vice-versa*, between electron-deficient dienes and electron-poor dienophiles are uncommon. Recently unprecedented cycloaddition reactions between azoalkenes carrying electron-withdrawing substituents and electron-deficient dienophiles were reported,[34] conducting to novel tetrahydropyridazines **72** with a high degree of regio- and stereo-selectivity (Table 1).



Scheme 21

Table 1. Diels-Alder reactions of electron-deficient azoalkenes **70** with electron-deficient acrylate esters **71**.



70 **71** **72**

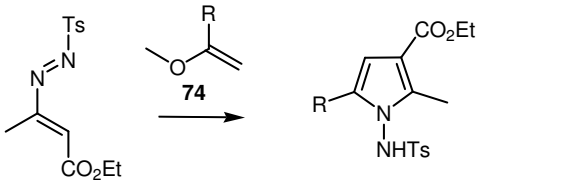
Entry	R	R^1	R^2	R^3	R^4	yield %
1	H	Me	OEt	Me	H	65
1	H	Et	OMe	Me	H	78
1	Ph	Me	OMe	Me	H	52
1	Ph	Me	NMe_2	Me	H	-
1	H	Me	NMe_2	Me	H	-
1	H	Me	OEt	H	H	48
1	Ph	Me	OEt	H	Me	64

The authors postulate that these are Diels-Alder reactions with inverse electronic demand. The interaction between similar size coefficients of the LUMO and HOMO orbitals of azoalkene and of dienophile, respectively, will account for the observed selectivity.

3.2. [3+2] Cycloadditions

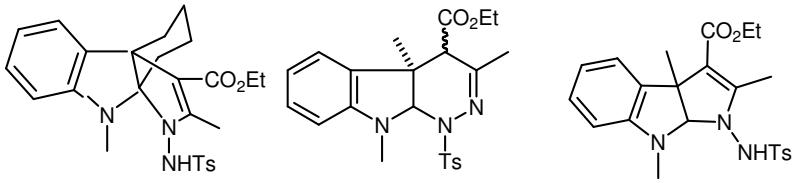
As previously mentioned, there are several examples in the literature where this type of reaction competes with the [4+2] cycloaddition.[18,21]

The [3+2] reaction is predominant, or exclusive, when highly substituted enamines[35,36] and highly substituted vinyl ethers,[21b] further activated by the inclusion of electron-donor substituents, are used. Ethers such **74a** gave predominantly pyrroles by this type of reaction with tosyl azoalkene **73**[21b] (Scheme 22).



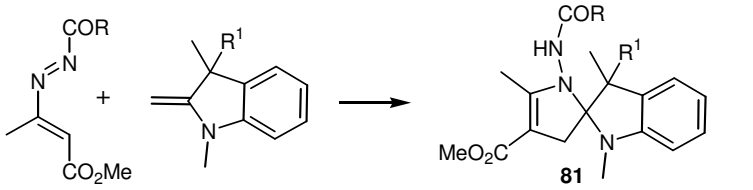
Scheme 22

Cyclic enol ethers, such 5,6-dihydro-2-methyl-4*H*-pyran and 4,5-dihydro-2-methylfuran, produced dihydropyrroles similarly, although in an impure and inseparable mixture. This substituted dihydrofuran contrasts with unsubstituted 2,3-dihydrofuran, which gave the corresponding tetrahydropyridazine *via* a [4+2] reaction mechanism.[21b] *N*-Methyltetrahydrocarbazole also preferably produced the corresponding dihydropyrrole **76** in 53% yield, although 1,3-dimethylindole produced a mixture of epimeric tetrahydropyridazines **77** (55%) and the corresponding dihydropyrrole **78** in 34% yield (Scheme 23).



Scheme 23

With 2-methyleneindolines, electrophilic azoalkenes such as **79** gave rise to spiro-dihydropyrroles **81**, likely resulting from a [3+2] cycloaddition process, since neither spirotetrahydropyridazines from a possible [4+2] cycloaddition nor Michael addition products were detected[37] (Scheme 24).



a) R = NH_2; R^1 = Me 88%
b) R = OMe; R^1 = Me 93%
c) R = OCM_3; R^1 = Me 85%
d) R = NH_2; R^1 = Et 87%
e) R = OMe; R^1 = Et 96%
f) R = OCM_3; R^1 = Et 85%
g) R = NH_2; R^1 = Ph 94%
h) R = OCM_3; R^1 = Ph 81%

Scheme 24

Gilchrist *et al.*[21b] postulated that a possible extreme zwitterionic mechanism could be operating, in which the nucleophilic olefin would add to the azoalkene, this being in a transoid conformation (and not in a *cis* conformation as required for the [4+2] cycloaddition), which then would collapse to an azomethine imide. Pyrroles and dihydropyrroles could then be formed from these by proton transfer (Figure 2). However such mechanism would be sensitive to the polarity of the solvent and this was not experimentally observed.

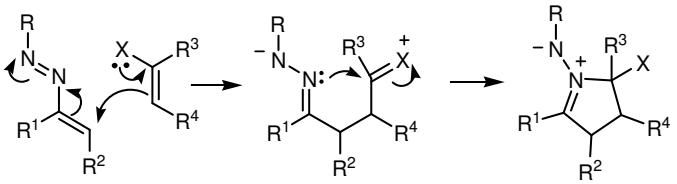


Figure 2. Eventual zwitterionic mechanism.

These observations led the authors to propose a concerted mechanism through a highly unsymmetrical transition state, in which C–C bond formation is more advanced than the C–N. The reaction could be initiated by the attack of the nucleophile on the transoid azo-olefin, but that as the reaction proceeds, the C–N–N fragment of the azo-olefin twists out of the plane, aligning the lone pair on the central nitrogen atom with the developing electrophilic centre of the α-carbon atom of the nucleophile (Figure 3).

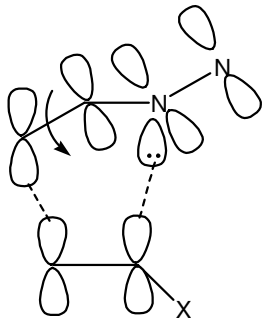
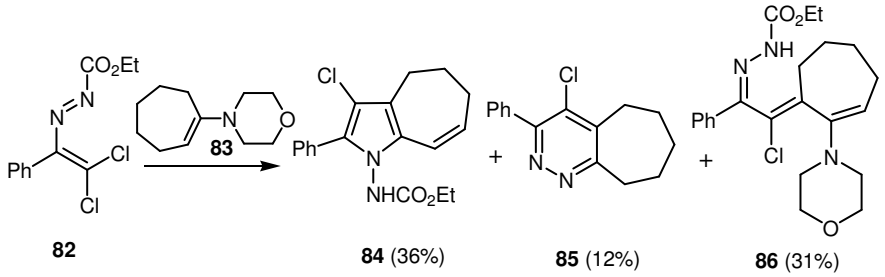


Figure 3. Proposed concerted [3+2] mechanism.

In the reactions of 4,4-dichloroazodienes **82** with enamines, pyrroles, pyridazines and hydrazones were isolated[38] (Scheme 25).



Scheme 25

This variety of products and the verified possibility of interconversion between some of them led to the presumption that both [3+2] and [4+2] reaction mechanisms were operating, but in a stepwise mode and not in a concerted mechanism. This would better account for the obtained results, although in clear contradiction with results encountered before with monochloroazoalkenes.[13g]

Recently Attanasi et co-workers,[39] in kinetic studies aiming at the quantification of the electrophilicity of different azoalkenes in the reactions with α,β-disubstituted enamines, have isolated 1-aminopyrrole derivatives, arising from [3+2] reactions and beside the corresponding hydrazones resulting from 1,4-additions. Moreover, they found that experimental rate constants were larger than theoretically predicted and the strongest deviation was found for the reaction between the least electrophilic azoalkene with the least nucleophilic enamine. Thus this particularly high acceleration rate for the slowest reaction led the

authors to postulate a reaction mechanism with zwitterionic intermediates and transition states in which Coulombic attractions would explain the increased reactivity (Figure 4). This mechanism will accommodate the eventual addition of the enamines to both *Z*- and *E*-azoalkenes and also, as discussed above, the observations that enamines with no α-substituents gives rise to tetrahydropyridazines by [4+2] cycloaddition reactions. Although not ruling out the possibility of similar [4+2] reactions also occurring with these α,β-disubstituted enamines, the authors point out that these reactions would profit much less from Diels-Alder concertedness.

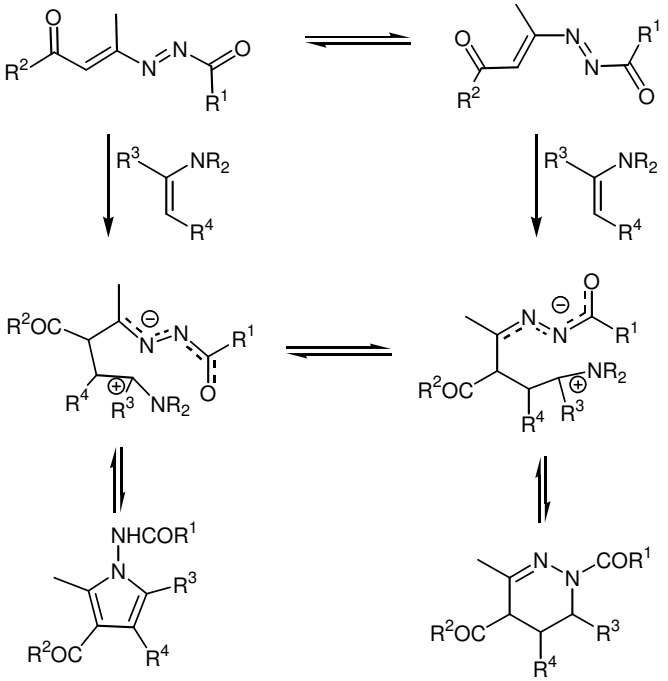
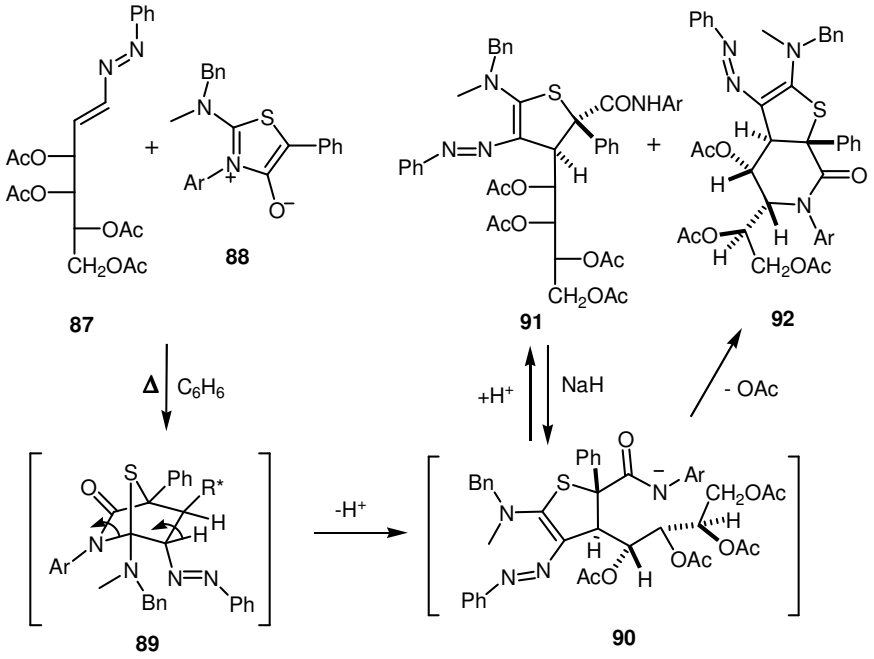


Figure 4. Postulated zwitterionic mechanism.

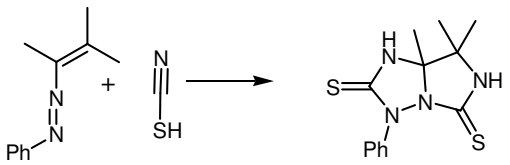


Ar = Ph; $C_6H_4(OMe)$-4; $C_6H_4(NO_2)$-4

Scheme 26

Five-membered heterocycles have also been obtained in reactions of mesoionic compounds, acting as 4π reaction partners, with azoalkenes, these now acting as the 2π components. Thioisomunchnones were utilized as starting dipoles and reacted with homochiral azoalkenes bearing an acyclic D-*arabino* carbohydrate derived side chain affording diastereomeric mixtures of 4,5-dihydrothiophenes.[40] When D-*lyxo* or D-*glycero* based carbohydrate azoalkenes were used, the primarily formed cycloadducts **89** evoluted to didhydrothiophenes **91** and *trans*-fused bicyclic dihydrothieno[2,3-*c*]piperidines **92** with stereo-differentiation. These latter can also be obtained by treating those with NaH[41] (Scheme 26). The chemoselectivity of this type of reactions should be emphasized since only the C=C double bond that was involved, therefore showing a higher electrophilicity/reactivity.

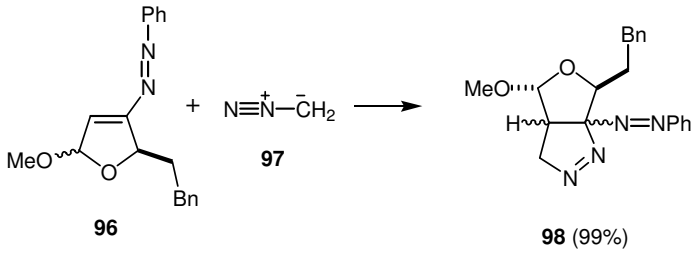
New imidazolinethiones, screened as potential inhibitors of retroviral HIV replication agents, have been synthesized *via* [3+2] cycloaddition reactions of azoalkenes with thiocyanic acid.[42,43] This strategy was latter extended[44] when phenylazoalkene **93** was allowed to react with excess of thiocyanic acid affording 2,3,5,6,7,7a-hexahydro-7,7,7a-trimethyl-3-phenyl-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5-dithione **95** as a result of two consecutive [3+2] cycloaddition steps (Scheme 27).



93 **94** **95** (91%)

Scheme 27

Dihydro-pyrazole **98** has been obtained regioselectively when diazomethane was intercepted by azoalkene **96**[45] (Scheme 28).



96 **97** **98** (99%)

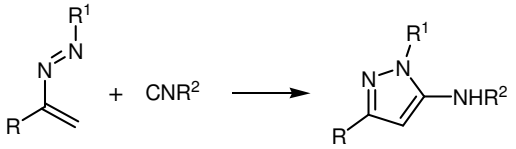
Scheme 28

3.3. [4+1] Cycloadditions

In the search for a preparation of Fipronil®, a new fluorinated pyrazole with high insecticidal activity, and as well in search for anti-histaminic pyrazoles, Rhone-Poulenc (now BASF holds the patent rights for producing and selling Fipronil) researchers disclosed another type of cycloaddition reaction in which azoalkenes also participate as a 4π component, the formal [4+1] reaction of azoalkenes with isocyanides[46] (Table 2).

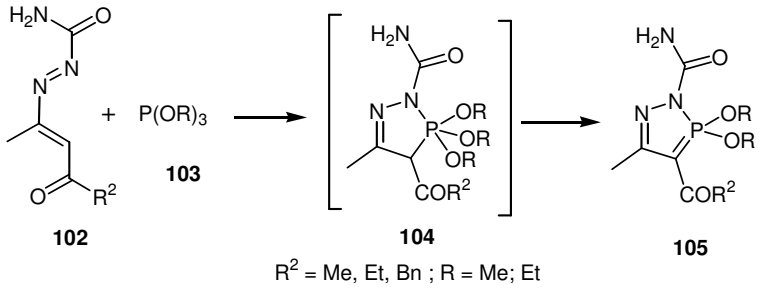
The reactions were more efficient when both R and R^1 were electron-withdrawing groups, in which cases good yields were obtained with almost equimolar amounts of reagents.

Table 2. Reactions of azoalkenes with isocyanides.



28a, 99 **100** **101**

Entry	R	R^1	R^2	yield %
1	Ph	CO_2CMe_3	CMe_3	63
2	CO_2Et	CO_2CMe_3	CMe3	80
3	CO_2Et	CO_2CMe_3	o-tolyl	56
4	CO_2Et	CO_2CMe_3	CH_2CO_2Et	57
5	CO_2Et	CO_2CMe_3	$CH_2CH(OMe)_2$	60
6	CO_2Et	2,4-dinitrophenyl	CMe_3	96
7	CO_2Et	COPh	CMe_3	0
8	Me	CO_2CMe_3	CMe_3	0
9	CO_2Et	CO_2CMe_3	2-carbomethoxy-phenyl	50



R^2 = Me, Et, Bn ; R = Me; Et

Scheme 29

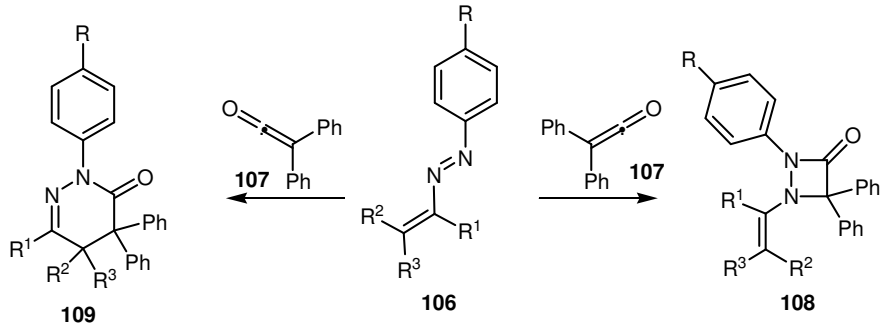
Trialkyl phosphites and electrophilic azoalkenes, *via* the same reaction mechanism and under nitrogen atmosphere, provided a general protocol for the selective preparation of alkyl 3,3-dialkoxy-2*H*-1,2,3λ^5-diazaphosphole-4-carboxylates **105** in high yields[47a] (Scheme 29). Similarly, 3-alkoxy-3-phenyl-2*H*-1,2,3λ^5-diazaphospholes were obtained in reactions of azoalkenes **102** with dialkylphenylphosphonites under solvent free conditions without the need to exclude moisture.[47b]

Diazaphosphole derivatives have also been obtained by reaction of azoalkenes with various phosphorus sources, such as dichlorophenylphosphine,[48] phosphorus trichloride[49] and fused benzothia-diphospholes.[50]

3.4. [2+2] Cycloadditions

This type of cycloaddition of azoalkenes is much less common and the sole report involves the N=N bond and not the carbon-carbon double bond. *(E)*-Arylazoalkenes **106** readily react with diphenylketenes **107** providing *N*-vinyl-1,2-diazetidinones **108** and/or pyridazinones **109** by the more usual [4+2] reaction mechanism[51] (Scheme 30).

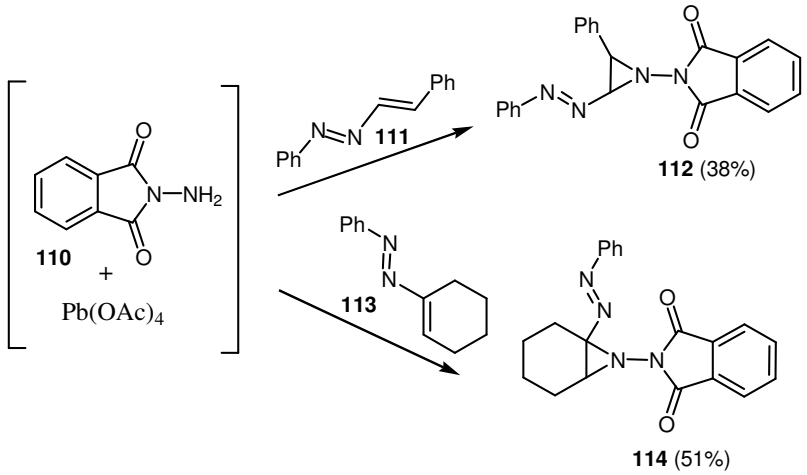
Analogous reactions involving a [4+2] and/or a [2+2] mechanism have been described between 1,3-diaza-1,3-butadienes and ketenes affording pyrimidinones and/or azetidinones.[52]



Scheme 30

3.5. [2+1] Cycloadditions

The synthesis of three-membered ring heterocycles have been achieved *via* the reaction of *N*-amino-phthalimide with conjugated azoalkenes and lead tetraacetate.[53] The carbon-carbon double bond of azoalkenes **111** and **113** reacted chemoselectively producing the unknown C-azoaziridines (Scheme 31). The reaction is not general, since, by changing cyclohexene to the apparently very similar cyclopentene, dissimilarly products such as triazole derivatives were obtained.



Scheme 31

4. Final remarks

During the last three decades, the chemistry of conjugated azoalkenes has progressed amazingly. Their use either as 4π or 2π reaction partners in cycloaddition reactions has allowed the production of a great variety of heterocyclic compounds with interesting biological, pharmaceutical and chemical properties, using methodology based on accessible starting materials and easy scale-up. This, combined with the spectacular development of the 1,4-conjugate additions, demonstrates once again the efficiency of conjugated azoalkenes in heterocycles synthesis.

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NUCLEOPHILIC SUBSTITUTION OF HYDROGEN – AN EFFICIENT TOOL IN SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Dedicated to Professor Janusz Jurczak on the occasion of his 70th birthday.

Abstract. *In this chapter, we present the rich possibilities offered by nucleophilic substitution of hydrogen in electron-deficient arenes for synthesis of heterocyclic compounds. A review of the subject was published by us six years ago in Chemical Reviews.[1] In recent years, though, a great deal of reports in this field have appeared, so that we consider it appropriate to publish now a review collecting new concepts and late results.*

Contents

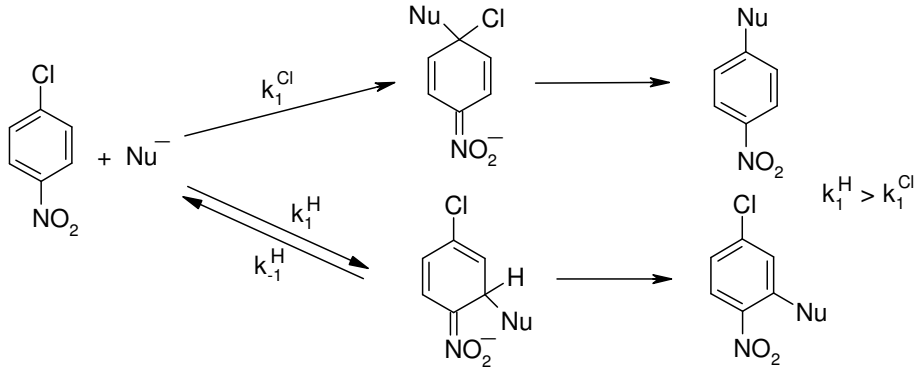
1. Introduction

The chapter is constructed in the following way. In the Introduction, we will present basic principles of nucleophilic substitution of hydrogen, mechanistic features of numerous variants of this process, its scope and limitations. The main message of this part is that examples of nucleophilic substitution of hydrogen in nitroarenes and other electron-deficient arenes are not incidental, but primary processes of wide scope and great value in organic synthesis, whereas conventional nucleophilic substitution of halogens, S_NAr reaction is just a secondary process.[2] In the following parts, the use of these reactions for introduction of substituents into heteroarenes, constructions of heterocyclic ring system and synthesis of biologically active and natural products reported after 2004 will be presented. When necessary, references to earlier papers are given.

Reactions of nucleophilic agents with electron-deficient arenes can proceed *via* addition at the positions occupied by halogens and other nucleofugal groups X or at the positions occupied by hydrogen. In

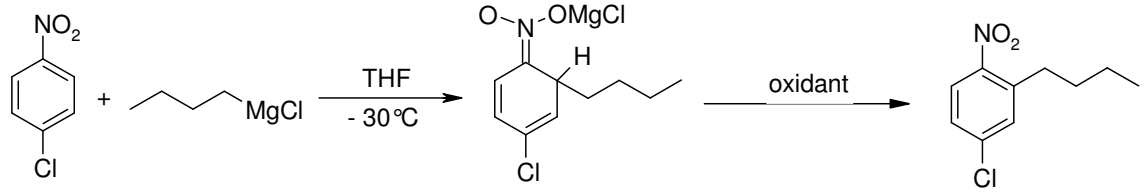
the former case, the formed σ^X adducts undergo rapid conversion into the products *via* spontaneous departure of X^- anions. This is a common process of aromatic nucleophilic substitution, S_NAr, known for many years and widely used in chemical industry and in laboratories of organic synthesis.[3]

However, the addition of nucleophiles at the positions occupied by hydrogen to form σ^H adducts proceeds faster than at similarly activated ones occupied by halogens. Contrary to the σ^X adducts, though, the spontaneous departure of hydride anion from σ^H adducts does not proceed due to the high energy of the C–H bond and the low stability of H^-. Due to reversibility of the addition, the formation of the σ^H adducts is often unnoticed and S_NAr reaction is considered as the main process. The situation can be presented as in Scheme 1. The fast preferential formation of σ^H adducts of nucleophiles to halonitroarenes, that precedes the formation of the σ^X adducts, can be efficiently exploited as a first step of nucleophilic substitution of hydrogen provided there are ways for their fast conversion into products.

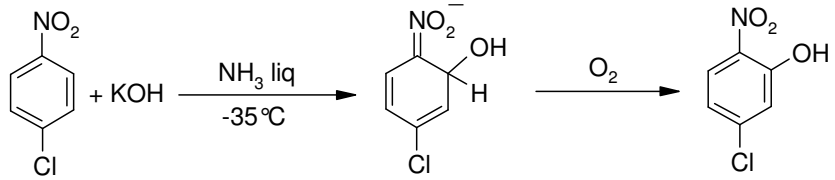


Scheme 1

Simple examination of the Scheme 1 indicates that an obvious way of conversion of the σ^H adducts into products of nucleophilic substitution of hydrogen is the removal of the hydride anion by an external oxidant with simultaneous rearomatization. Although this process, the oxidation of σ^H adducts, suffers from some limitations mainly due to the sensitivity of nucleophilic agents to the oxidation, the oxidative nucleophilic substitution of hydrogen (ONSH) is of fairly general character and can be used for the introduction of oxygen, nitrogen and particularly carbon substituents into electron-deficient arenes.[4–6] This can be exemplified by the oxidative nucleophilic alkylation of 4-chloronitrobenzene with *n*-butylmagnesium chloride (Scheme 2)[7] and the hydroxylation of 4-chloronitrobenzene (Scheme 3).[8]

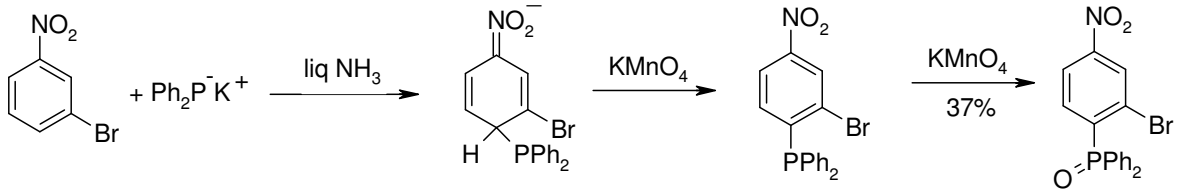


Scheme 2



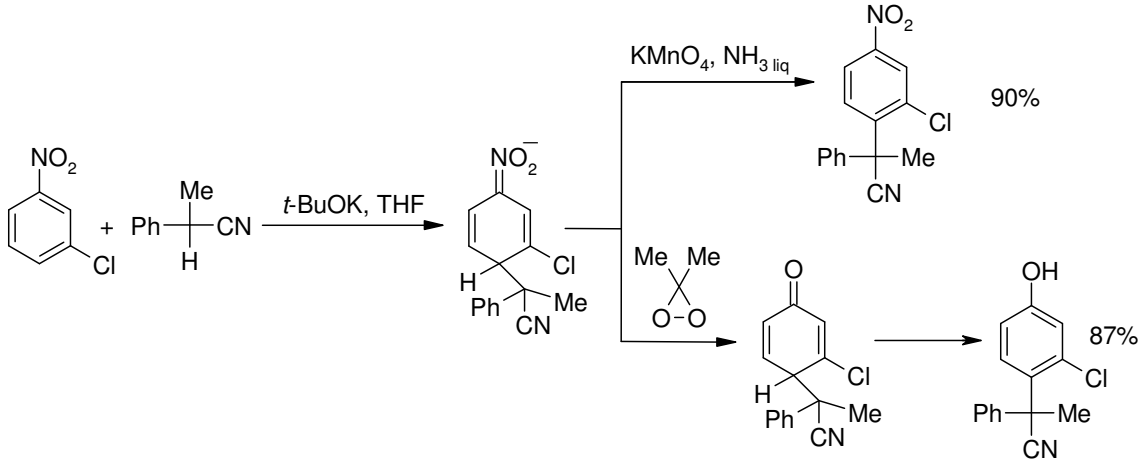
Scheme 3

Highly electron-deficient arenes such as *m*-dinitrobenzene or 3-nitropyridine can be aminated with ammonia and $KMnO_4$ as oxidant. This is valuable oxidative variant of the Chichibabin reaction.[9] ONSH can also be used for introduction of phosphorous substituents into nitroarene rings in reactions with diarylphosphine anions. Under the reaction conditions, the initially formed triarylphosphines were oxidized to the corresponding oxides (Scheme 4).[10]



Scheme 4

Interestingly, the oxidation of σ^H adducts formed by attack of some carbanions onto nitroarenes can proceed at the addition site to give substituted nitroarenes[11] or at negatively charged nitro group giving substituted phenols[12] (Scheme 5).



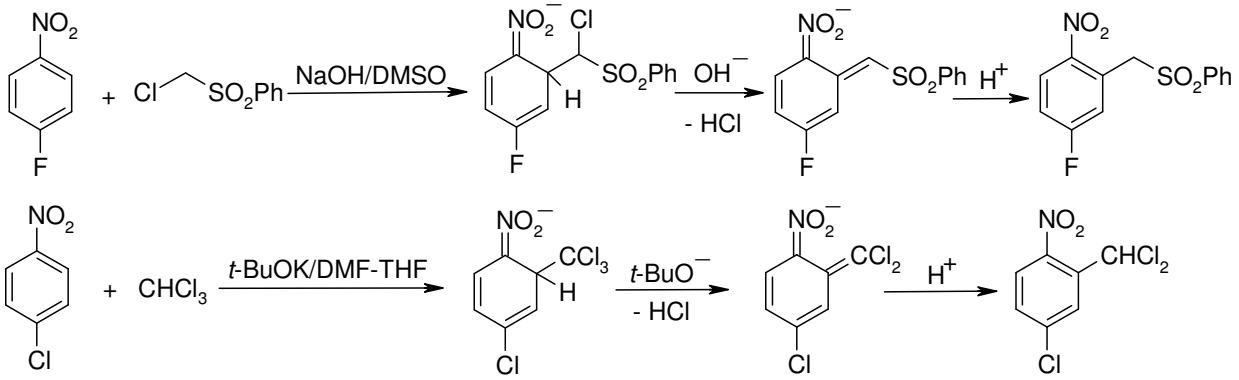
Scheme 5

The second and most general way of conversion of σ^H adducts proceeds when nucleophiles contain leaving groups L at the nucleophilic centre. Such nucleophiles as *e.g.*, α-chlorocarbanions add to nitroarenes to produce σ^H adducts that enter base induced β-elimination of HCl to form products of substitution of the ring hydrogen with the carbanion moiety. This process named vicarious nucleophilic substitution (VNS)[13,14] can be exemplified by the reactions of *p*-fluoronitrobenzene with the carbanion of chloromethyl phenyl sulfone[15] or of *p*-chloronitrobenzene with the carbanion of chloroform (Scheme 6).[16]

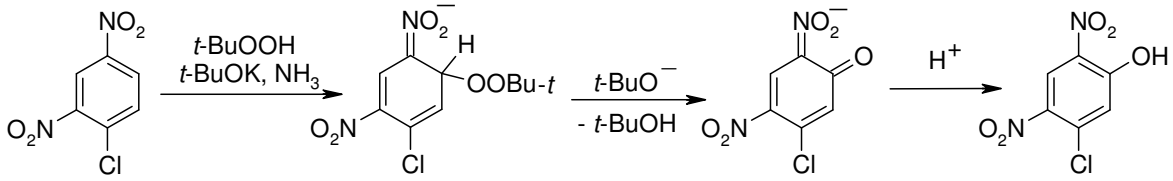
Even 2,4-dinitrofluorobenzene, the Sanger reagent, known for rapid nucleophilic substitution of fluorine, reacts with α-halocarbanions according to the VNS pathway.[17] The VNS reaction is a general process in respect of nitroarenes and carbanions that contain such nucleofugal groups L as halogens, aryloxy, arylthio, etc., able to be eliminated from the σ^H adducts as HL.[14]

The VNS reaction is also an efficient tool for hydroxylation and amination of nitroarenes. Readily available *t*-butyl and cumyl hydroperoxides upon deprotonation produce moderately nucleophilic anions that

can add to active electron-deficient arenes to form σ^H adducts. Further base-induced β-elimination of alcohols from such σ^H adducts gives phenols. For example, the treatment of a solution of 2,4-dinitro-1-chloro-benzene and *t*-butyl-hydroperoxide in liquid ammonia with an excess of *t*-BuOK gave 2,4-dinitro-5-chloro-phenol (Scheme 7).[18–20]

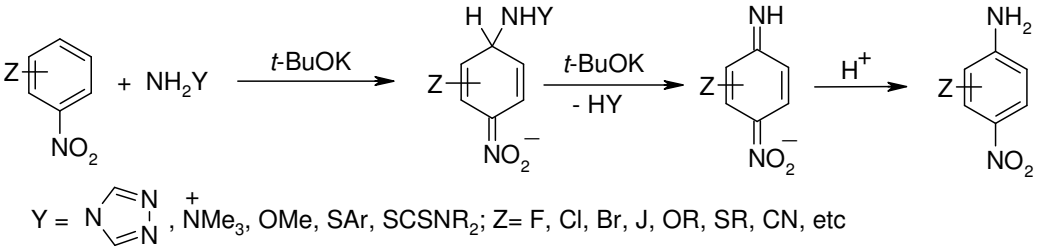


Scheme 6



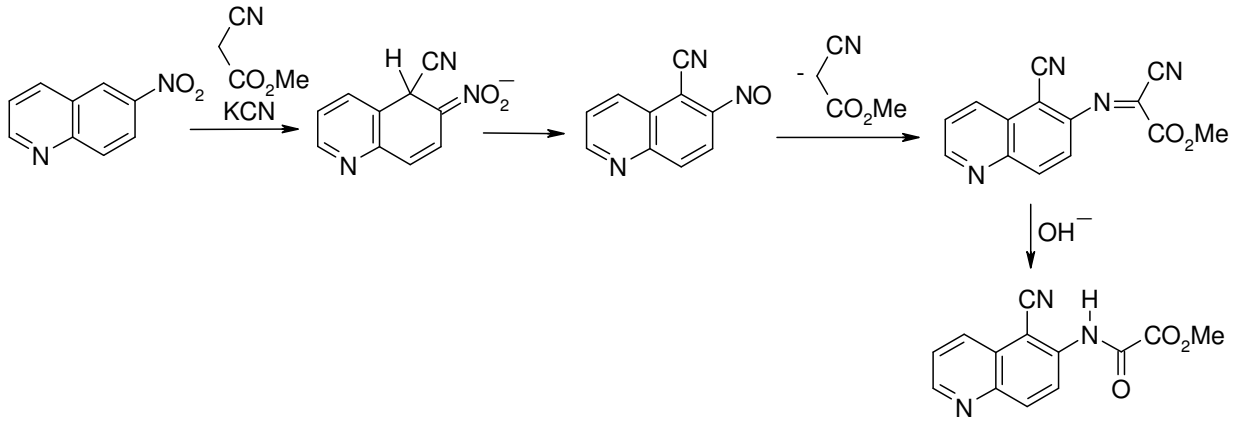
Scheme 7

For amination of nitroarenes and other electron-deficient arenes *via* VNS reaction, a series of aminating agents was developed, mostly derivatives of hydrazine (trimethyl-hydrazonium iodide,[21] 4-amino-1,2,4-triazole[22]) and hydroxylamine (methoxamine,[23] arylsulfenamides[24]) (Scheme 8).



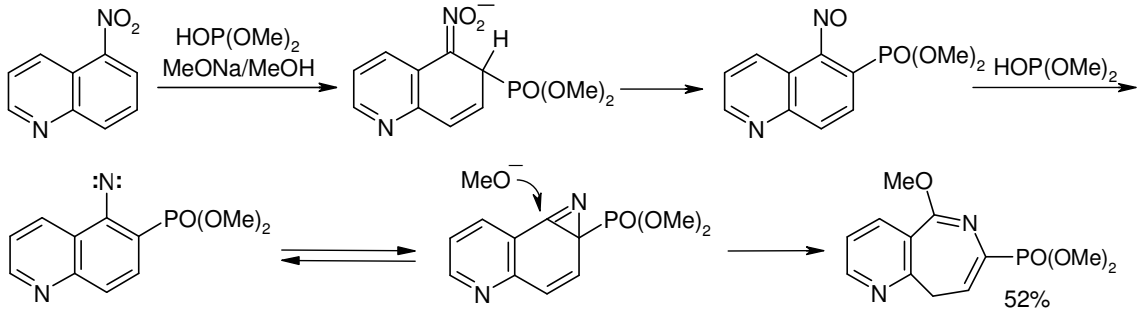
Scheme 8

The third efficient way of conversion of the σ^H adducts of nitroarenes into products of nucleophilic substitution of hydrogen consists in the formal elimination of OH^- anion at the expense of the ring hydrogen and of one oxygen of the nitro group to produce substituted nitrosoarenes. Thus the overall stoichiometry of such a reaction corresponds to an intramolecular redox process. Since nitrosoarenes are chemically more active than nitroarenes and the reaction mixtures often contain nucleophilic and basic agents, initially formed nitrosoarenes cannot be isolated, but enter further transformations. A variety of further conversion processes of nitrosoarenes in the reaction mixtures can produce valuable and interesting products (Scheme 9).[25,26]



Scheme 9

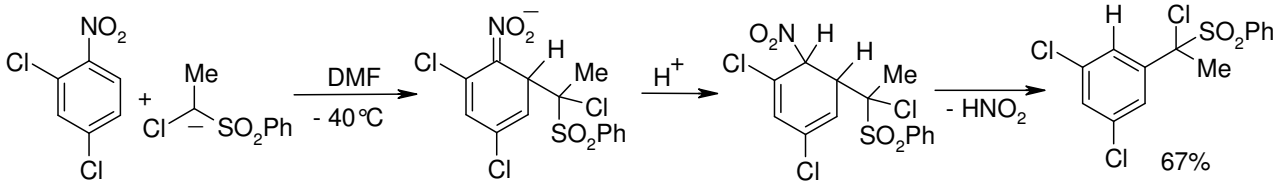
In the reactions of 5-nitroquinoline with dimethyl phosphite anion, the intermediate nitroso compound is rapidly deoxygenated to form nitrene that reversibly is transformed to azirine. The addition of methoxide anion or other nucleophile to the azirine gives aziridine that undergoes a ring expansion to pyridobenzazepine (Scheme 10).[27]



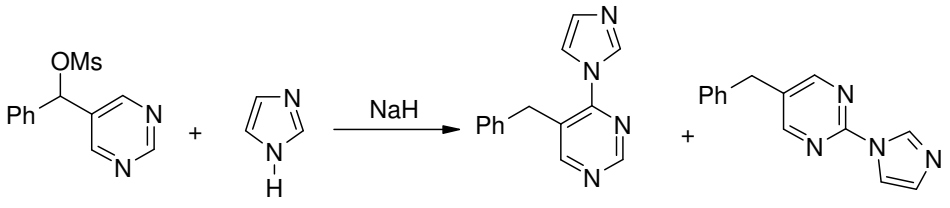
Scheme 10

The isolation of the intermediate nitrosoarenes is possible when the addition of nucleophilic agents to nitroarenes proceeds to completion and further conversion of the σ^H adducts is executed in absence of nucleophiles and bases.[7,28]

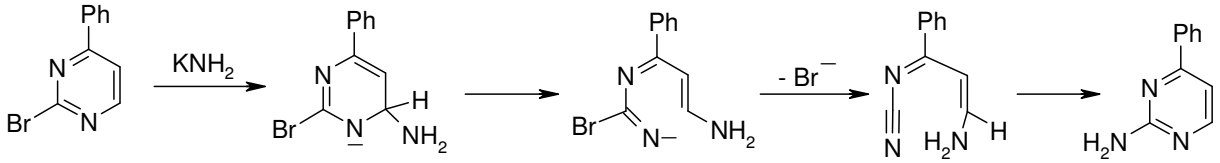
There are a few other ways for the conversion of σ^H adducts of lesser generality and practical value. The elimination of a leaving group from the σ^H adducts, adjacent to the addition site, is known as *cine*-substitution,[29] whereas the elimination of a leaving group from a remote position is termed *tele*-substitution.[29] These types of reactions are exemplified in Schemes 11[30] and 12,[31] respectively. The conversion of σ^H adducts of some heteroarenes containing halogen in activated position can proceed *via* ring opening, elimination of halide anion and ring closure [ANRORC mechanism (Scheme 13)].[32]



Scheme 11



Scheme 12



Scheme 13

It should be stressed that nucleophilic substitution of hydrogen in electron-deficient arenes proceeding *via* conversion of the initially formed σ^H adducts (in a variety of ways) is the main reaction whereas conventional nucleophilic substitution of halogen (S_NAr reaction) shown in the Scheme 1 is just a secondary process. For a more detailed discussion of a variety of ways of conversion of σ^H adducts and the relation between S_NH and S_NAr in electron-deficient arenes, see *e.g.*, some recent reviews.[2,4]

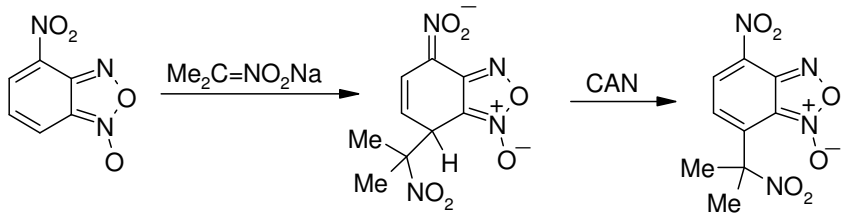
2. Introduction of substituents into heterocyclic systems *via* nucleophilic substitution of hydrogen

2.1. Carbon substituents

The introduction of carbon substituents into electron-deficient aromatic and heteroaromatic rings *via* nucleophilic substitution of hydrogen is a process of substantial importance because the products can be of interest *per se* and can also serve as valuable intermediates in further synthesis, particularly hetero-cyclization.

In this section, we will present examples of introduction of carbon substituents into heteroarenes *via* oxidative and vicarious nucleophilic substitution of hydrogen without further conversion of the obtained products into heterocyclic systems. Full account of the subject was given in our earlier reviews.[1,33,34] Here we present recent results in this area.

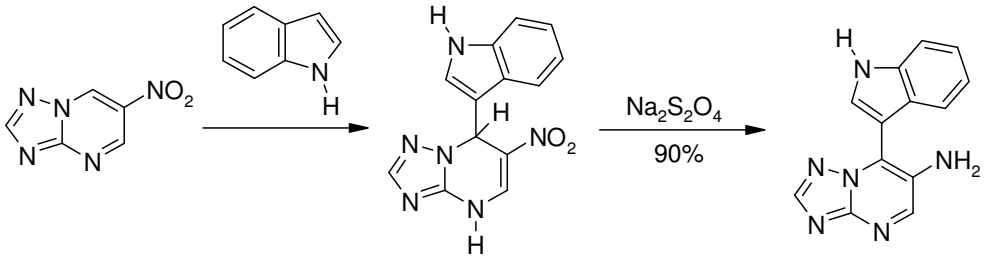
A weak C-nucleophile such as 2-nitropropenide anion adds quantitatively to superelectrophilic nitro-benzofurazan and nitrobenzofuroxan rings. Further oxidation of the formed σ^H adduct results in the introduction of α-nitroisopropyl substituent into these heterocyclic systems (Scheme 14).[35]



Scheme 14

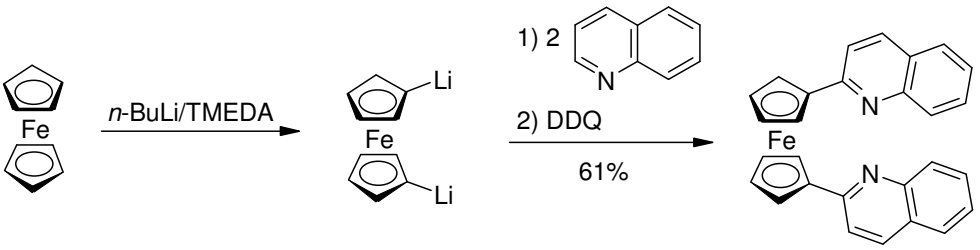
Highly electron-deficient 6-nitrotriazolopyrimidines add such nucleophiles as indoles, pyrroles, methyl ketones, dialkyl malonates or phenols to form relatively stable σ^H adducts.[36,37] Upon treatment of these σ^H

adducts with some reducing agents, they undergo an intramolecular redox process to form substituted 6-aminotriazolopyrimidines (Scheme 15).[38]



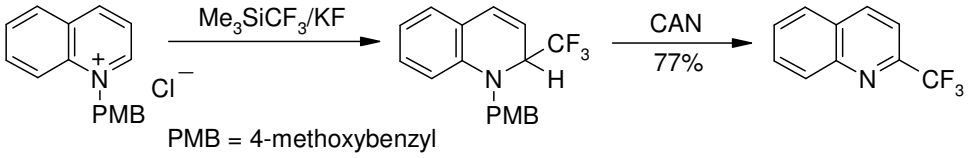
Scheme 15

Ferrocenyl moiety can be introduced into azine rings *via* addition of ferrocenyllithium followed by DDQ oxidation of the produced σ^H adduct (Scheme 16).[39]



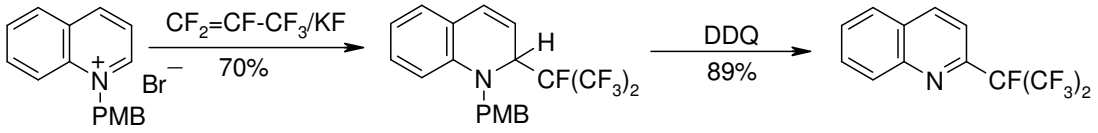
Scheme 16

Of substantial interest is the introduction of trifluoromethyl and perfluoroisopropyl substitutents into azine rings of pyridine, quinoline, etc. *via* addition of the respective carbanions to *N*-(4-methoxybenzyl)azinium salts followed by oxidative dealkylation-aromatization of the produced dihydroazines (Schemes 17 and 18).[40,41]



PMB = 4-methoxybenzyl

Scheme 17

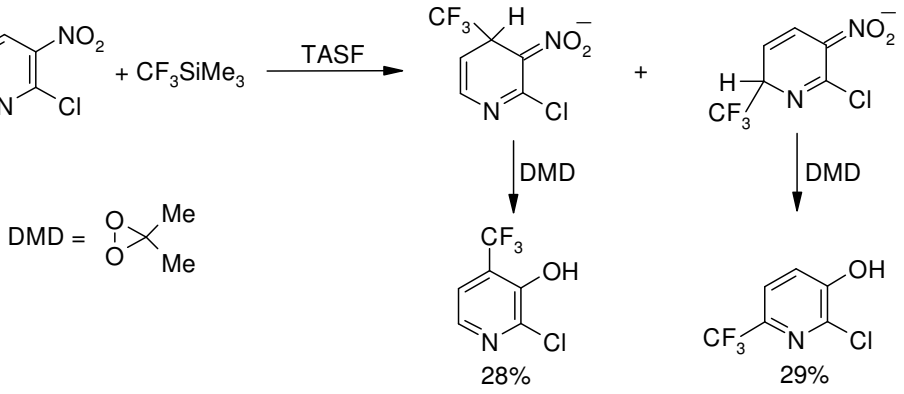


Scheme 18

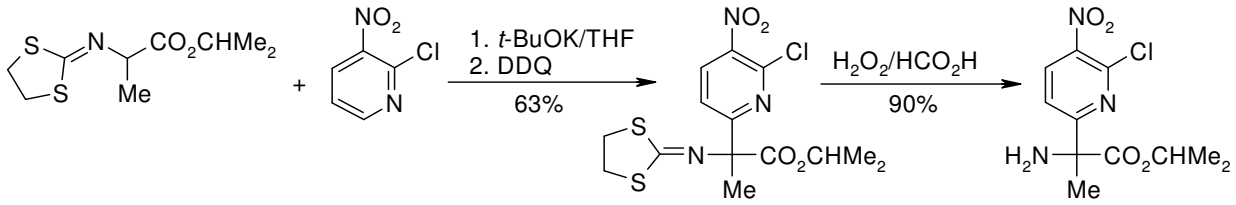
The oxidation of σ^H adducts of trifluoromethyl carbanion generated from the Ruppert reagent to 2-chloro-3-nitropyridine with dimethyldioxirane (DMD) gives two isomeric 2-chloro-4-(and 6-)trifluoromethyl-3-hydroxypyridines (Scheme 19).[42]

The oxidative nucleophilic substitution in nitropyridines with carbanions of protected esters of aminoacids provides simple access to nitropyridyl alanine, serine and threonine.[43–45] *N*–(1,3-Dithiolane-2-

ylidene)alanine isopropyl ester readily available from alanine ester, carbon disulfide and 1,2-dibromoethane adds in the presence of *t*-BuOK in THF to nitroarenes and their heteroanalogs to form σ-adducts that upon oxidation with DDQ give protected nitroarylalanine derivatives. For example, this approach permits the synthesis of nitropyridylalanine (Scheme 20).[44]

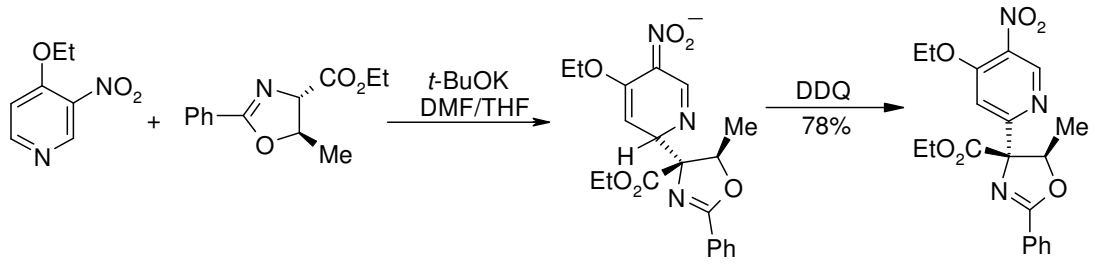


Scheme 19



Scheme 20

In a similar process, protected serine and threonine esters can be transformed into α-(nitropyridyl) aminoacid derivatives.[45] It should be mentioned that the addition of the carbanion of protected threonine to the nitropyridine ring proceeds with high diastereoselectivity controlled by the second chiral centre (Scheme 21).[45]

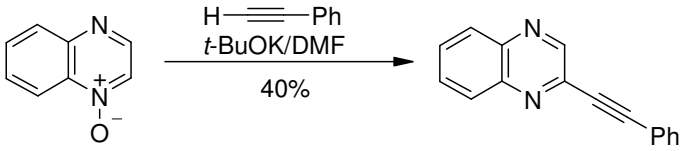


Scheme 21

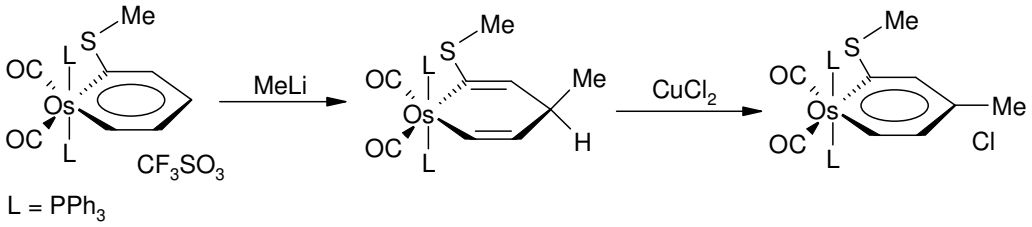
The synthesis of a variety of phenylethynylazines can be simply executed *via* direct nucleophilic replacement of hydrogen in the reactions of azine *N*-oxides with the carbanion of phenylacetylene (Scheme 22).[46]

An interesting class of compounds that can be considered as heteroarenes are metallobenzenes that are benzene analogues in which one carbon atom is replaced by iridium, osmium, etc. Recently, nucleophilic aromatic substitution of hydrogen in highly electron-deficient cationic metallobenzenes was reported with

MeLi and sodium ethoxide as nucleophiles and DDQ or copper(II) chloride as oxidant. Reaction of osmabenzene complex with methyllithium is exemplified in the Scheme 23.[47]

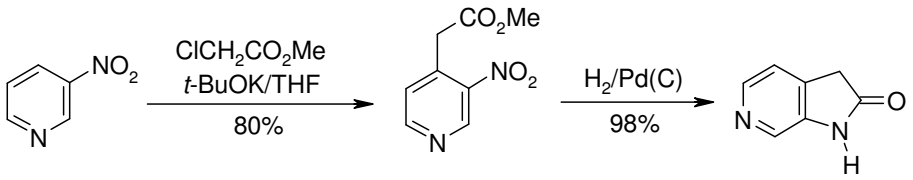


Scheme 22



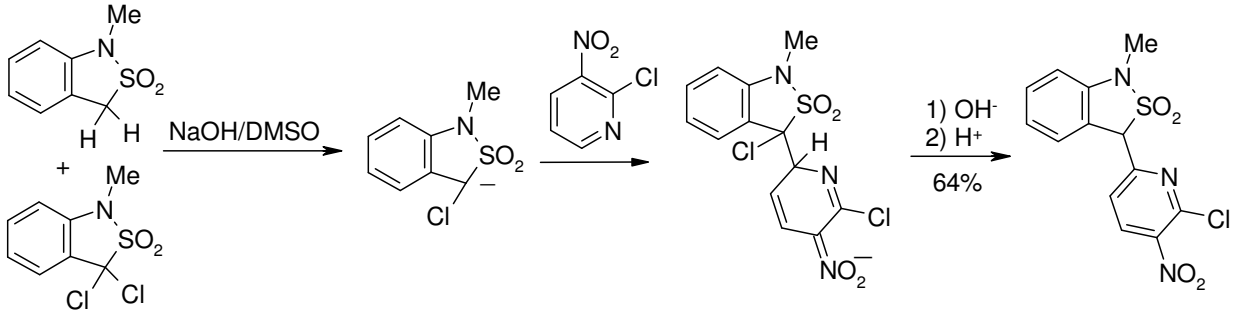
Scheme 23

VNS reaction is an efficient tool for introduction of functionalized carbon substituents into nitro derivatives of a variety of azines. Thus the reactions of 3-nitropyridine with the carbanion of either chloroform or methyl chloroacetate provide dichloromethylnitropyridine and ethyl nitropyridyl acetates (Scheme 24).[48,49]



Scheme 24

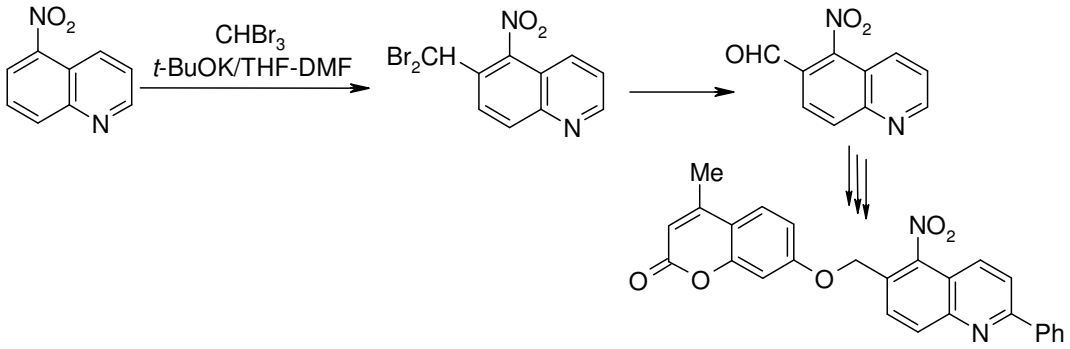
Monochlorobenzosultam carbanion, generated by sym-proportionation of equimolar mixture of benzosultam and its dichloro-derivative, adds to 2-chloro-3-nitropyridine and, after elimination of HCl from the produced σ^H adduct forms 3-pyridinylbenzosultam according to the VNS mechanism (Scheme 25).[50]



Scheme 25

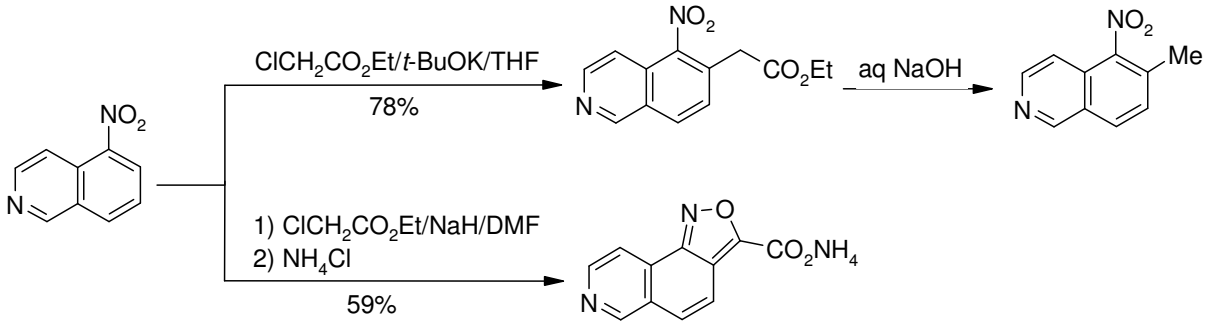
The VNS reaction of 5-nitroquinoline with tribromomethyl carbanion produces 6-dibromomethyl-5-nitroquinoline that upon hydrolysis forms aldehyde. The aldehyde is a starting step of a reaction sequence

leading to coumarine derivative, a potential prodrug system undergoing a reductive bioactivation to form cytotoxic quinolino-aza-xylylene (Scheme 26).[51]



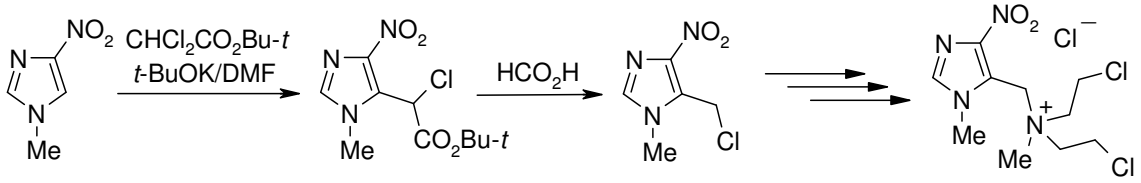
Scheme 26

The treatment of 5-nitroisoquinoline with the carbanion of ethyl chloroacetate under standard VNS condition in the presence of *t*-BuOK in DMF gives the expected (5-nitroisoquinol-6-yl)acetate that upon hydrolysis and decarboxylation is transformed into 6-methyl-5-nitroisoquinoline (Scheme 27).[52] The reaction seems sensitive to the conditions since when sodium hydride is used as a base, after quenching of the reaction mixture with ammonium chloride, an isoxazole derivative is obtained.



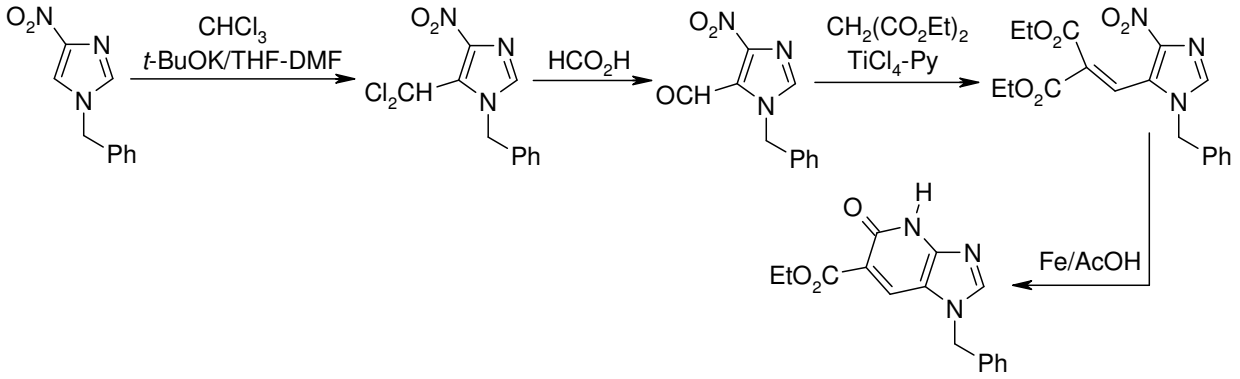
Scheme 27

The nitroimidazole moiety is present in numerous biologically-active compounds. (Chloromethyl) nitroimidazoles obtained *via* a VNS approach developed by us[53] are used for the synthesis of (nitro-heteroaryl)methyl mustards that are tested as hypoxia-selective cytotoxins (Scheme 28).[54,55]



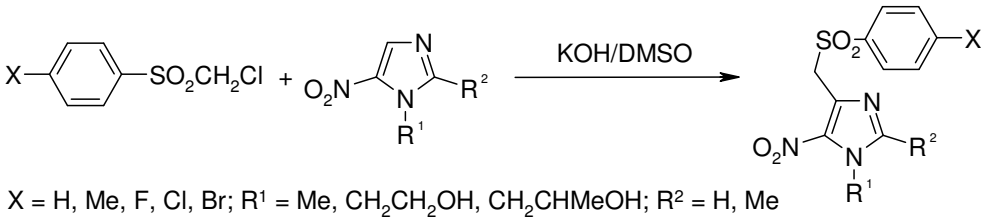
Scheme 28

1-Benzyl-4-nitroimidazole enters VNS reaction with trichloromethyl carbanion to produce the 5-dichloromethyl derivative. Its hydrolysis and condensation of the resulting aldehyde with diethyl malonate gives alkene that upon reduction is transformed into an imidazopyridone (Scheme 29).[56]



Scheme 29

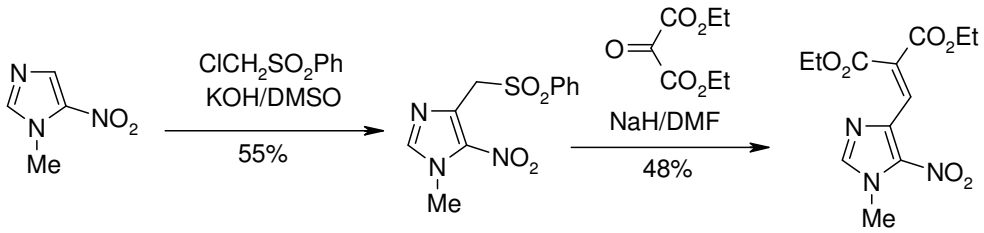
In search for new antiparasitic agents active against *Trichomonas vaginalis* a series of 5-nitroimidazole derivatives are subjected to VNS with variously substituted aryl chloromethyl sulfones (Scheme 30).[57]



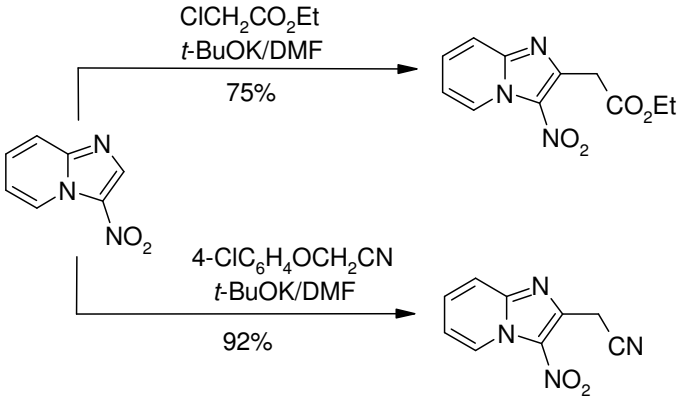
X = H, Me, F, Cl, Br; R^1 = Me, CH_2CH_2OH, $CH_2CHMeOH$; R^2 = H, Me

Scheme 30

Introduction of diethyl methylenemalonate substituent in the position 4- of 5-nitroimidazole is executed *via* VNS reaction of 5-nitroimidazole with the carbanion of chloromethyl phenyl sulfone[57,58] followed by condensation of the produced 4-(phenylsulfonyl)methyl derivative with diethyl bromomalonate[59] or diethyl mesoxalate (Scheme 31).[56]

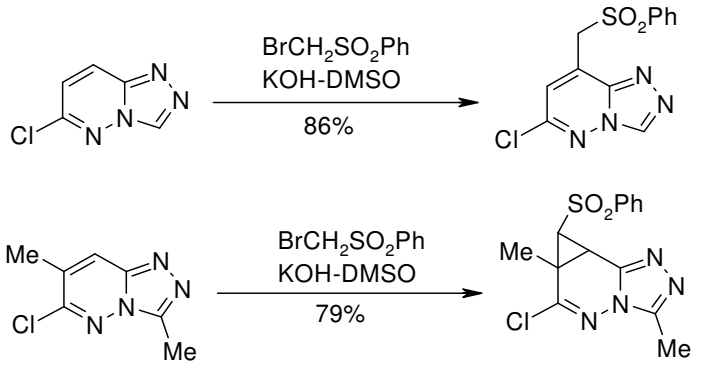


Scheme 31

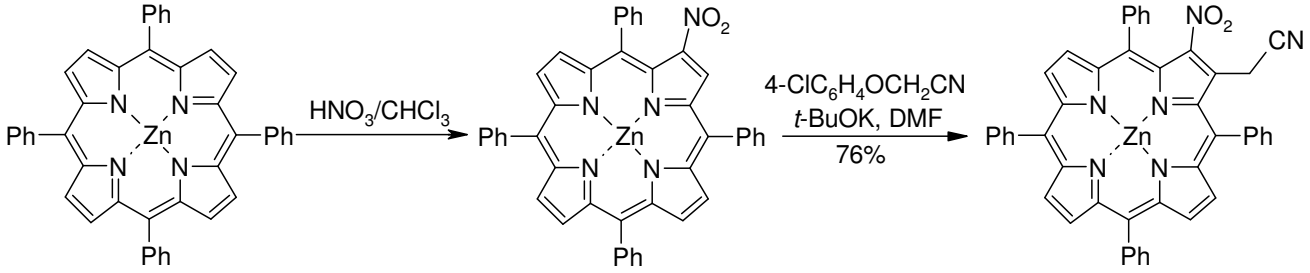


Scheme 32

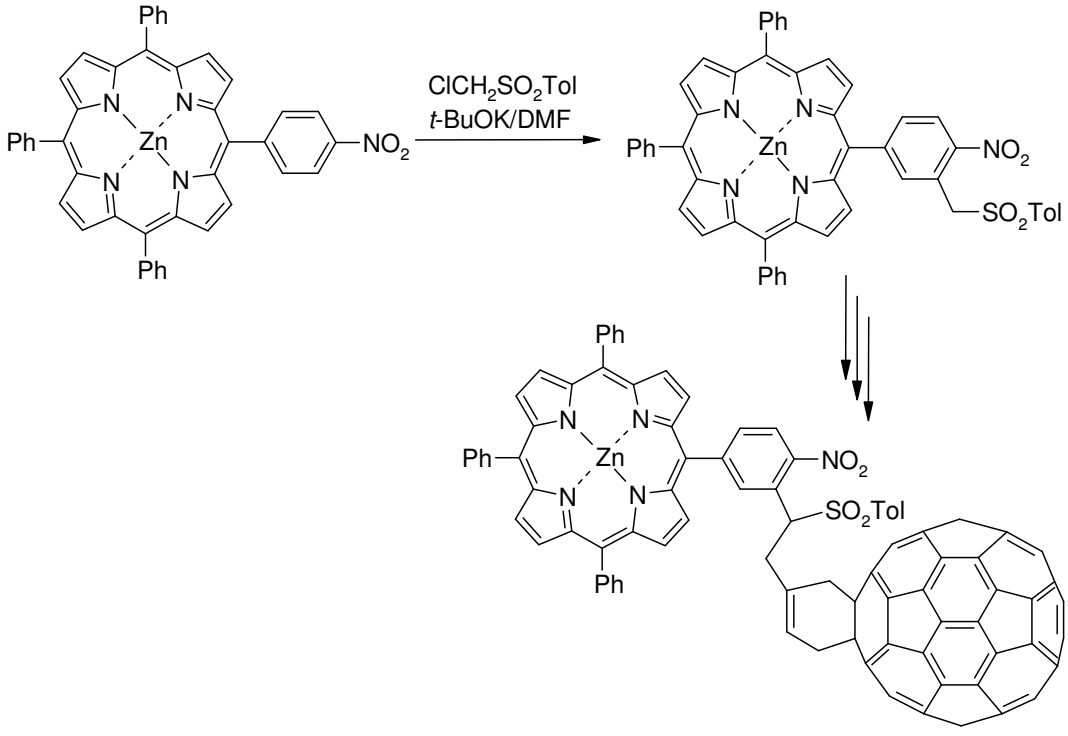
3-Nitroimidazo[1,2-a]pyridine is reported to react efficiently with carbanions of ethyl chloroacetate or (4-chlorophenoxy)acetonitrile to give the expected VNS products containing ethoxycarbonylmethyl or cyanomethyl groups at the position 2 (Scheme 32).[60]



Scheme 33



Scheme 34



Scheme 35

Azolopyridazines that do not contain nitro group are sufficiently active electrophiles to enter the VNS reaction. However, similarly to the case of quinoxalines[61] and pyridazinones,[62] the σ^H adduct generated by

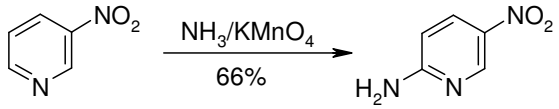
the bromomethyl phenyl sulfone carbanion, depending on the structure of these heterocycle, reacts further in two ways: β-elimination, leading to the VNS product and intramolecular substitution, resulting in the formation of a cyclopropane ring (Scheme 33).[63]

Ostrowski has shown that *meso*-tetraarylporphyrins can be selectively nitrated in the pyrrole or the aryl rings. The nitration site can be controlled by formation of Zn complex, kind of nitrating agent, and reaction conditions.[64] Both types of nitroporphyrins, those containing the nitro group in pyrrole and aryl rings enter VNS reaction with α-halocarbanions giving expected substitution products in good yields[64] as exemplified in Schemes 34 and 35.

Particularly interesting is a sequence of VNS, alkylation, ene-yne metathesis and Diels-Alder reactions leading to porphyrin-fullerene dyad, a compound of potential application as photosensitizer in photodynamic therapy (PDT) (Scheme 35).[65]

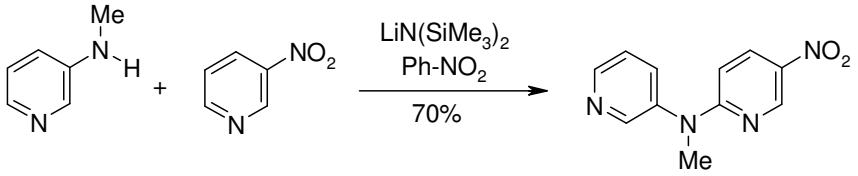
2.2. Heteroatomic substituents

Oxidative amination of 3-nitropyridine with ammonia, alkyl- and dialkylamines and $KMnO_4$ as oxidant is reported by Bakke (Scheme 36).[49]



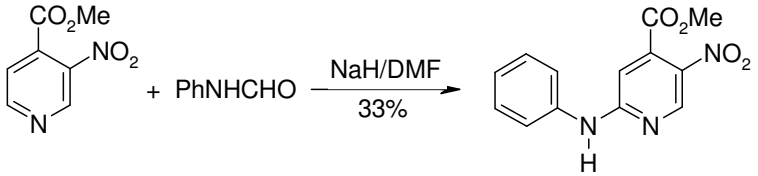
Scheme 36

A thorough study on the mechanism of oxidative amination of 3-nitropyridine, quinazoline and 1,3-dinitrobenzene including determination of the kinetic isotope effect of the oxidation step was recently reported.[66] Nitropyridines are oxidatively aminated with 2-, 3-, and 4-aminopyridines in the presence of nitrobenzene as an oxidant leading to *N,N'*-dipyridinylamines in good yields as exemplified in Scheme 37.[67]



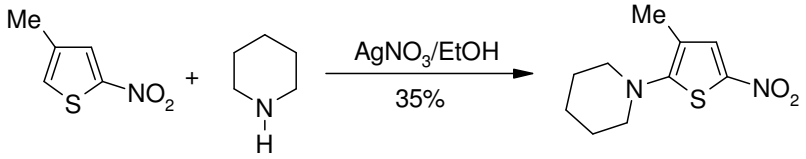
Scheme 37

3-Nitro-1,5-naphthyridines[68] are oxidatively methylaminated with liquid methylamine and potassium permanganate. Direct oxidative amination of 3-nitronicotinate with formanilide proceeding with a substitution of hydrogen at position 6 results in the formation of anilinopyridine (Scheme 38).[69] This result is contradictory to the previously observed strong tendency of substitution of the nitro group with such nucleophilic anions as azide, phenoxide, phenylthiolate.[70]



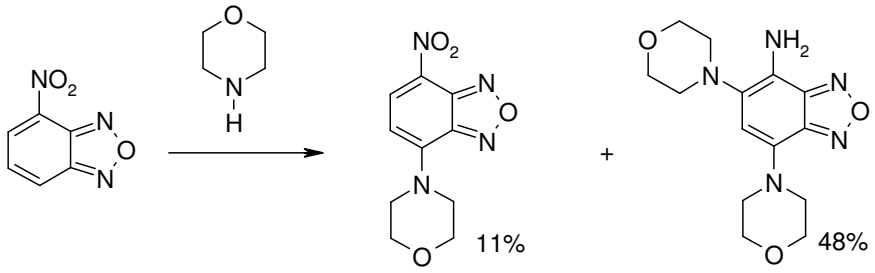
Scheme 38

Thorough studies on the oxidative substitution of hydrogen and competing reactions involving ring opening of 2- and 3-nitrothiophenes with dialkylamines were reported (Scheme 39).[71]



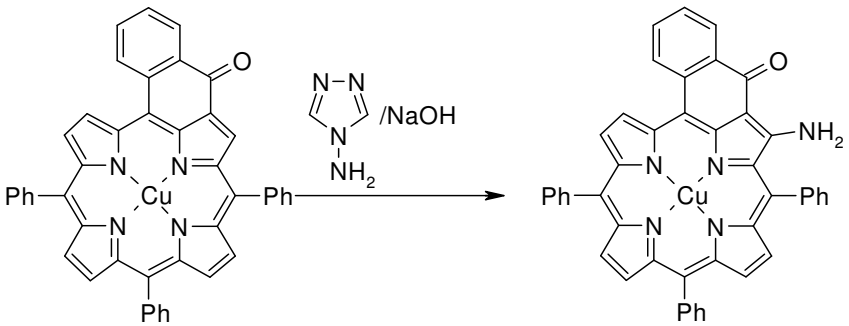
Scheme 39

An unusual reaction course is observed in the reaction of dialkylamines with 4-nitrofurazan.[72] For example, the treatment of this reagent with an excess of morpholine results in the formation of two products, one of them being the result of the oxidative substitution of hydrogen at position 7, while the second, the bis-morpholinyl derivative, is the result of a redox process (Scheme 40).



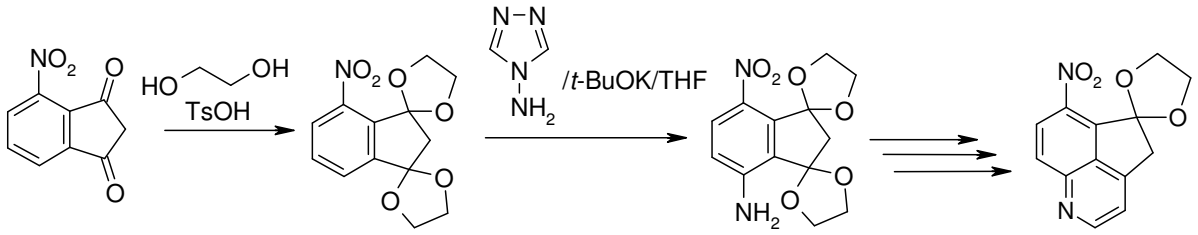
Scheme 40

The VNS amination requires as starting materials ammonia derivatives bearing leaving groups at nitrogen. Thus derivatives of hydrazine (trimethyl-hydrazonium halides and 4-amino-1,2,4-triazole) and hydroxylamine (methoxyamine and arylsulfenamides) are used as nitrogen anion precursors. It was shown that VNS amination of 3-nitropyridine and its substituted derivatives proceeds efficiently with 4-amino-1,2,4-triazole and hydroxylamine.[49] Amination of nitroquinolines,[73,74] nitrobenzimidazoles[75] and dinitro-indazoles[76] with 1,1,1-trimethylhydrazinium iodide was recently reported. The same reagent was used for amination of 2-phenyl-4-nitro-1,2,3-triazole.[77] Triphenylporphyrine derivatives in which an internal ring is activated by a carbonyl group containing fragment were aminated with 4-amino-1,2,4-triazole (Scheme 41).[78,79]



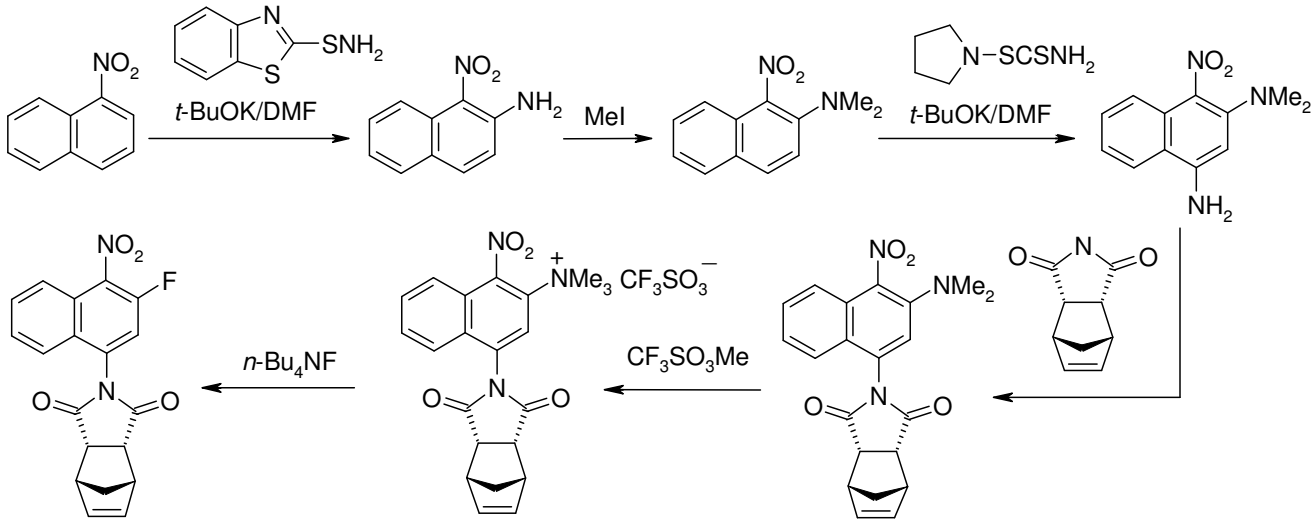
Scheme 41

The amination of 4-nitroindan-1,3-dione derivative with 4-amino-1,2,4-triazole was used in the synthesis of condensed quinoline, a key intermediate in a partial synthesis of aaptosine (Scheme 42).[80]



Scheme 42

Consecutive amination of 1-nitronaphthalene employing benzothiazole-2-sulfenamide and *N*-tetramethylenethiocarbamoylsulfenamide was used in synthesis of fluorine-18-labeled non-steroidal androgen receptor antagonist tested in a prostate cancer therapy (Scheme 43).[81]

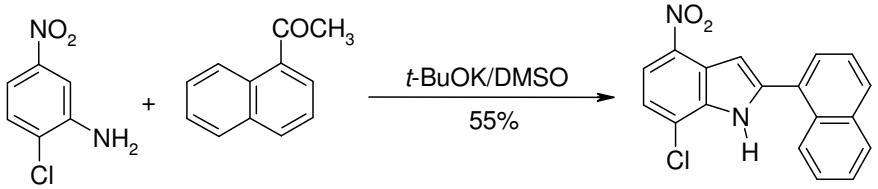


Scheme 43

3. Synthesis of heterocyclic systems *via* nucleophilic substitution of hydrogen

3.1. Indoles

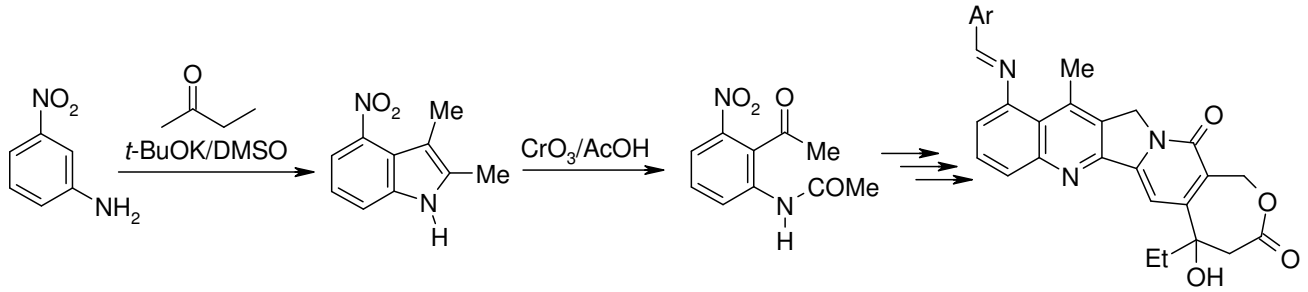
Nucleophilic substitution of hydrogen opens a wide avenue for the synthesis of indoles bearing a variety of substituents in both rings, as well as it enables the synthesis of condensed indole and azaindole derivatives. The simplest, and most efficient, in sense of atom economy, is undoubtedly the synthesis of 4- and 6-nitroindoles *via* reaction of 3-nitroanilines with enolates of ketones (Scheme 44).[82,83]



Scheme 44

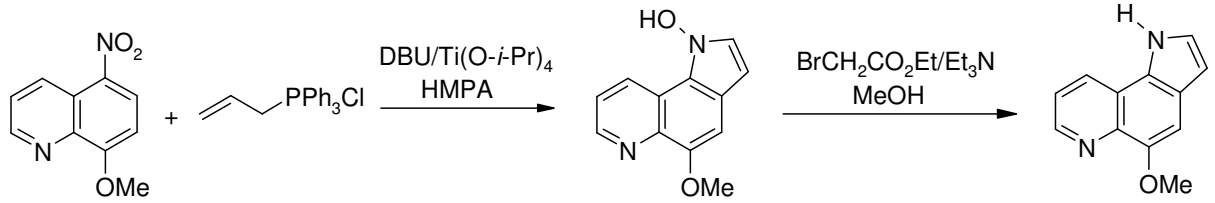
In spite of simplicity and versatility of this new approach, we have found only two its recent applications to the synthesis of compounds of biological interest.[84,85] 2,3-Dimethyl-4-nitroindole obtained from *meta*-nitroaniline and butan-2-one[82,83] was used as a starting material in the synthesis of homokamptotecin derivatives tested for potential activity as inhibitors of DNA topoisomerase I (Scheme 45).[85]

Some 4-nitroindoles[83] were incorporated into oligonucleotides and were found to destabilize their DNA duplexes.[84]



Scheme 45

Phosphonium ylide generated from allyl triphenylphosphonium chloride adds to 1-nitronaphthalene and 5-nitroquinoline in the presence of titianium isopropoxide to form an unstable *N*-hydroxyindole that upon action of ethyl bromoacetate is transformed into benzo- or pyrido-indoles (Scheme 46).[86]



Scheme 46

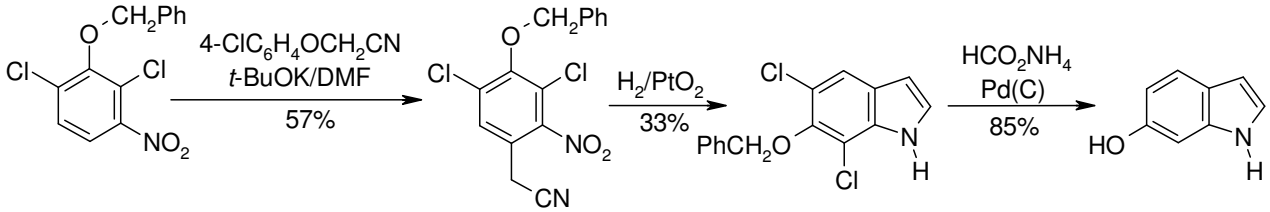
Much wider application have found two other ways of indole synthesis based on the VNS reaction:

-introduction of cyanomethyl substituent in *ortho* position to the nitro group *via* VNS in nitroarenes with carbanions of aryloxyacetonitriles, followed by hydrogenation that gives indoles directly;[87]

-introduction of sulfonylmethyl substituent in *ortho* position to the nitro group *via* VNS in nitroarenes with easily available chloromethyl aryl sulfones. Reduction of the formed *ortho*-nitrobenzyl sulfones gives *ortho*-aminobenzyl aryl sulfones that upon condensation with various reagents (aldehydes,[88] orthoesters,[89] etc.) form indoles.

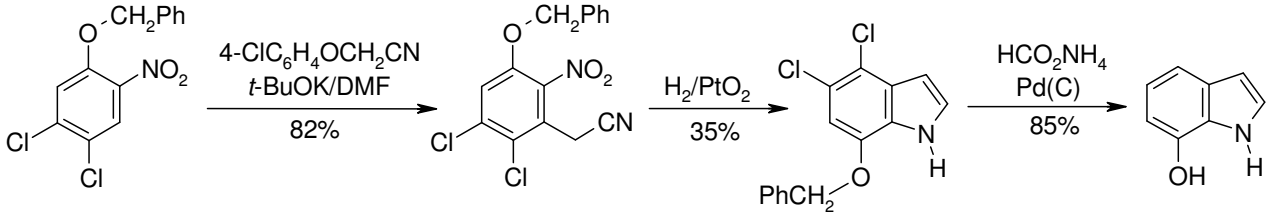
3.1.1. Indoles *via* cyanomethylation

In one of our previous papers, we described a general methodology enabling synthesis of hydroxy- and alkoxy-indoles *via* VNS in 2-, 3-, and 4-nitrophenol derivatives.[87] Our original way of synthesis of hydroxy-indoles is somewhat improved by using alkoxydichloronitrobenzenes.[90] Thanks to the presence of two halogen substituents in the nitroaromatic ring the VNS cyanomethylation with 4-chlorophenoxy-acetonitrile is more selective and efficient (Scheme 47).



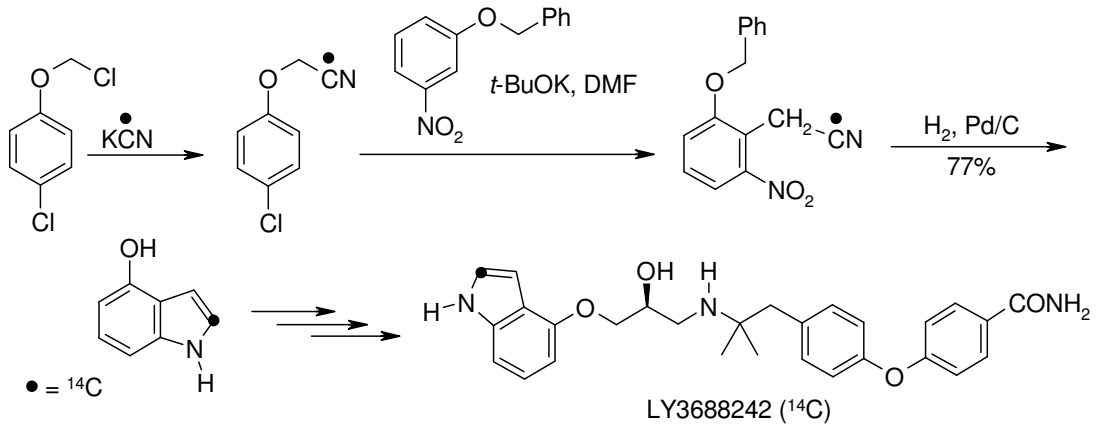
Scheme 47

Similar approach is used in the synthesis of 7-hydroxyindole starting from 4,5-dichloro-2-nitro-phenol (Scheme 48).[90] Probably further optimization of the reduction of 2-nitrophenylacetonitriles to indoles would be desirable.

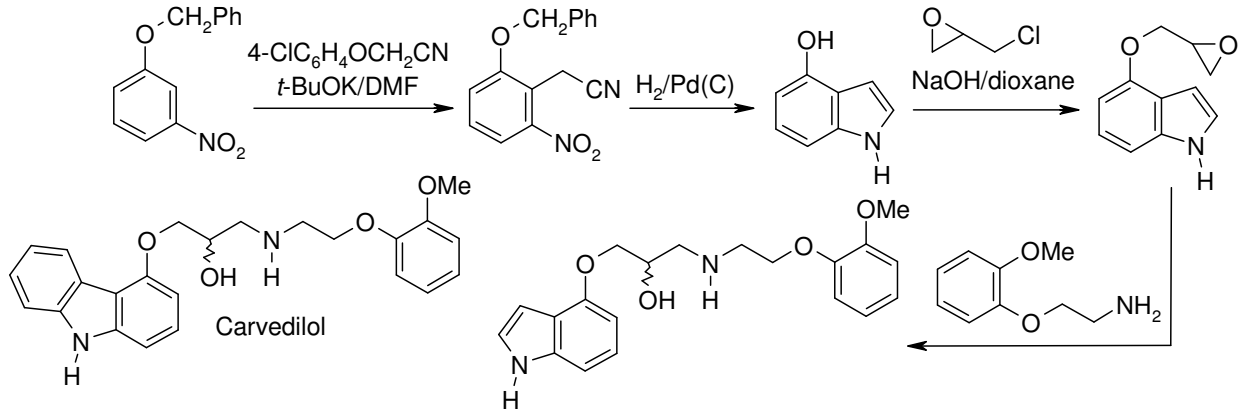


Scheme 48

4-Hydroxyindole is a starting material for the synthesis of β-blockers (*e.g.*, Pindolol). Cyanomethylation of 3-benzyloxynitrobenzene with ^{14}C labeled 4-chlorophenoxyacetonitrile is used for the synthesis of 2-^{14}C labeled 4-hydroxyindole (Scheme 49).[91] In a similar way, 4-hydroxyindole is prepared for the synthesis of a Carvedilol analogue (Scheme 50).[92]

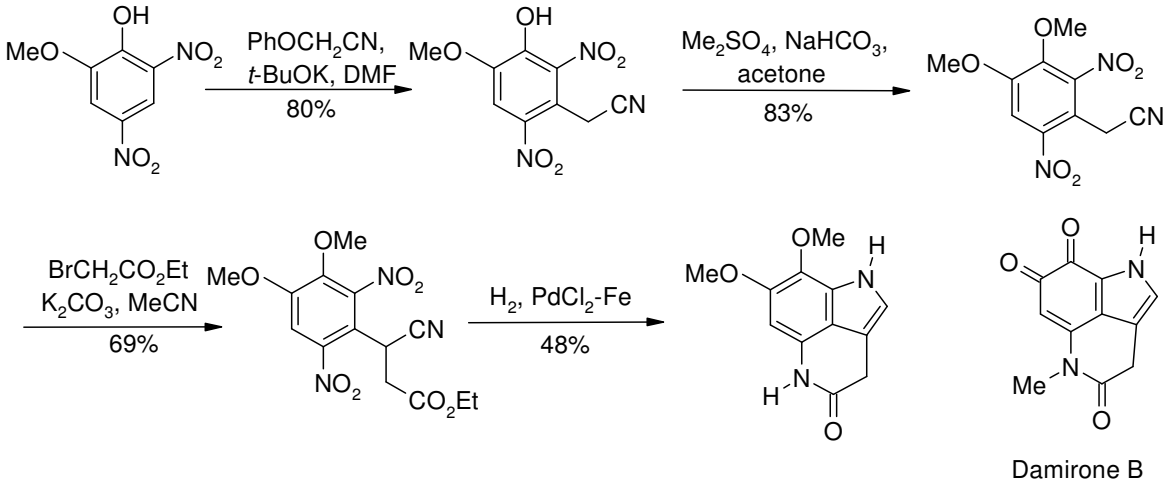


Scheme 49



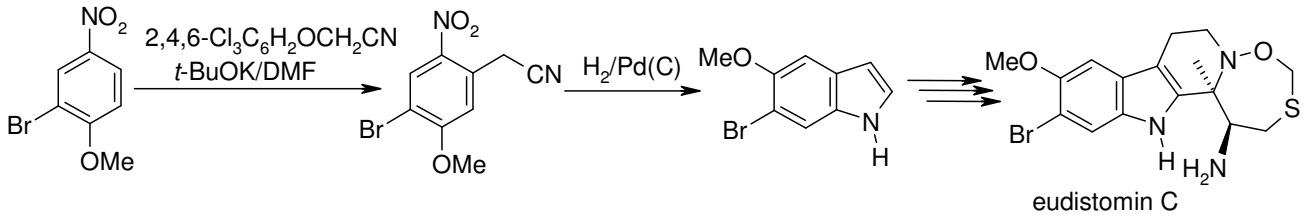
Scheme 50

In the synthesis of damirone B, specific orientation of the VNS in dinitrophenols is used.[93,94] Cyanomethylation of dinitroguaiacol proceeds exclusively at position 5. Further standard transformations (Scheme 51) lead to the damirone precursor.



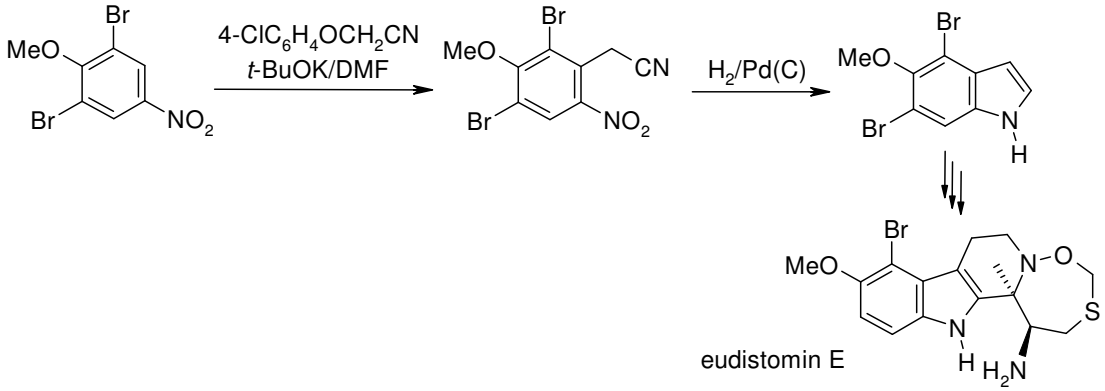
Scheme 51

In the synthesis of eudistomins C and E, both indole unit precursors are prepared *via* vicarious nucleophilic substitution with aryloxyacetonitriles.[95] In the synthesis of eudistomin C, a bulky carbanion precursor, 2,4,6-trichlorophenoxyacetonitrile, is used to avoid substitution of hydrogen at position 3 of 2-bromo-4-nitroanisole. The obtained 6-bromo-5-methoxyindole is then transformed in a few steps into eudistomin C (Scheme 52).[95]



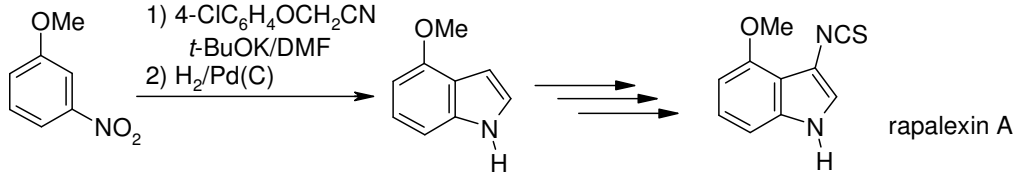
Scheme 52

In the synthesis of eudistomin E, 2,6-dibromo-4-nitroanisole and 4-chlorophenoxyacetonitrile are used as starting materials for cyanomethylation (Scheme 53).[95] The reduction of the formed nitrile leads to a dibromoindole, that in several steps is transformed into eudistomin E.



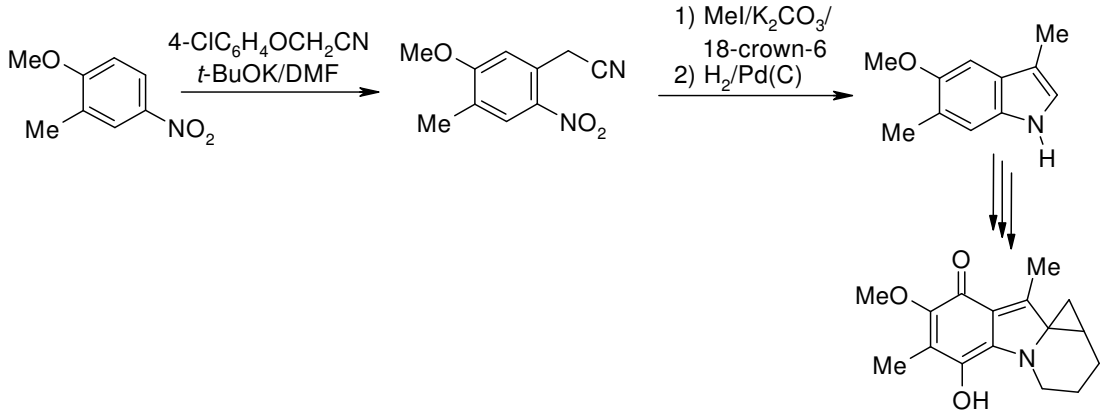
Scheme 53

4-Methoxyindole, prepared *via* VNS reaction in 3-nitroanisole with the carbanion of (4-chlorophenoxy)acetonitrile is transformed in three simple steps into rapalexin A, unusual isothiocyanate alkaloid derived from *Brassica rapa* (Scheme 54).[96]



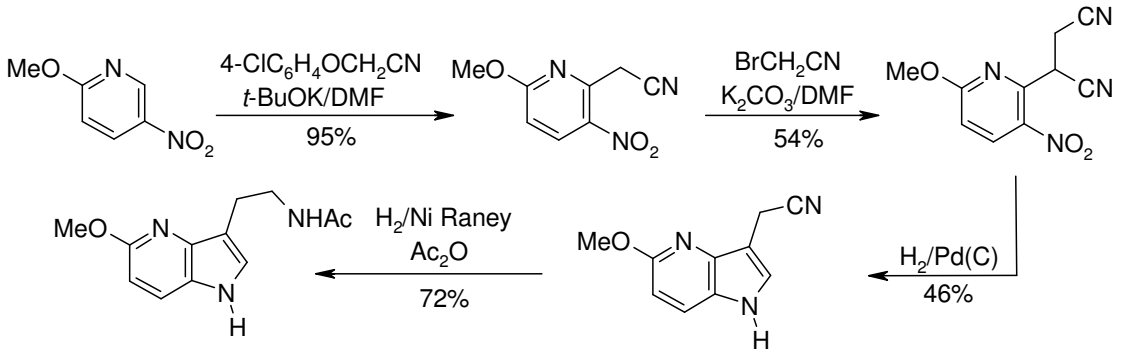
Scheme 54

3,6-Dimethyl-5-methoxyindole, prepared *via* VNS cyanomethylation of 3-methyl-4-methoxy-nitrobenzene, is used as starting material in the synthesis of cyclopropyl quinone methide, a reductive alkylating agent for studies on its *in vitro* interactions with deoxyguanosine-5'-monophosphate (Scheme 55).[97]



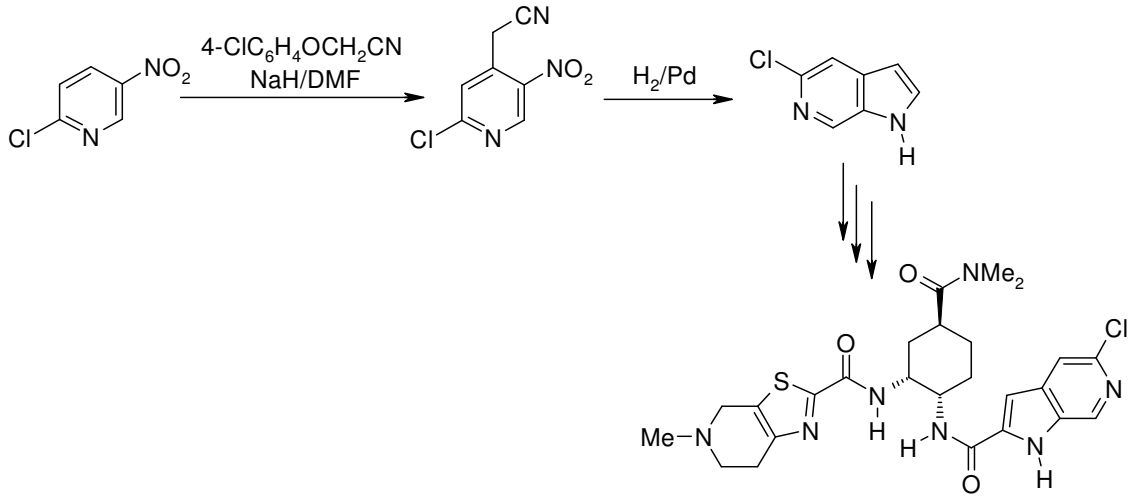
Scheme 55

Substituted 4- and 6-azaindoles are readily available *via* VNS cyanomethylation of 3-nitropyridine derivatives and subsequent hydrogenation of the so-formed *ortho*-nitropyridylacetonitriles. VNS of hydrogen in 2-methoxy-5-nitropyridine leads to pyridylacetonitrile, that, by alkylation with bromo-acetonitrile, followed by a two-step reduction, is efficiently transformed into 5-azamelatonine (Scheme 56).[98] The addition of cyanomethylpyridine, accessible from 3-nitropyridine and aryloxyacetonitrile *via* VNS, to ethyl acetamidoacrylate furnishes a cyanoester that, after hydrogenation, gives an azatryptophan derivative, albeit in low yield.[98]



Scheme 56

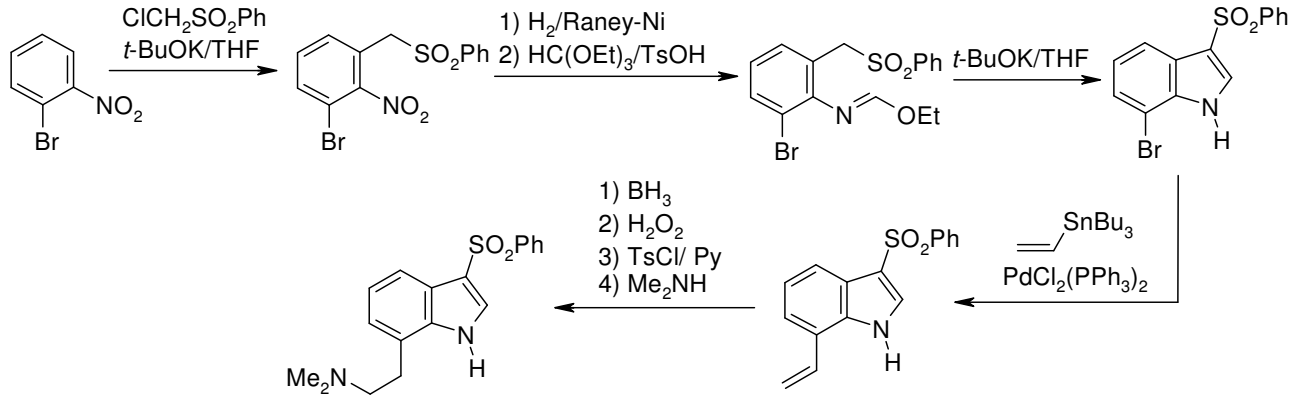
VNS cyanomethylation of 2-chloro-5-nitropyridine provides a nitrile that upon hydrogenation cyclizes to 5-chloro-6-azaindole, a key starting material for the synthesis of a potential inhibitor of the factor Xa (Scheme 57).[99]



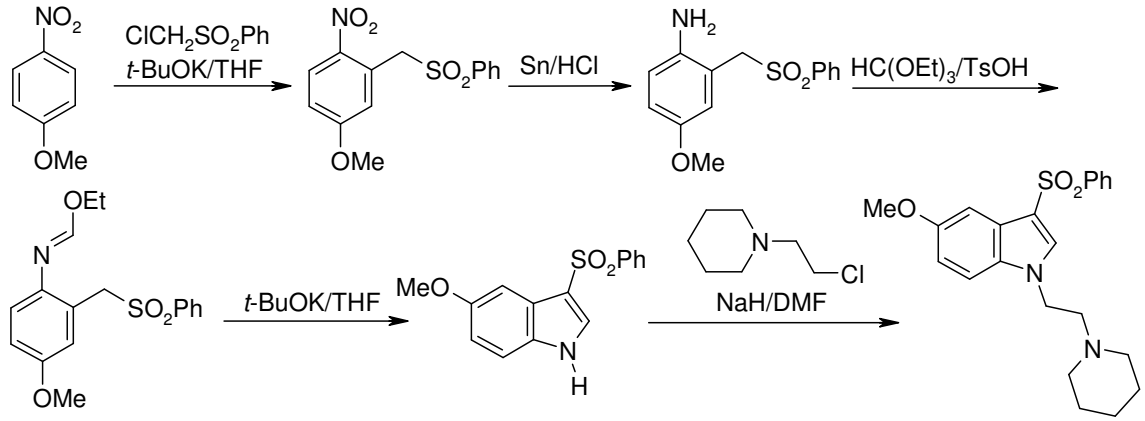
Scheme 57

3.1.2. Indoles from 2-nitrobenzyl sulfones

o-Nitrobenzyl aryl sulfones, readily available *via* VNS in nitroarenes with the carbanions of chloromethyl aryl sulfones, upon reduction and conversion of the amino group into imidate[89] or imine[88] functionality undergo cyclization to form substituted indoles. This procedure is particularly useful because the VNS proceeds selectively in *ortho* to the nitro group when carried out in *t*-BuOK/THF.[100]



Scheme 58

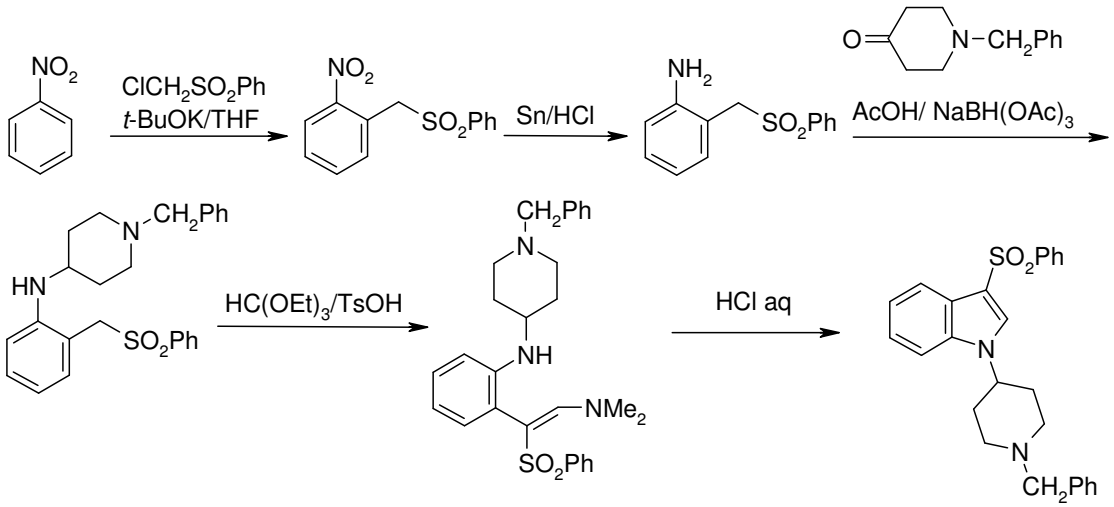


Scheme 59

This way is used for the synthesis of 5- and 7-bromo-3-sulfonylindoles that are subsequently functionalized by a Stille coupling with tributyl(vinyl)tin and the intermediate vinyl derivatives are then transformed into amines which are tested as norepinephrine reuptake inhibitors and 5-HT_{2A} receptor antagonists (Scheme 58).[101]

The 5-methoxy-3-sulfonylindoles obtained in this way are alkylated with 2-chloroethylamines to form derivatives that are tested as a "flipped" serotonergic ligands (Scheme 59).[102,103]

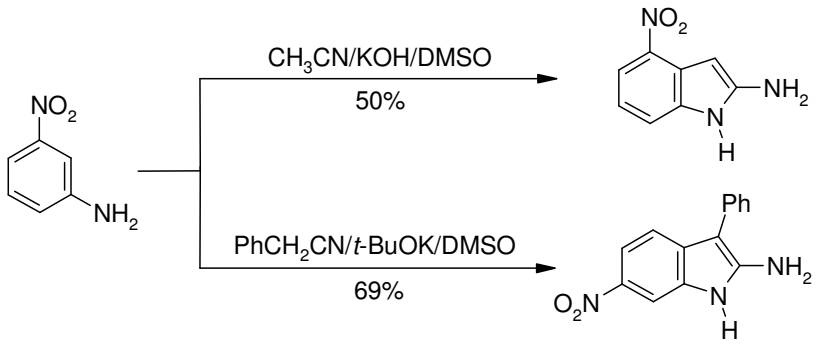
Another way of transformation of 2-aminobenzyl sulfones consists in the reductive amination of a ketone followed with the enamination with dimethylformamide dimethylacetal. The obtained compounds are tested as 5-HT_6 receptor modulators (Scheme 60).[103]



Scheme 60

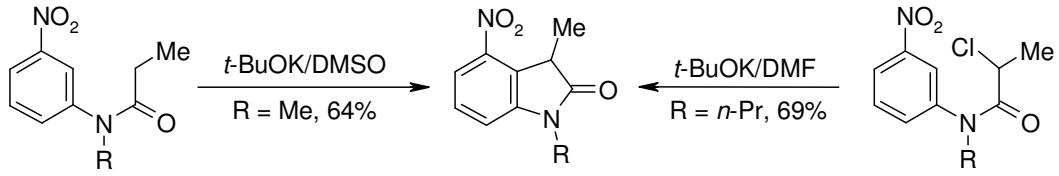
3.1.3. Aminoindoles and oxindoles

A novel simple method of synthesis of 2-aminoindoles consists in the direct oxidative nucleophilic substitution of hydrogen in *meta*-nitroanilines with carbanions of alkanenitriles. For example, the reaction of *meta*-nitroaniline with acetonitrile leads to 2-amino-4-nitroindole while in the reaction with phenylacetonitrile the 6-nitro isomer is formed (Scheme 61).[104]



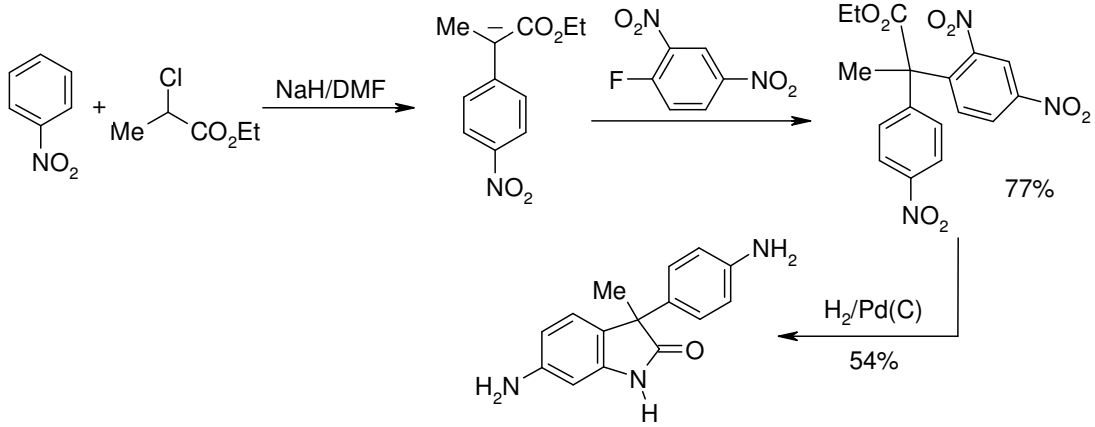
Scheme 61

The nucleophilic substitution of hydrogen is widely used for the synthesis of a variety of oxindole derivatives. Intramolecular ONSH[105] and VNS[106] reactions of carbanions generated from *meta*-nitroanilides of alkanoic[105] and α-chloroalkanoic[106] acids offer direct access to nitrooxindoles (Scheme 62).



Scheme 62

VNS at the *para* position of nitrobenzenes with ethyl α-chloropropionate followed by S_NAr of fluorine in *ortho*-fluoronitrobenzene derivatives provides 2,4,4'-trinitrodiarylpropionates that upon hydrogenation give 3-aryloxindoles (Scheme 63).[107,108]

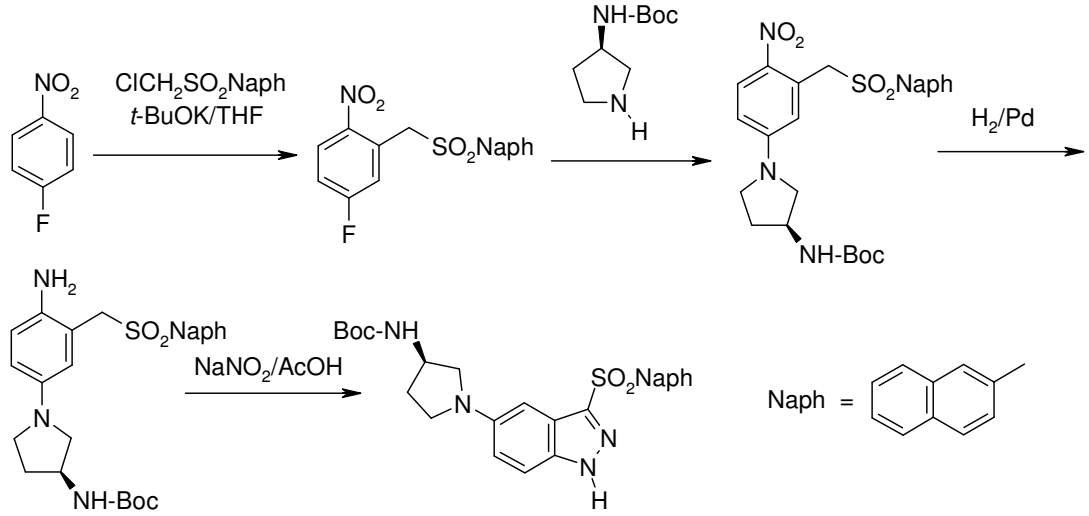


Scheme 63

A simple synthesis of azaoxindoles *via* VNS reaction of 3-nitropyridines with α-chloroalkanoates[48] followed by hydrogenation is shown in the Scheme 24.[109]

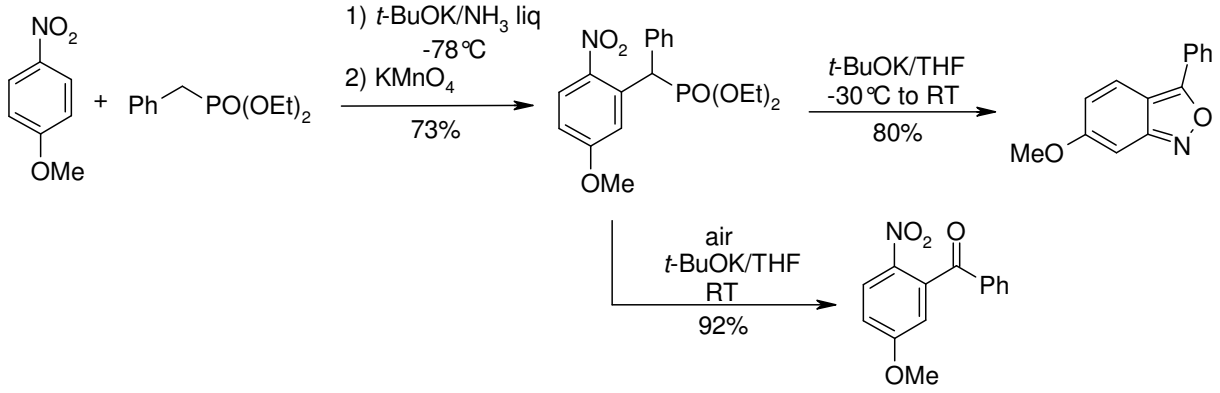
3.2. Other condensed heterocycles obtained *via* nucleophilic substitution of hydrogen

3-Arylsulfonylindazoles, novel 5-HT_6 receptor antagonists, are synthesized *via* VNS in *para*-substituted nitrobenzenes with carbanion of chloromethyl aryl sulfones followed by hydrogenation. Further reaction of *ortho*-aminobenzyl sulfones with sodium nitrite-acetic acid give the desired 5-(*N*-pyrrolidinyl) substituted indazoles (Scheme 64).[110,111]



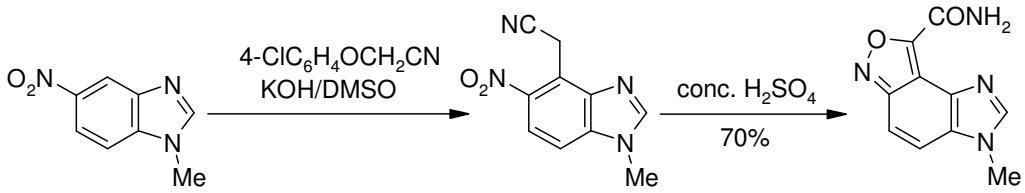
Scheme 64

3-Phenyl-2,1-benzisoxazoles can be obtained directly in the reaction of *para*-substituted nitrobenzenes with carbanions of arylacetonitriles generated in the protic media. The reaction proceeds *via* conversion of the initially formed σ^H adducts into nitroso compounds that undergo further transformations.[112] Alternative synthesis of such benzisoxazoles consists in ONSH reaction at the *ortho*-position of nitroarenes with the carbanion of diethyl benzylphosphonate. Carbanion of the produced α-(*ortho*-nitrophenyl)benzyl phosphonate under anaerobic conditions undergoes spontaneous conversion into benzisoxazole, while its oxidation leads to benzophenone derivative (Scheme 65).[113]



Scheme 65

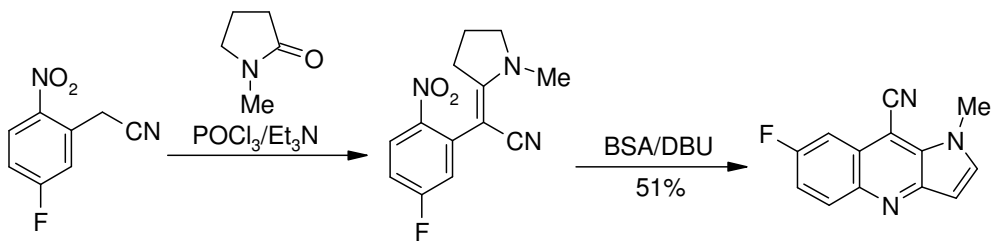
VNS cyanomethylation of nitroarenes in the *ortho*-position is a key step not only for the synthesis of indoles but also of benzisoxazoles. Treatment of *ortho*-nitroarylacetonitriles with concentrated sulfuric acid leads directly to benzisoxazoles and their condensed derivatives (Scheme 66).[114]



Scheme 66

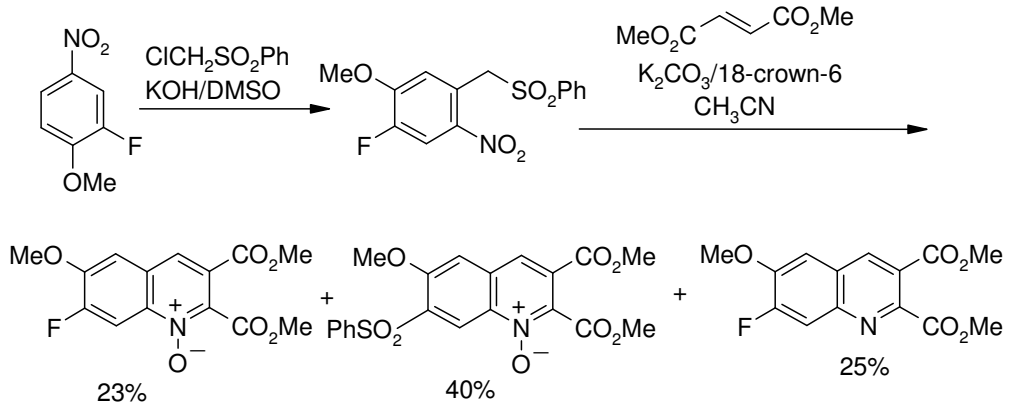
Benzisoxazoles are also formed as a result of alternative conversion of σ^H adducts of some carbanions in *ortho* position of bicyclic nitroarenes (Scheme 22).[52]

The Vilsmeier-Haack reaction of *ortho*-nitroarylacetonitriles with *N*-methylpyrrolidone followed by a cyclization induced by *bis*-trimethylsilylacetamide (BSA) in the presence of diazabicycloundecene (DBU) leads directly to pyrrolo[3,2-*b*]quinoline derivatives (Scheme 67).[115]



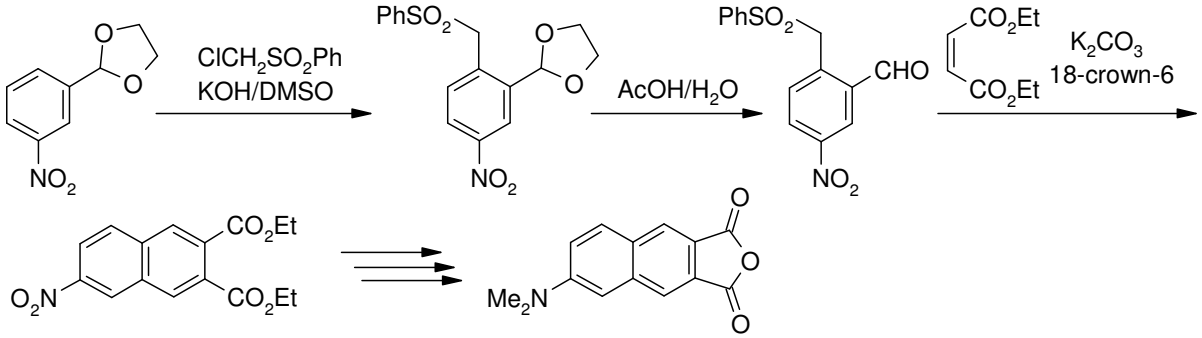
Scheme 67

Polysubstituted quinolines are produced from *ortho*-nitrobenzyl aryl sulfones, products of the VNS of hydrogen in suitably substituted nitroarenes with chloromethyl aryl sulfones. The Michael addition of such sulfones to dialkyl maleates and fumarates triggers a set of subsequent transformations – intramolecular attack of the carbanion on the nitro group, elimination of water and sulfinic acid to form substituted quinoline 2,3-dicarboxylate *N*-oxides.[116] This approach has been recently used for the synthesis of fluorine-substituted quinoline *N*-oxides. During this reaction S_NAr of fluorine leading to sulfone and partial deoxygenation of *N*-oxide also occurred (Scheme 68).[117]



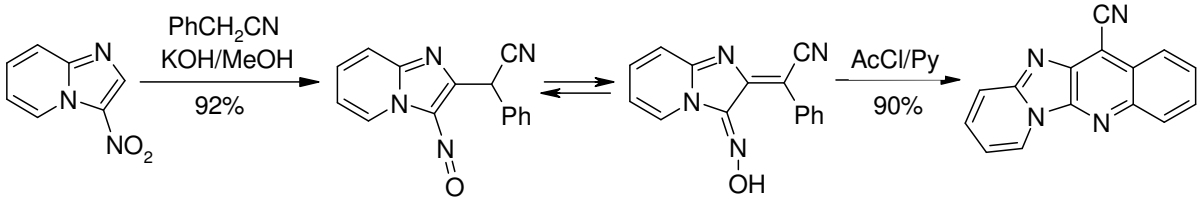
Scheme 68

VNS of hydrogen in protected *meta*-nitrobenzaldehyde with chloromethyl phenyl sulfone followed by deprotection and Michael addition to diethylmaleate are key steps in synthesis of naphthalic anhydride applicable as an environment-sensitive fluorophore in biochemical studies (Scheme 69).[118]



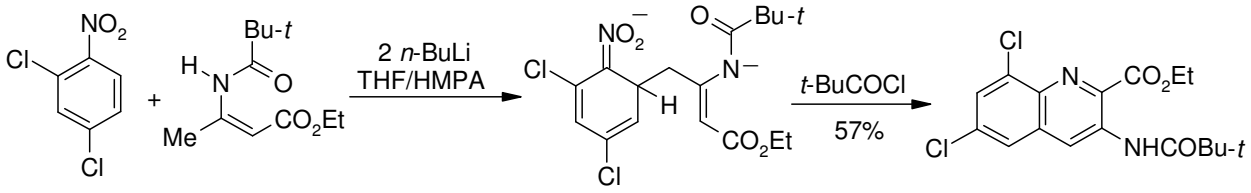
Scheme 69

The conversion of σ^H adduct of arylacetonitrile to 3-nitroimidazo[1,2-a]pyridine is a key step in synthesis of pyridoimidazoquinoline derivatives, compounds of potential application as highly fluorescent dyes (Scheme 70).[60]



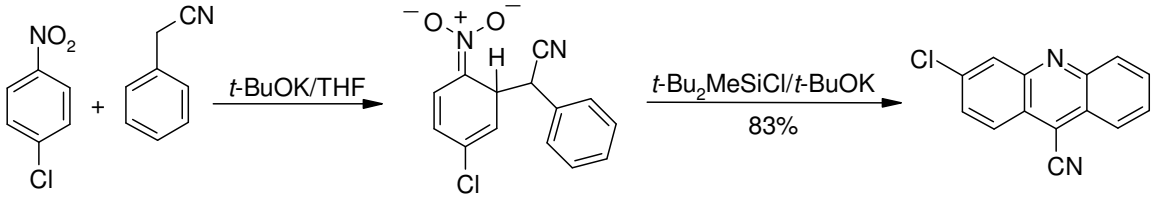
Scheme 70

A novel approach to the synthesis of substituted 3-aminoquinolines consists in the addition of the dianion of ethyl *N*-pivaloyl-3-aminocrotonate to nitroarenes, followed by silylation or acylation of the intermediate σ-adduct. Prolonged heating of the obtained amidoester with concentrated hydrochloric acid leads to 3-amino-quinolines as exemplified in the Scheme 71.[119]



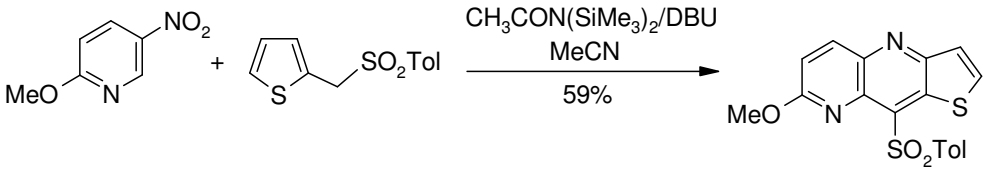
Scheme 71

σ^H-Adducts of carbanions of arylacetonitriles to nitroarenes in *ortho* position undergo slow cyclization to acridine derivatives upon treatment with trialkylchlorosilanes or pivaloyl chloride (Scheme 72).[120]



Scheme 72

Ethyl phenylacetate and benzyl sulfones (and their heteroanalogues) react in a similar way. This approach makes accessible sophisticated condensed heterocycles. For example, treatment of 2-methoxy-5-nitro-pyridine with thienylmethyl tolyl sulfone in the presence of bis-trimethylsilylacetamide and diaza-bicyclo-undecene enables to obtain thienonaphthyridine in good yield (Scheme 73).[121]

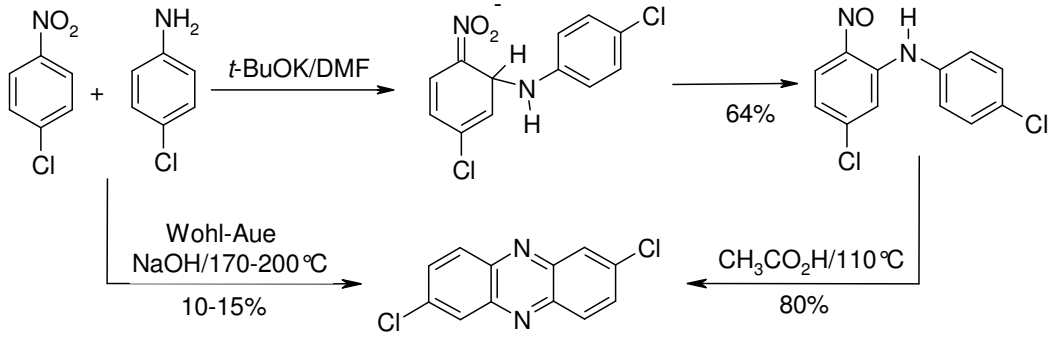


Scheme 73

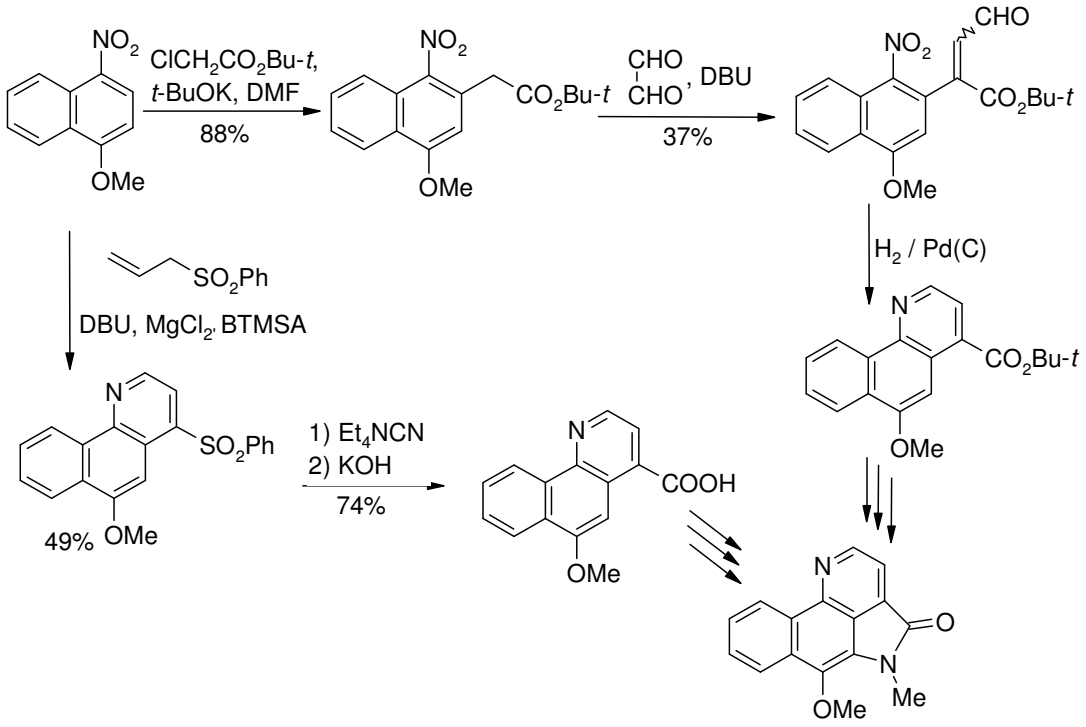
The reaction of anilines with nitroarenes under basic conditions (Wohl-Aue reaction) provides phenazines albeit in low yields.[122] The classic reaction proceeds under rather harsh condition. The new two-step process permits the synthesis of phenazines from the intermediate 2-nitrosodiphenylamines that are formed directly from anilines and nitroarenes under mild conditions (Scheme 74).[28] Treatment of 2-nitrosodiphenyl-amines with acetic acid leads to phenazines in high yields. It is worthy to mention that rhenium(I) complexes obtained from 2-nitrosodiphenylamines were tested *in vitro* for anticancer activity against human melanoma and leukemia cells.[123]

The nucleophilic substitution of hydrogen in 1-methoxy-4-nitronaphthalene is used for the synthesis of 6-methoxy-benzo[h]quinoline-4-carboxylic acid and its ester, intermediates for the synthesis of eupolauramine, an alkaloid from the bark of an african plant *Euopomatia laurina* (Scheme 75). In the first

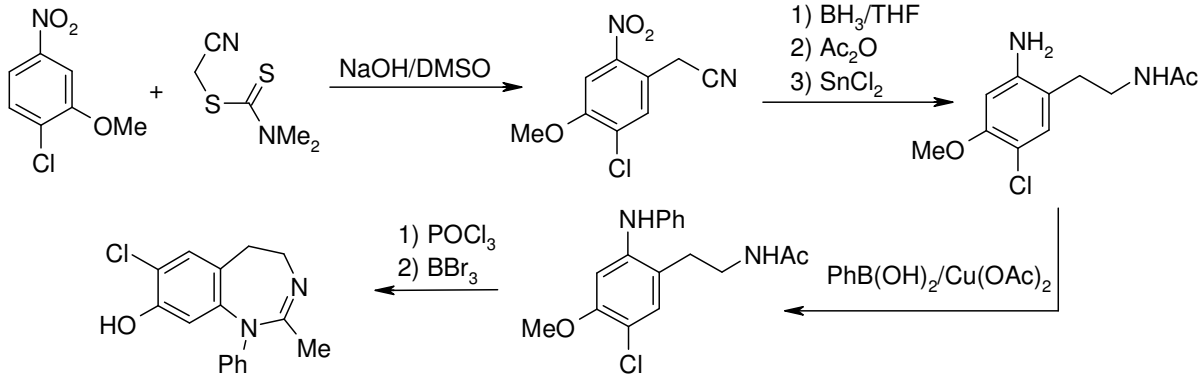
approach, VNS with *tert*-butyl chloroacetate is applied. The obtained ester is then transformed by means of standard steps into tricyclic derivative.[124] An even simpler approach deals with nucleophilic substitution of hydrogen with allyl sulfone carbanion.[125] The obtained tricyclic acid or its ester can be transformed into the final alkaloid according to a known procedure.[126]



Scheme 74



Scheme 75



Scheme 76

Novel dopamine antagonists containing 1,3-benzodiazepine fragment[127] are prepared from 2-chloro-5-nitroanisole and cyanomethyl dimethyldithiocarbamate *via* typical VNS procedure furnishing 5-chloro-4-methoxy-2-nitrophenylacetonitrile as exemplified in the Scheme 76.

4. Conclusion

We certainly hope that the examples of nucleophilic substitution of hydrogen and the use of this versatile and general reaction for the synthesis of heterocyclic compounds will attract attention of researchers working in the field of organic synthesis.

Acknowledgment

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HETERO DIELS-ALDER (HDA) REACTIONS OF 1-PHOSPHONO-1,3-BUTADIENES WITH AZO AND NITROSO DIENOPHILES: AN ENTRY TOWARDS VERSATILE HETEROCYCLIC SYNTHONS FOR AMINOPHOSPHONIC COMPOUNDS

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Abstract. *The review describes an original and general approach to the synthesis of various γ-amino-phosphonate derivatives of potential interest in medicinal chemistry. The strategy is based on the [4+2] cycloadditions of 1-phosphono-1,3-butadienes with azo (N=N) and nitroso (O=N) dienophiles, as the key step leading to the corresponding six-membered heterocycles, namely 6-phosphono-3,6-dihydro-1,2-pyridazines and 6-phosphono-3,6-dihydro-1,2-oxazines. An asymmetric version of this HDA reaction has been developed and computational studies have been performed to explain the regio- and stereo-selectivities. The above six-membered heterocycles, which feature a N–N or O–N bond and a C=C double bond, behave as versatile synthons due to their possible chemo-selective transformations, such as (i) the reduction of the C=C bond; (ii) the syn-dihydroxylation of the C=C bond; (iii) the O–N reductive cleavage; (iv) the phosphonate deprotection; (v) various FGI (functional group interconversions); and finally (vi) combinations of different steps. Accordingly, several novel, highly functionalized, aminophosphonic derivatives have been obtained in the aliphatic and heterocyclic series.*

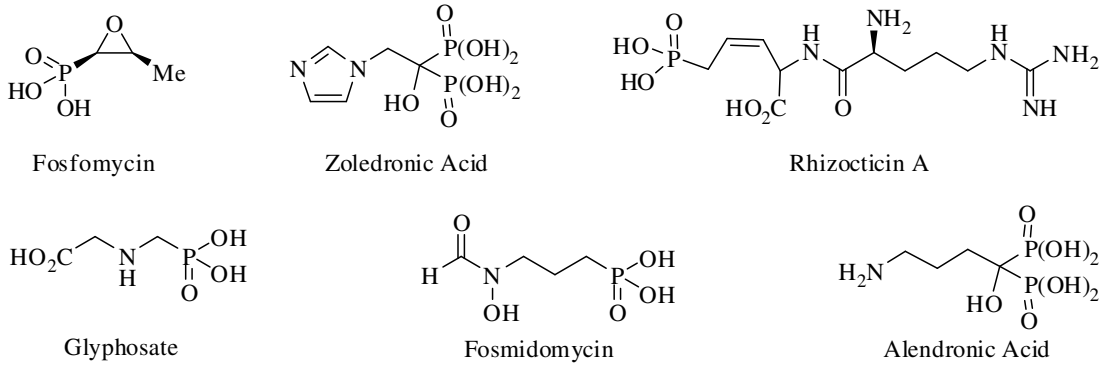
Contents

1. Introduction

1.1. Occurrence and importance of the aminophosphonate derivatives

The organophosphorus chemistry was born at the beginning of the nineteenth century thanks to the esterification of phosphoric acid with alcohols and the synthesis of alkylphosphites used in the Arbuzov reaction. During the twentieth century, the discovery of the Horner-Wadsworth-Emmons reaction and the formation of the phosphonate carbanions set the bases of the current phosphonate chemistry.[1]

Besides their recognized utility as reagents in organic synthesis, organophosphonate compounds were found to play a crucial role in nature and practically all living organisms.[2] The discoveries of natural compounds endowed with antiviral, antitumor or antibacterial activities, such as Fosfomycin,[3] Zoledronic acid[4] and Rhizocticin A[5] (Scheme 1), stimulated the interest of academic and industrial researchers. Due to the similarity with aminoacids, the class of amino(alkyl)phosphonates received a particular attention.[6] 2-Aminoethanephosphonic acid (AEP), also named Ciliatine, is the simplest natural aminophosphonate and the most ubiquitous.[7] Glyphosate [or *N*-(phosphonomethyl)glycine] is marketed under the trade-name Roundup® as a non selective herbicide[8] (Scheme 1). Fosmidomycin is a naturally occurring antimalarial drug[9] and Alendronate is a synthetic drug for osteoporosis treatment.[10]

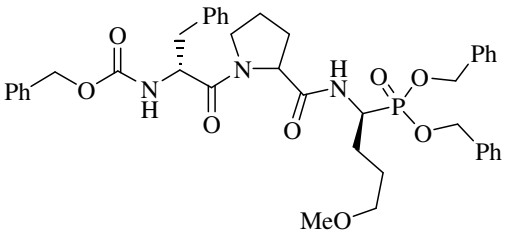


Scheme 1

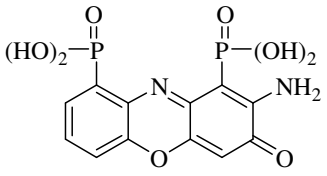
Despite significant differences in terms of pK_a, geometry, shape and lipophilicity, the phosphonate group is considered as a bioisoster of the carboxylate group in medicinal chemistry.[6] The replacement of proteinogenic aminoacid residues by their phosphonic analogs is one of the usual strategies for drug optimization.[11] Moreover the enhanced lipophilic character of the phosphonate bioisosters often provides an advantage in term of bioavailability.[12] The phosphonate motif has also been considered as a metabolically stable analog of phosphate or pyrophosphate substituents.[13] Since the sp^3 tetrahedral geometry of phosphorus

resembles that of the transition state of amide hydrolysis by peptidases, phosphonate compounds have been designed as enzyme inhibitors called "transition-state-analogs" as exemplified with thrombin inhibitors (Scheme 2).[14] The strong Lewis base character of the phosphonate group confers a high affinity for metallic cations; this property has been exploited in the development of matrix metalloproteinases (MMP) inhibitors.[15] Phosphonate analogs and homologs of glutamic acid (the major neurotransmitter in CNS) showed a potent action on the *N*-methyl-(D)-aspartate (NMDA) receptor.[16] Lastly, six-membered ring phosphonates have been reported as potent prodrugs against liver diseases and as antitumor agents.[17]

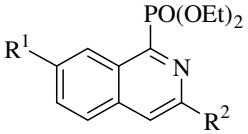
Several industrial applications of (poly)amino(poly)phosphonates arise from their chelating properties (water treatment, detergents, cleaners, bleaching of paper and textiles…).[2,18,19] Recently, water-soluble phenoxazinone dyes were obtained thanks to the introduction of phosphonate substituents onto the building blocks of the substrates used in a laccase-mediated oxidative dimerization process (Scheme 2).[20,21] Other biologically relevant heterocyclic compounds contain a phosphonate group, such as isoquinoline derivatives, developed for the inhibition of protein tyrosine phosphatase PTP1B (Scheme 2).[22] Nevertheless, the aminophosphonic compounds in the aliphatic series remain the most exploited ones and their increasing number of applications, in multiple domains, has stimulated the development of practical synthetic routes outlined in the next section.



Thrombin inhibitor S-2238



Phenoxazinone Dye



Isoquinolin-1-yl-phosphonate

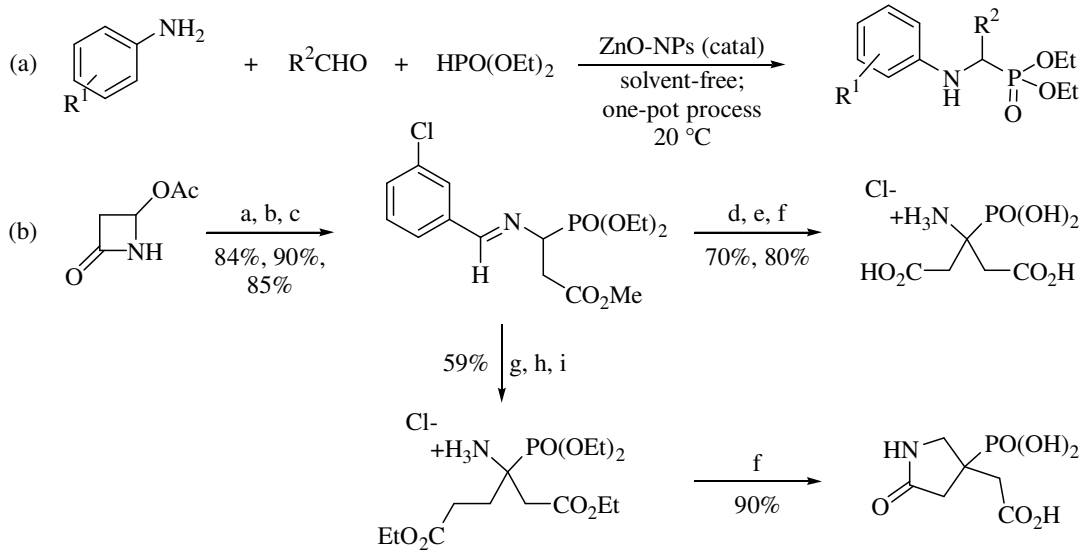
Scheme 2

1.2. Synthetic methods towards aminophosphonates

The most abundant literature concerns the α-aminoalkanephosphonic acids (or their esters derivatives) with several reviews on the subject[2,23,24] and a particular insight into asymmetric synthesis.[25,26] The common strategies are based on (a) the C–P bond formation *via* the addition of alkyl phosphites to imines (Kabachnick-Fields reaction)[27] and the substitution of halogenoalkylamines with phosphites (Arbuzov and Michaelis-Becker reations);[28] (b) the C–N bond formation *via* the insertion of α-phosphonocarbenes into amines[29] and the substitution of α-hydroxyphosphonates with activated NH (Mistunobu reaction);[30] (c) the C–C bond formation *via* the alkylation of phosphonoglycine derivatives[31] and the nucleophilic addition to iminophosphonates.[32] Recent examples of these methods are illustrated in Scheme 3.[33,34] Non-traditional strategies have also been applied, such as the copper-catalyzed aerobic phosphonation of a sp^3 C–H bond depicted in Scheme 4.[35]

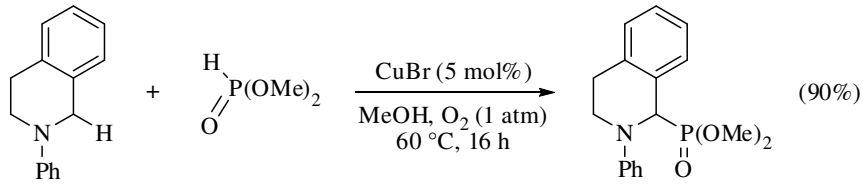
Current routes towards β-aminoalkanephosphonic acids (or esters), in racemic and chiral series, have been completely reviewed.[36,37] The simplest methods are based on the Michael addition strategy, that is either the aza-Michael reaction[38] or the phospha-Michael reaction.[39] Concerning the γ- and δ-amino-alkanephosphonic derivatives, the reports are very limited and dedicated to punctual targets. In this domain,

the usefulness of 1-phosphono-2-aza-1,3-dienes as precursors of diverse classes of aminophosphonates and azaheterocyclic phosphonates has been revealed.[40–43]



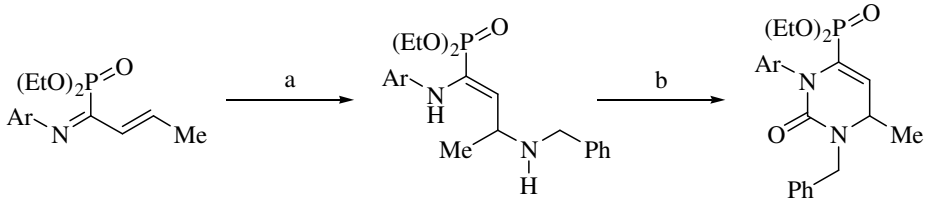
a. $P(OEt)_3$, toluene; b. $SOCl_2$, MeOH; c. *m*-ClPhCHO, $MgSO_4$, DCM; d. LDA, DMPU, THF; e. $BrCH_2CO_2Me$; f. 6 N HCl, reflux; g. NaOEt-EtOH; h. CH_2=CH-CO_2Et, reflux; i. 1 N HCl, CH_3CN, 20 °C

Scheme 3



Scheme 4

The 2-phosphono-1-aza-1,3-dienes have also been successfully used,[44–46] as illustrated in Scheme 5: conjugated addition of chiral amines to an α,β-unsaturated imine derived from α-aminophosphonate afforded α-dehydroaminophosphonates with a γ-stereogenic centre bearing an amino group. These intermediates could be further transformed into phosphonylated pyrimidine derivatives.[47]



a. H_2NCH_2Ph, DCM; b. Cl_3CO-CO-$OCCl_3$, Et_3N, DCM

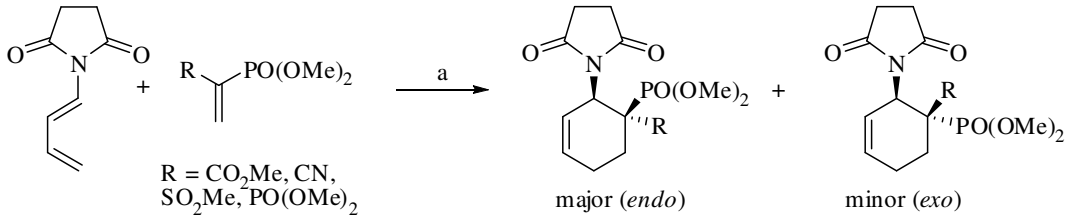
Scheme 5

1.3. The Diels-Alder strategy towards aminophosphonates

Facing the lack of general methods for the synthesis of aminophosphonate derivatives other than the α-ones, we proposed about 10 years ago to explore the Diels-Alder (DA) reaction, *i.e.* the [4+2] cycloaddition of dienes and olefins, with appropriate functionalized partners as a powerful synthetic route

towards aminophosphonate derivatives.[48,49] A tremendous amount of work has been dedicated to the DA reaction since its discovery in 1928, dealing with the synthetic,[50] mechanistic and theoretical aspects.[51] Thanks to its usually complete regioselectivity, the DA reaction has the advantage of opening the way to selectively functionalized β-(*ortho*), γ-(*meta*) or δ-(*para*) six-membered cycloadducts by changing the relative position of the substituents onto the reagents, *i.e.* the dienes and the dienophiles, respectively. Moreover, the DA cycloaddition proceeds with *cis*-stereospecificity, as a result of its concerted mechanism, and high *endo*-selectivity.[52] Hence, this reaction is well adapted for asymmetric synthesis, using chiral auxiliaries,[53] chiral catalysts,[54] organocatalysts,[55] biocatalysts[56] or chiral media.[57]

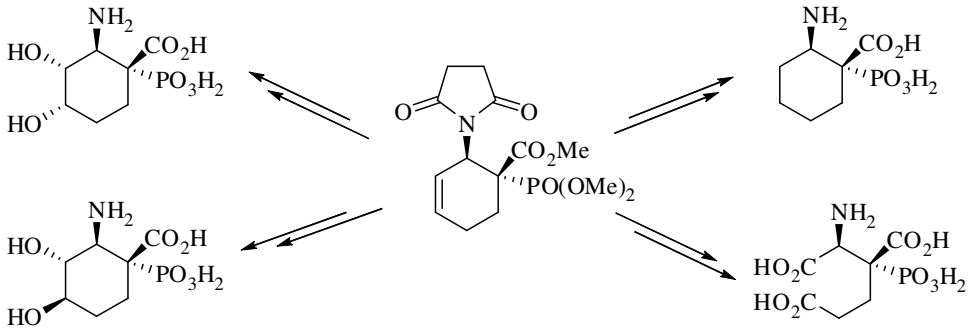
The successful use of the DA strategy for the formation of β- and γ-aminophosphonates has been demonstrated with the cycloadditions of 1-amino-1,3-butadienes to vinyl phosphonates.[48] Since the latter reagents are poorly reactive dienophiles,[58] they need to be activated by a strong electron-withdrawing group (EWG) placed geminally or vicinally regarding to the phosphonate substituent.[59] The results obtained upon reacting *N*-(butadienyl)succinimide with *gem*-substituted vinylphosphonates are shown in Scheme 6.[60,61]



a. ACN, reflux

Scheme 6

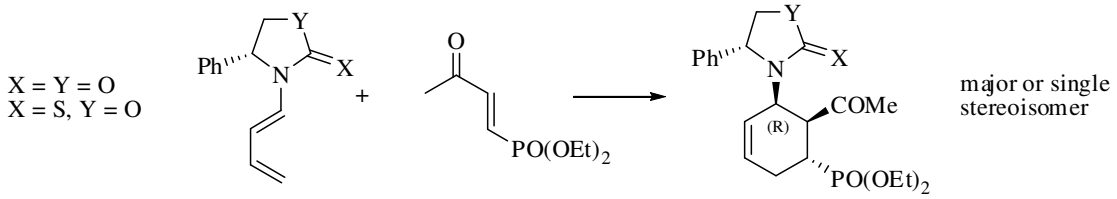
The regioselectivity is complete, leading to the β-(*ortho*) substituted cyclohexene adducts and the major stereoisomers feature the N– and P–substituents in the relative *endo* configuration. Various functionalized β-aminophosphonic compounds could be prepared from these cycloadducts as exemplified with the selective transformations of methyl 1-dimethoxyphosphonyl-2-succinimido-3-cyclohexene-1-carboxylate (Scheme 7),[62] *via* either reduction or oxidation of the C=C double bond (*syn*- and *anti*-dihydroxylation, cleavage by ozonolysis) followed by the usual deprotection steps.



Scheme 7

Using chiral aminodienes, an asymmetric version of the DA reactions of vinylphosphonates has been developed.[63,64] Scheme 8 illustrates the reaction of a vicinally substituted vinylphosphonate (EWG=COMe) with (R)-4-phenyl-2-oxazolidinone (X=O) and thione (X=S)-derived aminodienes. The nature of the chiral

auxiliary has a dramatic effect on the stereoselectivities: for X=O, the *endo* and facial selectivities are 92% and 95% respectively, while for X=S, both selectivities are 100%! This behaviour was in fact predicted by DFT calculations, as well as the absolute configuration (R) of the created *C–P chiral centre.[65,66] The structure of the cycloadduct (Scheme 8) has been confirmed by X-ray diffraction data: the complete regioselectivity, governed by the most powerful EWG (*i.e.* COMe *vs* $PO(OEt)_2$), leads exclusively to a γ-aminophosphonate derivative.[67,68]



Scheme 8

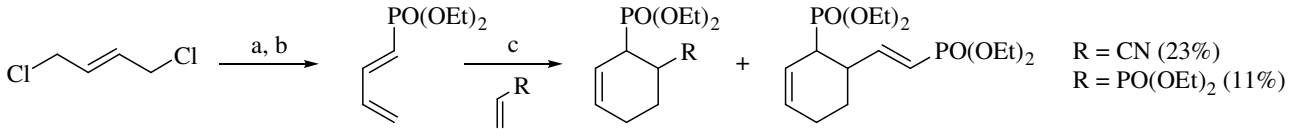
The next step to further develop the DA strategy involving a phosphonate partner obviously consisted in the combination of phosphono dienes with amino dienophiles. Since such reactions were found unexpectedly difficult to occur with C=C reagents, we turned to the hetero-Diels-Alder (HDA) strategy with N=N and O=N dienophiles; this subject forms the core of the present review.

2. Phosphono dienes – Literature survey and initial investigations

The ease of access to phosphono dienes and their reactivity in [4+2] cycloaddition reactions have been first screened through the literature. Surprisingly, only a restricted number of publications focuses on this type of reagents and the outcomes are quite discouraging, as detailed below.

2.1. 1-Phosphono-1,3-butadienes

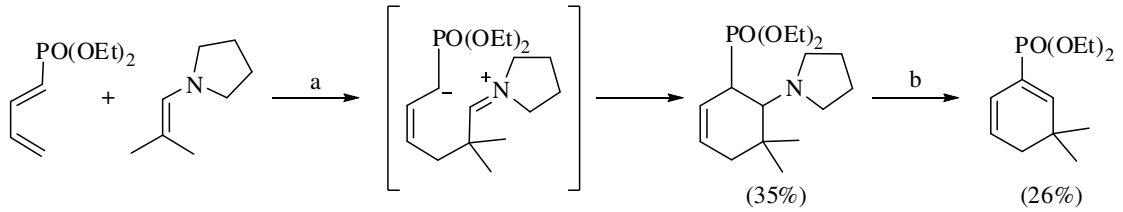
1-(Diethoxyphosphonyl)-1,3-butadiene was initially studied by Pudovik in 1963[69] and revisited by Griffin in 1970.[70] The diene is prepared in two steps, with modest yields, from 1,4-dichloro-2-butene by an Arbuzov reaction followed by HCl elimination (Scheme 9). Its reaction with classical dienophiles (namely acrylates, acrolein, acrylonitrile, maleates, fumarates, vinylphosphonates, acetylene dicarboxylates,…) requires harsh conditions and only yields to small amount of the desired product, mainly due to the diene dimerization (Scheme 9).



a. $P(OEt)_3$, 160 °C, 10 h; b. DBU, THF, 20 °C to 50 °C; c. neat, 120–150 °C, 12 h

Scheme 9

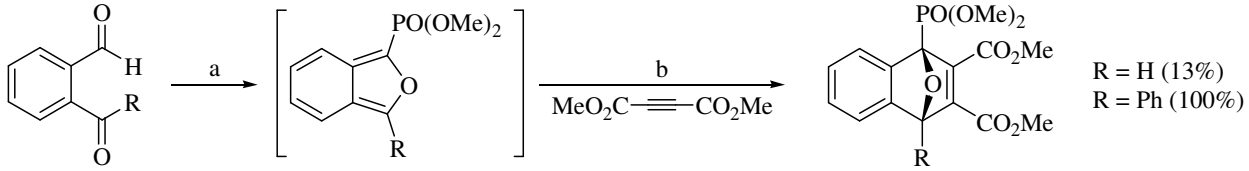
A few years later, Darling showed that better results could be obtained using electron-rich olefins as partners.[71] In fact, the cycloaddition proceeds *via* a Michael addition intermediate and the formal cycloadduct is thermally unstable (Scheme 10).



a. C_6H_6, reflux, 12 h; b. C_6H_6, reflux, 48 h

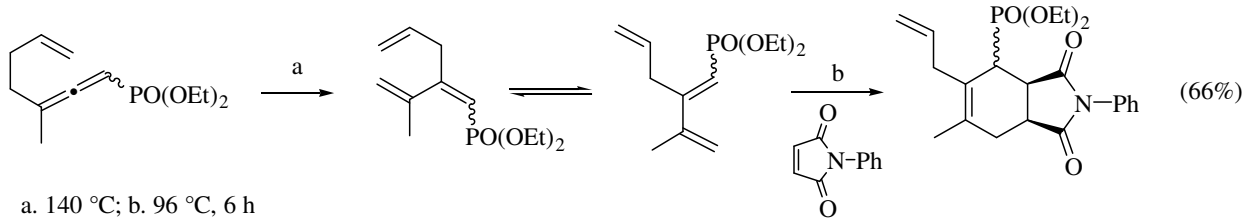
Scheme 10

Cyclic dienes such as 1-(dimethylphosphonyl)-8-phenyl-benzofurane (Scheme 11),[72,73] and 2,3-di-substituted dienes, such as 1-(diethylphosphonyl)-2-allyl-3-methyl-1,3-butadiene obtained by Cope rearrangement (Scheme 12),[74] appeared significantly more reactive, probably due to electronic factors (substituents effect) and conformational reasons (predominance of *cisoid* dienes). As exemplified in Schemes 11 and 12, cycloadditions with *N*-phenyl-maleimide and dimethyl acetylenedicarboxylate occur with excellent and good yields, respectively. Similarly, Scheme 13 depicts an example of tandem reactions (HDA, ene-reaction, intramolecular DA) involving activated phosphono dienes and a P≡C heterodienophile.[75]



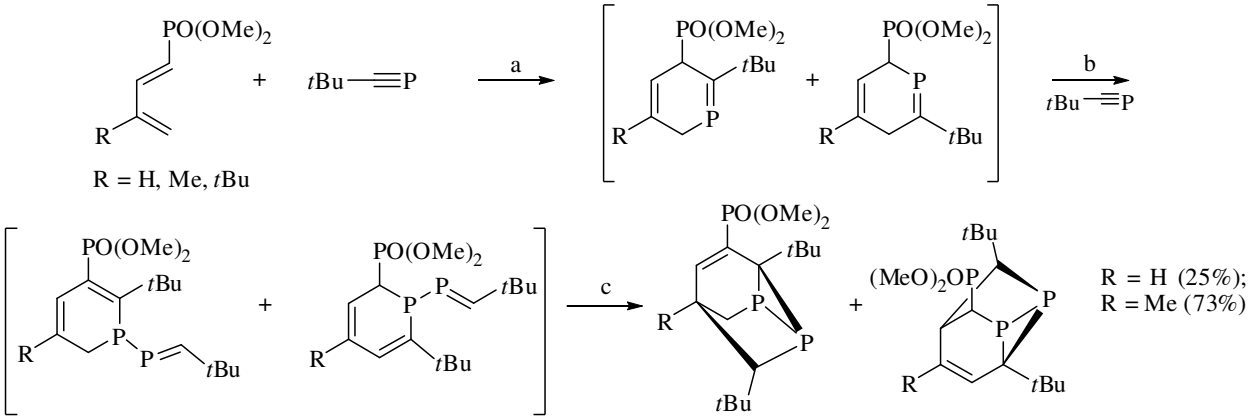
a. $P(OMe)_3$, BF_3·ether, MeCN, 25 °C; b. $CHCl_3$, 20 °C, 24 h

Scheme 11



a. 140 °C; b. 96 °C, 6 h

Scheme 12

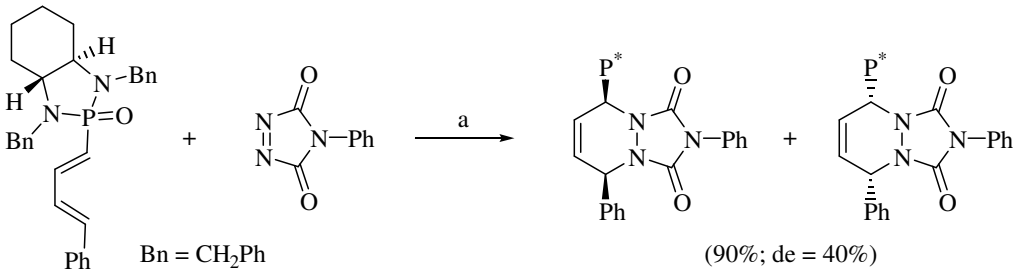


a. C_6H_6, 130 °C, 72 h; b. ene-reaction; c. intra-molecular DA

Scheme 13

Finally, only one example of activated chiral phosphono diene has been reported, giving high yield of cycloadduct with a N=N heterodienophile, but a modest diastereoisomeric excess of 40% (Scheme 14).[76]

Other 1-phosphonodienyl compounds have been synthesized, but never used as partners in cycloaddition reactions, because of their high steric hindrance or non-adapted geometry.[77,78] It is also worth mentioning that 1-(diethoxyphosphonyl)-1,3-butadiene, the most simple reagent (see Scheme 9), has also been used for other reactions than DA/HDA, such as Mannich reactions with cyclic ketones.[79]

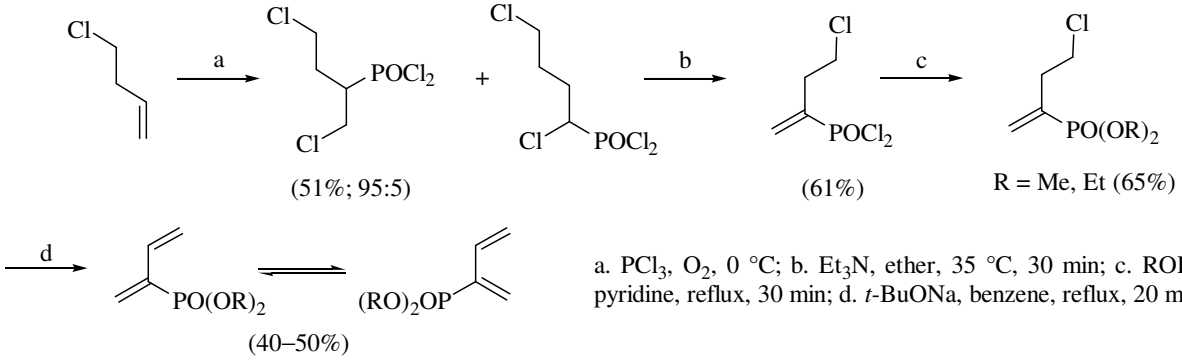


a. DCM, –40 °C to 20 °C, 2 h

Scheme 14

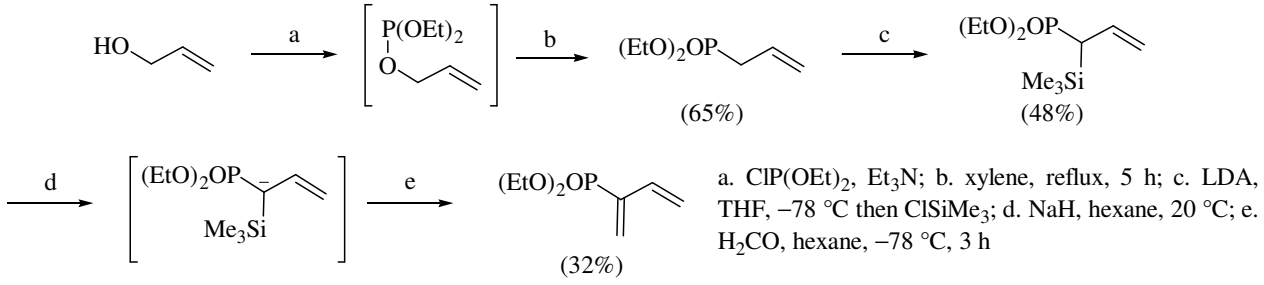
2.2. 2-Phosphono-1,3-butadienes

To date, several syntheses of 2-(diethoxyphosphonyl)-1,3-butadiene have already been reported, but using harsh experimental conditions and showing quite modest yields.[80–85] The most practical synthetic routes are described in Schemes 15[84] and 16.[85]



a. PCl_3, O_2, 0 °C; b. Et_3N, ether, 35 °C, 30 min; c. ROH, pyridine, reflux, 30 min; d. *t*-BuONa, benzene, reflux, 20 min

Scheme 15



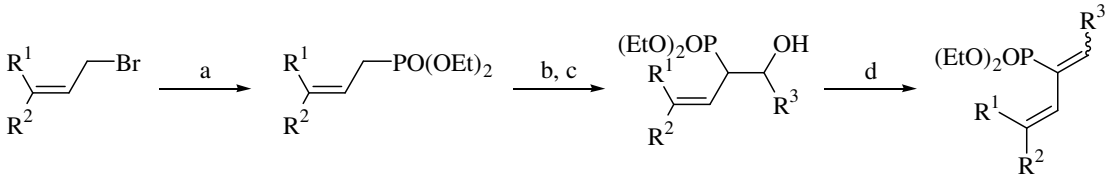
a. $ClP(OEt)_2$, Et_3N; b. xylene, reflux, 5 h; c. LDA, THF, −78 °C then $ClSiMe_3$; d. NaH, hexane, 20 °C; e. H_2CO, hexane, −78 °C, 3 h

Scheme 16

Unfortunately, in our hands, the synthesis of this diene appeared poorly reproducible. Hence, other original strategies have been investigated, but without any success because 2-(diethoxyphosphonyl)-1,3-

butadiene is prone to fast oligomerization.[86] It is worth noting that in the reported syntheses, the structural characterization of the diene is not convincing and/or the spectroscopic data are not fully detailed.

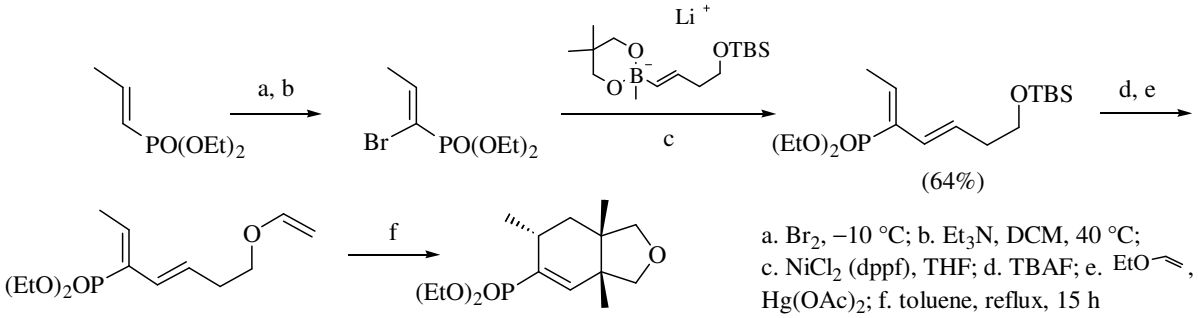
4-Substituted derivatives of 2-phosphonodiene could be obtained,[82,87,88] mainly *via* organometallic coupling reactions.[89–91] For the 1,4-polysubstituted-2-phosphonodienes, a general synthetic method has been proposed by Al-Badri, as depicted in Scheme 17.[92] An allyl bromide derivative is first transformed into the corresponding allyl phosphonate *via* the Arbuzov reaction. Then, an anion is formed in α-position of the phosphonate group and quenched with an aldehyde to yield the β-hydroxyphosphonate intermediate. Finally, a Cu(II)-catalyzed dehydration gives the diene in moderate to good yields. The synthesis of 2-(dimethoxyphosphonyl)-3-methyl-1,3-butadiene has also been reported.[93]



a. $P(OEt)_3$, reflux; b. LDA, THF, −70 °C, 20 min; c. R^3CHO, −70 °C and acidic work-up; d. DCC, $CuCl_2$ cat., DCM, 20 °C

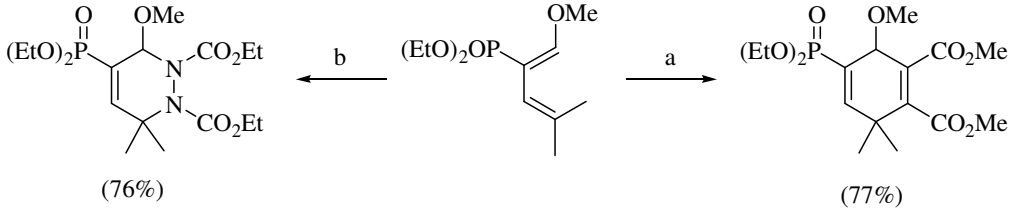
Scheme 17

Finally, a 1,4-*bis*-alkyl-2-phosphonobutadiene including a vinylether motif has been obtained *via* a Suzuki coupling strategy; upon heating, the intramolecular DA reaction occurred readily (Scheme 18).[94]



Scheme 18

Other examples of DA cycloadditions involving 2-phosphono-1,3-butadienes can be found in the literature,[95] but they usually concern NR_2[96] or OR derivatized reactants.[88] This is illustrated in Scheme 19, showing the cycloaddition of 1-methoxy-2-(diethoxyphosphonyl)-4,4'-dimethyl-1,3-butadiene onto dimethyl acetylenedicarboxylate and diethyl azodicarboxylate (DEAD).[88] The key-step for the preparation of the diene is a Peterson's olefination.



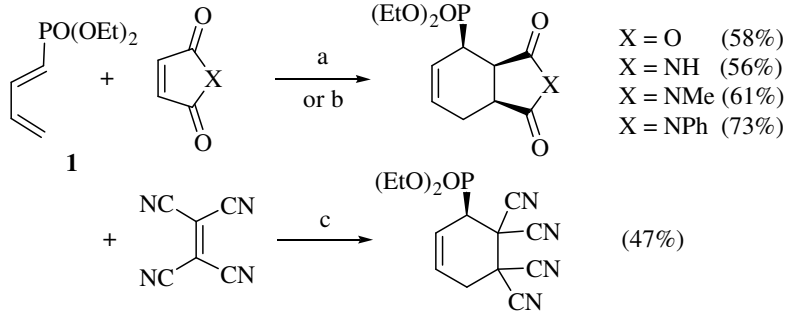
a. $MeO_2C\text{-}C{\equiv}C\text{-}CO_2Me$, toluene, reflux, 36 h; b. DEAD, CCl_4, 8 h

Scheme 19

2.3. Scope and limitation of the DA strategy based on 1-phosphonodiene

As we were unable to properly isolate the reactive 2-(diethoxyphosphonyl)-1,3-butadiene, we focussed on 1-(diethoxyphosphonyl)-1,3-butadiene only. This reagent can be produced on a large scale (home-made protocol adapted from references[97,98]) and stored for months in the freezer (−18 °C), in small sealed vials containing about 0.5 grams.[86]

From the previous literature survey, it clearly appears that the reactivity of 1-(diethoxyphosphonyl)-1,3-butadiene (**1**) had never been the subject of a systematic study, using standard experimental conditions. All our cycloadditions were thus performed in refluxing dichloroethane (DCE), in DCE under microwave activation (MW), or without solvent (neat) in the microwave oven or not. Equimolar amounts of **1** and dienophiles were used and the conversion was followed by ^{31}P NMR and ^{1}H NMR using the dienyl protons as internal reference. The scale of reactivity was qualitatively deduced from the reaction times and the yields of cycloadducts (*vs* the diene dimerization). The pure cycloadducts were isolated by successive column chromatographies and characterized using usual spectroscopies; the yields given below in Scheme 20 refer to isolated products.



a. MW activation, neat; b. DCE, reflux; c. MW activation, DCE

Scheme 20

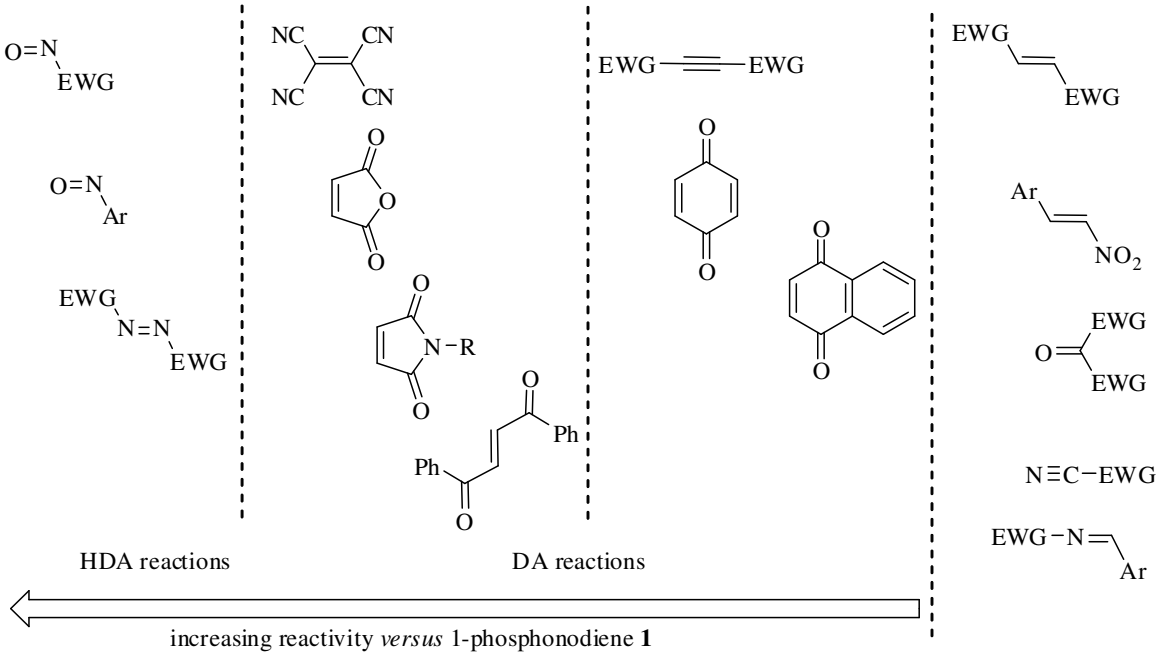
We screened first a series of C=C (or C≡C) dienophiles: the electron-rich partners are unreactive (*N*-vinylpirrolidone, *N*-vinylphthalimide,…) and the electron-poor olefins require usually several EWGs to allow the recovery of cycloadducts in moderate yields. For instance, tetracyanoethylene (DCE, MW, 140 °C, 4 h), maleic anhydride (neat, MW, 120 °C, 2 h), NH-maleimide (neat, MW, 120 °C, 1 h), *N*-methyl-maleimide (neat, 120 °C, 6 h), *N*-phenyl-maleimide (neat, 120 °C, 1 h) and (*E*)-1,4-diphenyl-2-butene-1,4-dione (neat, 120 °C, 7 h) reacted well (Scheme 20), but dimethyl acetylene dicarboxylate, 1,4-benzoquinone and naphthalene-1,4-dione gave only traces of cycloadducts (<10%), while dimethyl fumarate, fumaronitrile and β-nitrostyrene were totally inert *versus* the diene **1**.[86]

We next considered representative C=X (or C≡N) heterodienophiles where X=O and N, namely diethyl ketomalonate, phenylglyoxal, O-methyl benzaldoxime, *N*-tosyl benzaldimine, *N*-propyl benzaldimine and ethyl cyanoformate. None of these reagents led to cycloadducts.[86]

Lastly, we used Y=X heterodienophiles where Y=X=N or Y=N and X=O. Fortunately, the azo and nitroso reagents were able to react with 1-(diethoxyphosphonyl)-1,3-butadiene under acceptable conditions (see the next section).

The reactivity scale of the usual dienophiles *versus* the phosphono diene **1** is summarized in Scheme 21. The reactions proceed well under classical thermic activation or under microwave heating. This latter

activation method allows to reduce the reaction times, but the so-called MW effect is moderate in the case of [4+2] cycloadditions and not always observed as significant, in our hands.[86]



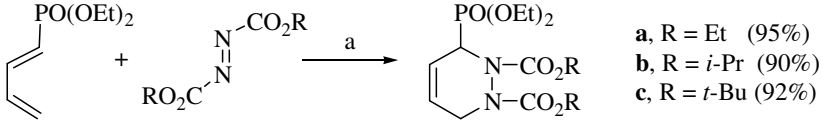
Scheme 21

From the above preliminary investigations and the literature survey, we concluded that the best opportunity to successfully exploit 1-phosphonodienes is to use them in hetero Diels-Alder (HDA) reactions. This will allow to obtain novel phosphonylated heterocycles, in turn leading to various aminophosphonate derivatives after the cleavage of the N–X heterocyclic bond.

3. The HDA reactions of 1-phosphonodienes

3.1. Cycloadditions with azo compounds

The diene **1** reacted readily with the commercial azodicarboxylate derivatives **2a–c**, under microwave heating, to afford 1,2-(dialkoxycarbonyl)-3-(diethoxyphosphonyl)-3,6-dihydro-1,2-pyridazines (**3a–c**) in high yields (Scheme 22).[99,100] Cyclic azo compounds **4a,b**, also commercially available, behaved similarly, giving the corresponding cycloadducts **5** that feature a novel bicyclic structure shown in Scheme 23.[86]

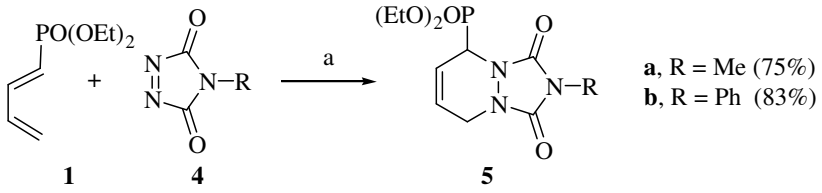


1 **2** **3**

a. MW activation, DCE, 1 h

Scheme 22

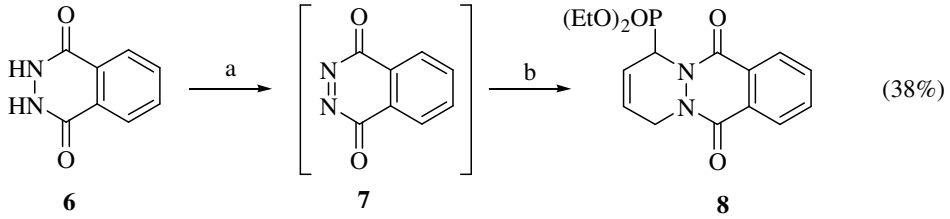
Thanks to the presence of the phosphonate substituent, the heterocyclic framework **5** is endowed with interesting complexation properties *versus* numerous metallic cations (Ca^{2+}, Zn^{2+}, Mn^{2+}, Mg^{2+}, Eu^{3+}, La^{3+}); stable complexes involving one or two ligands **5b** have been detected in solution (EtOH and MeCN) by HR-Mass Spectrometry.[101]



a. MW activation, DCE, 30 min

Scheme 23

Oxidation of the diazo precursor **6** by lead tetraacetate[102] produced the six-membered azo dienophile **7** (the formation of phthalazine-1,4-dione is assessed by the deep-green colouring of the solution) which was trapped *in situ* by the diene **1** at low temperature (0 °C). After chromatography, the tricyclic adduct **8** was obtained in moderate yield (Scheme 24). Under similar experimental conditions, pyridazine-3,6-dione does not react with diene **1**, but polymerizes.

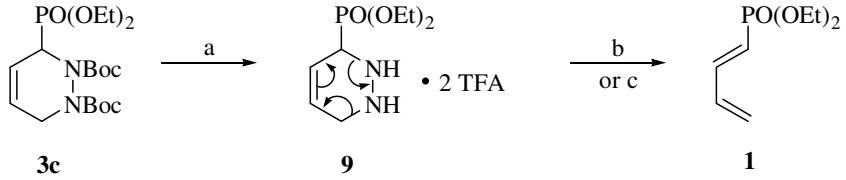


a. $Pb(OAc)_4$, ACN, 0 °C; b. diene, ACN, 0 °C, 2 h

Scheme 24

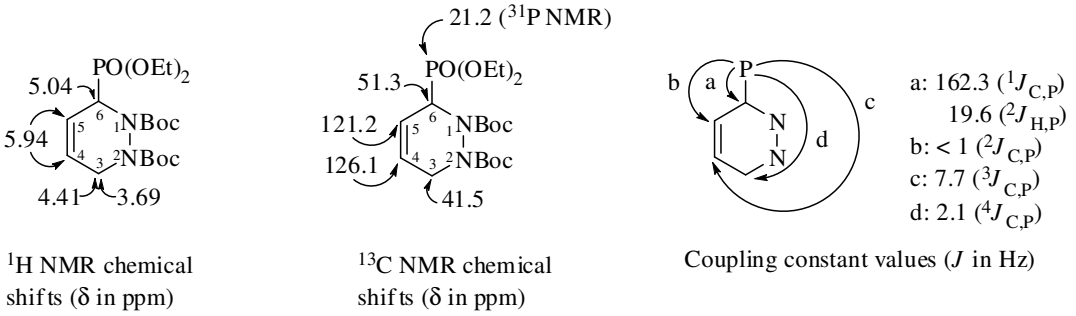
Starting from the cycloadduct **3c**, we planned to produce 6-(diethyloxyphosphonyl)-1,2-pyridazine by a two-step sequence involving Boc-deprotection and oxidative aromatization. The deprotection proceeded well with trifluoroacetic acid, but the resulting tetrahydro-1,2-pyridazine **9** was stable only as the *bis*-TFA salt. Under neutralization conditions, a retro-Diels-Alder reaction occurred rapidly and the diene **1** was recovered. Even in the presence of an oxidant, this process prevailed over the desired aromatization (Scheme 25).[100]

The accurate structural assignment of the cycloadducts **3**, **5** and **8** has been made using mainly the ^{1}H, ^{13}C and ^{31}P NMR spectroscopies. The $J_{H\text{-}P}$ and $J_{C\text{-}P}$ coupling constants are very helpful.[103–105] A typical example of NMR parameters is given in Scheme 26.



a. TFA, DCM, 0 °C; b. $NaHCO_3$-H_2O; c. chloranil

Scheme 25



1H NMR chemical shifts (δ in ppm)

13C NMR chemical shifts (δ in ppm)

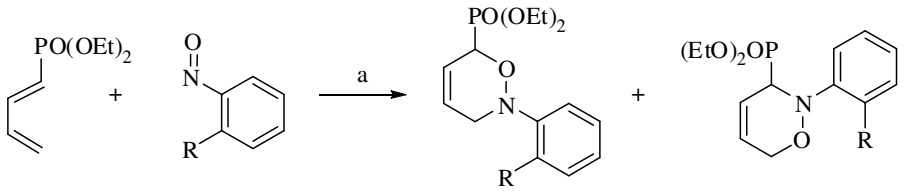
Coupling constant values (*J* in Hz)

Scheme 26

3.2. Cycloadditions with nitroso compounds

The nitroso compounds, thanks to their high reactivity, are classical tools for regioselective organic synthesis.[106,107] By contrast to azodicarboxylate reagents, the nitroso derivatives can exist either as monomers or dimers, *i.e.* azodioxy compounds (*E* and *Z* stereoisomers).[108] The dimers are colourless, but the monomers are strongly blue (aliphatic) or green (aromatic) due to n→π* transitions at 630–790 nm. The homodimers (non reactive species)[109] behave as a reservoir of "stabilized" nitroso reagents: indeed, in solution, the dimerization equilibrium is usually shifted towards the monomers (reactive species for cycloadditions)[108] which can be trapped *in situ* by dienes. However, in the case of acylnitroso reagents, the dimerization leads to an important competitive degradation route *via* the production of N_2O (Kirby's degradation pathway).[110,111]

The HDA reactions of nitroso dienophiles and 1-(diethoxyphosphonyl)-1,3-butadiene (**1**) has a regioselectivity issue, obviously not encountered in the case of azo dienophiles. The two possible regioisomers of cycloadducts are named *proximal* (*i.e.* the oxygen atom in *ortho* position regarding the phosphonate group) and *distal* (*i.e.* the oxygen atom in *meta* position) respectively, according to the nomenclature introduced by Boger.[112] As a consequence of the configurational instability around a nitrogen atom, the *endo*/*exo* selectivity is not a relevant question in the case of nitroso-HDA reactions. The first HDA cycloadditions of **1** and O=N dienophiles **10** has been performed with commercially available reagents, namely phenyl and α-tolyl derivatives (Scheme 27).[86,99] Under classical thermic conditions (refluxing DCE, 12 h), we recovered a 95:5 mixture of *proximal* (**11**) and *distal* (**12**) regioisomers. There is no significant solvent effect on the reaction rate and regioselectivity (THF, DMF, MeCN). Interestingly, under microwave heating, the reaction proceeded in 1 hour with a complete *proximal* regioselectivity. This reaction could be scaled up to 20 g of **1** (using a six-entry parallel synthesis rotor in the MW oven) and also performed under the microreactor technology (continuous flow production of 0.56 g per hour).[113]

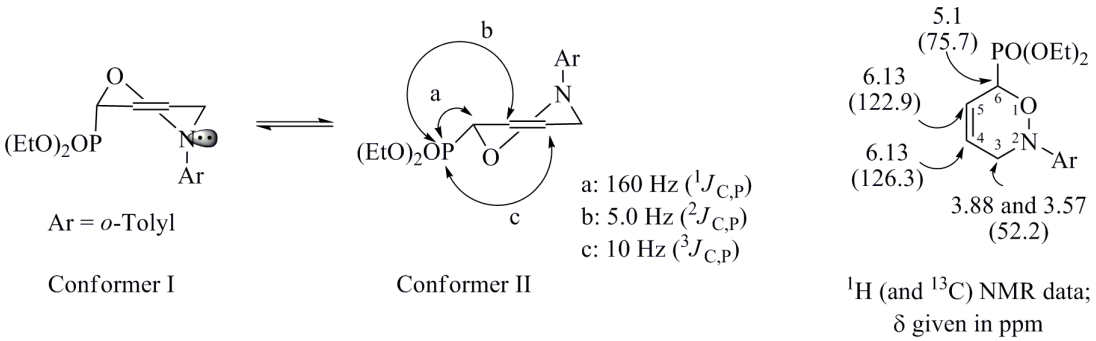


1 **10** **11a**, R = H (82%); **b**, R = Me (95%) **12** (very minor regioisomer)

a. MW activation, DCE, 30 min

Scheme 27

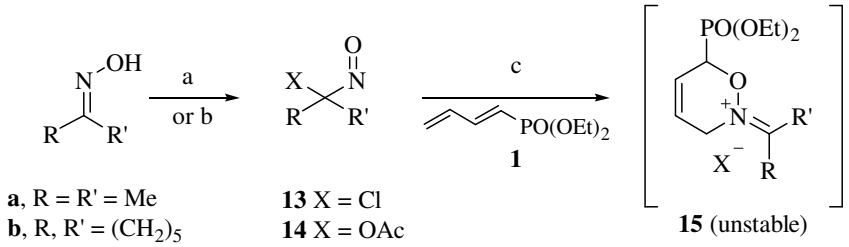
Two stable conformers, I and II, have been computed for the 3,6-dihydro-1,2-oxazine framework **11**, at the B3LYP-6/31G** level of theory.[114] Both conformers show the tolyl substituent in a pseudo-axial position (thus releasing the nitrogen lone pair in a pseudo-equatorial position), but I presents the phosphonate group in a pseudo-axial position while II orientates this group in a pseudo-equatorial position (Scheme 28). This latter conformer is the most stable one (ΔE=4.2 kcal·mol^{-1}). Our experimental NMR data are in good agreement with the conformer II ($^3J_{P,C}$=10 Hz corresponding to a P–C_6–C_5–C_4 dihedral angle θ of 137°). Other structural features are described in Scheme 28.



Scheme 28

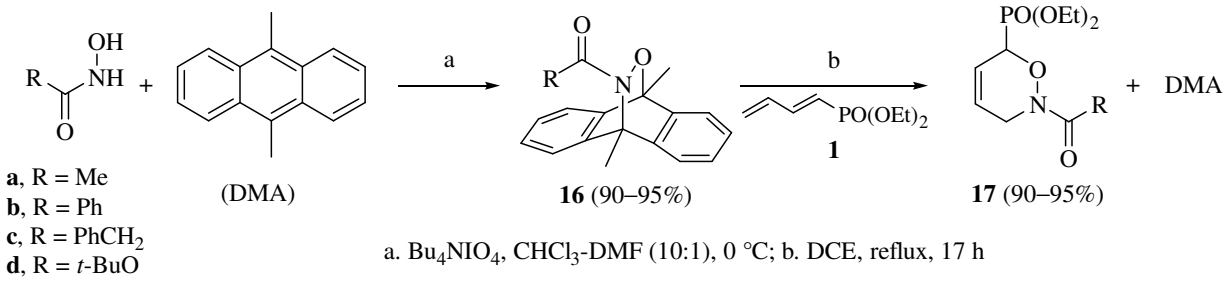
The α-chloro- and α-acetoxy-nitroso dienophiles offer the advantage of easily producing NH-oxazine derivatives by simple alcoholysis of the crude cycloadducts.[115,116] 2-Chloro-2-nitrosopropane (**13a**) and 1-chloro-1-nitrosocyclohexane (**13b**) were prepared by oxidation of the corresponding oximes with *t*-butylhypochlorite.[117] Similarly, 2-acetoxy-2-nitrosopropane (**14a**) and 1-acetoxy-1-nitrosocyclohexane (**14b**) were obtained *via* the oxime precursors oxidation with lead tetraacetate.[118] Freshly prepared solutions of **13** or **14** were engaged to react with **1** at room temperature. The dienophiles disappeared (NMR analysis) but the expected cycloadducts **15** could not be identified (Scheme 29).[114] After several days, the diene **1** was regenerated, as well as under methanolic work-up. The instability of **15** will be explained further below.

We were more successful using next acyl-nitroso compounds as dienophiles. We found that the best condition to deliver slowly pure acyl-nitroso reagents into a solution of diene **1** consists in the thermic decomposition (retro-Diels-Alder process) of the precursors **16** (Scheme 30).[119–121] These come from the DA cycloaddition onto 9,10-dimethylanthracene (DMA) of acyl-nitroso compounds produced *in situ* by the oxidation of the corresponding hydroxamic acids with tetrabutylammonium periodate. Upon mixing the precursors **16** and the diene **1** (1:1 to 1.5:1 ratios) in refluxing dichloroethane, overnight, the expected *N*-acyl 6-(diethoxyphosphonyl)-3,6-dihydro-1,2-oxazines **17a–d** were formed in very high yields (Scheme 30).[122] The only presence of *proximal* regioisomers was confirmed by NMR data.



a. *t*-BuOCl, $CHCl_3$, 0 °C; b. $Pb(OAc)_4$, DCM, 0 °C; c. $CHCl_3$, EtOH 5%, 20 °C

Scheme 29

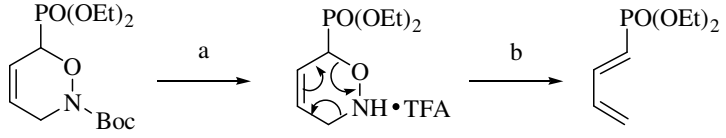


a, R = Me
b, R = Ph
c, R = $PhCH_2$
d, R = *t*-BuO

a. Bu_4NIO_4, $CHCl_3$-DMF (10:1), 0 °C; b. DCE, reflux, 17 h

Scheme 30

N-Boc deprotection of the cycloadduct **17d** with trifluoroacetic acid led to an unstable intermediate **18** that decomposes under neutralization *via* a retro-Diels-Alder process (Scheme 31).[114] Thus, the *N*-unsubstituted heterocycles, 3,6-dihydro-1,2-oxazine and 3,6-dihydro-1,2-pyridazine (see above, Scheme 25) are thermally unstable: reduction or functionalization of the C=C double bond is required for their stabilization (see section 5: transformation of the cycloadducts).

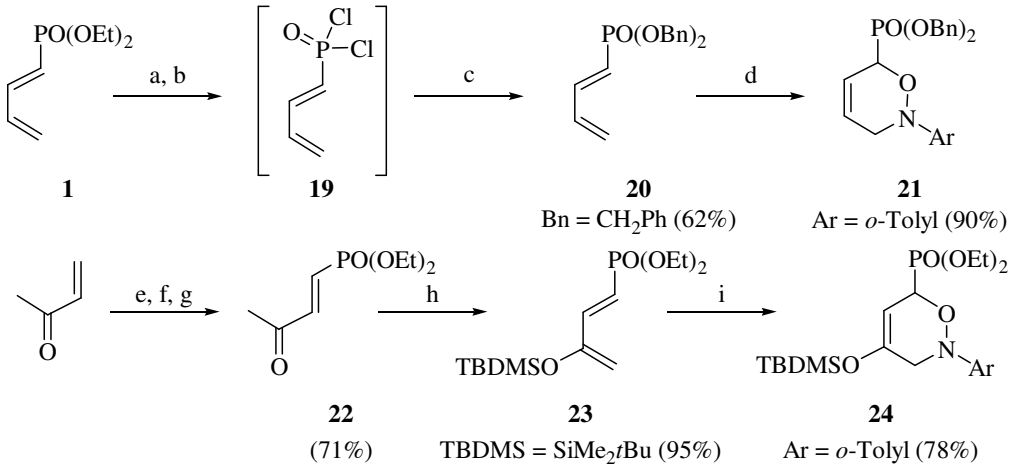


17d **18** **1**

a. TFA, DCM, 0 °C; b. $NaHCO_3$-H_2O

Scheme 31

Structural variations on the 1-phosphonodiene scaffold have been performed, such as the modification of the phosphonate OR groups and the introduction of a silyloxy substituent in position C_3 (analogy with the Danishefsky's dienes).



1 **19** **20** **21**
Bn = CH_2Ph (62%) Ar = *o*-Tolyl (90%)

22 **23** **24**
(71%) TBDMS = $SiMe_2tBu$ (95%) Ar = *o*-Tolyl (78%)

a. TMSBr, DCM, 20 °C; b. $(COCl)_2$, DMF cat., THF, 0 °C; c. BnOH, pyridine, THF, 0 °C; d. ArN=O, MW activation, DCE; e. $P(OEt)_3$, 50 °C; f. Br_2, CCl_4, 0 °C; g. Et_3N, 0 °C to 20 °C, CCl_4; h. TBDMSCl, DBU, THF, 20 °C; i. ArN=O, DCE, reflux, 4 h

Scheme 32

Ester exchange was readily performed from diene **1** by a three-step sequence involving the deprotection of the P–OEt groups with trimethylsilyl bromide, the formation of the phosphoryl dichloride

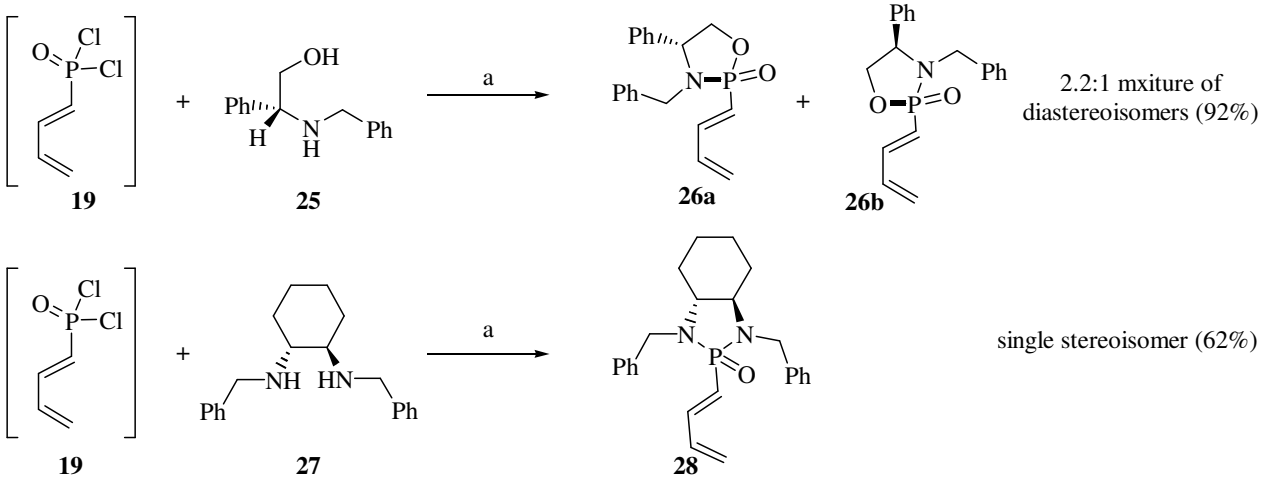
intermediate **19** by reaction with oxalyl chloride and the re-esterification with the selected alcohol in the presence of pyridine. This process is illustrated in Scheme 32 with the synthesis of the dibenzyl phosphonate **20** and its reaction with *o*-nitrosotoluene to yield the oxazine **21**.[122]

1-(Diethoxyphosphonyl)-3-(*t*-butyldimethylsilyloxy)-1,3-butadiene (**23**) was obtained from the β-keto-vinylphosphonate **22**[123] *via* adapted conditions of silyl enol ether synthesis.[122] As expected, the diene **23** (activated by an electron-donating group, EDG) was more reactive than **1** and **20**, but also more prone to oligomerization. The cycloadduct **24** with *o*-nitrosotoluene was formed rapidly without MW activation (Scheme 32).[122]

3.3. Asymmetric synthesis

In general, there are three main strategies for the development of asymmetric DA reactions: (i) the use of a chiral catalyst; (ii) the use of a chiral auxiliary placed on the dienophile; (iii) the use of a chiral auxiliary placed on the diene. In our case, *i.e.* HDA reactions of phosphonodienes, the catalytic route could not be applied for at least two reasons: (i) the Lewis acid-type catalysts strongly coordinate the phosphonate groups, preventing efficient complexation-decomplexation equilibria; (ii) the organometallic catalysts activate the dimerization of the O=N dienophiles. Some chiral nitroso dienophiles have been already applied in asymmetric HDA reactions.[124,125] Nevertheless, we preferred to exploit chiral phosphono dienes as a more versatile and possibly general route towards chiral phosphonylated heterocycles. Although chiral phosphorus reagents are well known in organic synthesis,[126] chiral auxiliaries for DA phosphono partners are scarcely described in the literature and usually concern vinyl phosphonates.[76]

To build a chiral phosphono diene, we first considered the introduction of the chirality on the phosphorus atom. As shown in Scheme 33, the capture of the diene **19** by the aminoalcohol **25** derived from (L)-phenylglycine led to a 2.2:1 mixture of diastereoisomers **26**.[127] Since they could not be separated, these dienes are void of interest for asymmetric cycloadditions. We next turned our attention on C_2-symmetry chiral auxiliaries derived from *trans* (*R*,*R*)-1,2-diamino-cyclohexane, initially developed by Hanessian.[128] The chiral diene **28** was readily obtained as a single stereoisomer by reacting **19** with the diamine **27** (Scheme 33).[127]

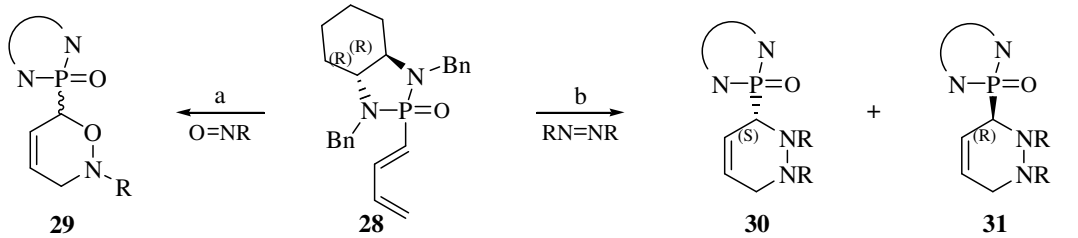


a. pyridine, THF, 0 °C to 20 °C

Scheme 33

Disappointingly, the cycloaddition of **28** on *o*-nitrosotoluene gave a 1:1 mixture of diastereoisomers **29** (determined by ^{31}P NMR).[127] The absence of facial discrimination is explained in the next section devoted to the computational investigations. But, using azodicarboxylates as dienophiles, we could observe a diastereoselectivity which increases from *de*=44% to *de*=100%, when the steric control is enhanced by two bulky substituents (Scheme 34).[127] However, in this case, microwave activation is mandatory and the yields of cycloadducts **30b,c** are relatively modest; it is the prize to pay for the complete stereoselectivity!

The quite low reactivity of 1-phosphono dienes regarding the classical electron-rich or electron-poor dienes traditionally used in DA and HDA reactions deserves to be examined in the light of the theoretical chemistry (see next section).



29
R = *o*-Tolyl (72%)
1:1 mixture of diastereoisomers

28
Bn = $PhCH_2$-

30
a, R = CO_2Et, 1/0.56 mixture of diast.
b, R = CO_2i-Pr, single diast. (S) (30%)
c, R = CO_2t-Bu, single diast. (S) (40%)

31

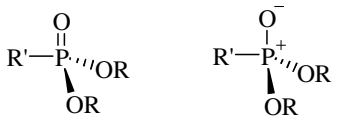
a. DCE, reflux, 12 h; b. MW activation, toluene / DMF (3:0.1), 1–4 h

Scheme 34

4. Computational investigation of the HDA reactions

4.1. The phosphonate effect

Classically, the phosphonate substituent has been considered as a mesomeric withdrawing group[129] by analogy to the carbonyl group. Indeed, the usual drawing of the P=O motif of the phosphonate wrongly suggests the existence of a mesomeric effect similary to C=O [Figure 1 (A)]. In fact, it has been demonstrated that the participation of the phosphorus *d* orbitals into this P=O bond is less than 10% and that this bond is strongly polarized towards oxygen (about 90%).[130] Accordingly, a more realistic picture of the phosphonate substituent is a zwitterionic species as given in Figure 1 (B).



(A) (B)

Figure 1

Nowadays, the most widespread use of the phosphonate group is for the stabilization of α-negative charges, such as in the Horner-Wadsworth-Emmons reaction.[131] A recent theoretical study using the electronic Fukui function demonstrated the emergence of a negative hyperconjugation in phosphorus stabilized carbanions.[132] This back-bonding from the carbanion lone pair towards σ^* P–O orbitals leads to a significant stabilization. From that study, it becomes clear that the best description for the phosphonate group through its interaction with a carbanion is a σ-donor/π-acceptor system.

In contrast, only a small interaction is detected between the phosphonate function and neutral organic patterns such as vinyl or butadienyl moieties.[133–135] This interaction is dominated by the phosphorus atom: the presence of a positively charged third row element renders the bound carbon atom very negative and consequently polarizes the adjacent carbon skeleton. The phosphonate group can therefore be considered as a polarizing group for the π systems. Recent calculations showed that this feature gives rise to asynchronicity in carbo Diels-Alder cycloadditions, *i.e.* to an increase in electron transfer at the transition state (TS) by comparison with the reference butadiene+ethylene couple.[136] Nevertheless, the global activation brought by the phosphonate substituent remains weak, especially when placed in position 1 of the diene. In positions 2 (diene) and 6 (dienophile), the activation of the π system leads to a decrease of the activation barrier by comparison with the reference reaction.

These theoretical results are in good agreement with the experimental data available from the literature: 1-phosphonodienes display poor reactivity in DA reactions towards a broad range of C=C dienophiles; 2-phosphonodienes have been scarcely illustrated (as a consequence of their instability) and vinylphosphonates are used indeed as dienophiles, but mainly as Michael acceptors.[137–139]

4.2. HDA cycloadditions of 1-(diethoxyphosphonyl)-1,3-butadiene (1a)

A way to overcome the low activation of diene **1a** is to match it with highly reactive dienophiles. As mentioned above, we have selected activated nitrogen-containing partners, namely azodicarboxylate and nitroso dienophiles in our strategy dedicated to the synthesis of aminophosphonic derivatives. In addition, nitroso dienophiles can lead to regioisomeric mixtures of cycloadducts.

The previous theoretical investigations on these latter non-symmetrical reagents underlined the impact of the diene activation on the regiochemistry of nitroso HDA reactions.[140] The rule is: higher the butadienyl activation, higher the regioselectivity (Figure 2).

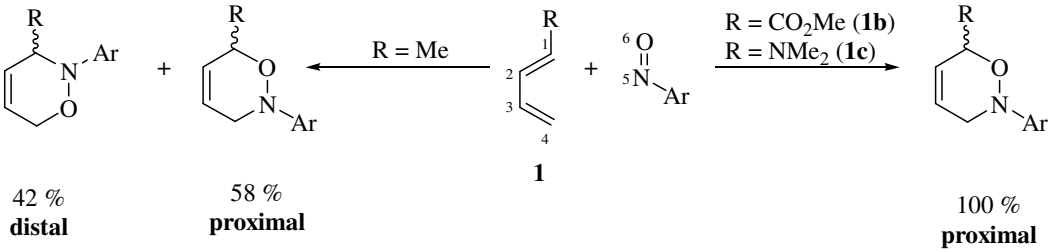


Figure 2

Given that the butadienyl activation by a phosphonate substituent is very low, one may expect a poor regioselecivity for the cycloadditions of 1-(diethoxyphosphonyl)-1,3-butadiene (**1a**) and nitroso dienophiles. This deduction contrasts with the experimental facts and prompted us to start a computational study. Our objective was to provide quantitative insights into the governing parameters of these reactions, namely the activation barriers and the regioselectivity.[141]

We have computed the global static properties of representative 1-substituted dienes at the B3LYP/6-31G** level.[142] The chemical potential (μ) and the global electrophilicity (ω) are listed in Table 1 for butadiene (R=H), piperylene (R=Me), 1-(diethoxyphosphonyl)-1,3-butadiene [R=PO(OEt)$_2$, **1a**], (*E*)-N,N-dimethylbuta-1,3-dien-1-amine (R=NMe$_2$, **1b**) and (*E*)-methyl penta-2,4-dienoate (R=CO$_2$Me, **1c**).

Table 1.

Entry	Diene	μ (au)	ω (eV)
1	Butadiene	–0.127	1.05
2	Piperylene	–0.119	0.94
3	**1a** [$PO(OEt)_2$]	–0.150	1.58
4	**1b** (NMe_2)	–0.088	0.58
5	**1c** (CO_2Me)	–0.154	1.79

The relatively low ω values calculated for butadiene, piperylene and **1b** indicate their lower electrophilic character in comparison with **1a** and **1c**. The calculated ω values for butadiene, **1a** and **1c** show that the phosphonate moiety weakly increases the global electrophilicity of the butadienyl moiety, in good agreement with its polarizing effect. The computed chemical potential (μ) for representative nitrosodienophiles, ranging from –0.154 to –0.185 au, is generally higher than for the selected dienes. It means that a charge transfer will occur from the diene to the dienophile along the reaction coordinates according to a DA reaction with a normal electronic demand.

Table 2.

Entry	Diene	$\Delta E^{\neq}$ (kcal·mol^{-1})		Regioselectivity
		Proximal	*Distal*	
1	Butadiene	8.8	/	/
2	Piperylene	8.4	8.8	0.4
3	**1a** [$PO(OEt)_2$]	7.8	13.6	5.8
4	**1b** (NMe_2)	2.7	11.2	8.5
5	**1c** (CO_2Me)	5.9	9.1	3.2

We further considered the cycloaddition reactions of the selected dienes with nitrosomethane (RNO with R=Me, **a**) as a model compound. The transition states (TSs) associated with the *endo* approach are the only ones to be considered for this discussion since the *exo* approach is disfavored by 4–10 kcal·mol^{-1}.[140] The resulting activation barriers ($\Delta E^{\neq}$) are listed in Table 2. As expected, the effect of the phosphonate substituent on the activation barrier of this cycloaddition is low: the computed barriers (*proximal* and *distal*) are indeed comparable to those obtained for butadiene and piperylene (entries 1–3). In contrast, dienes **1b,c** show a significant decrease of their activation barriers (entries 4 and 5). Clearly, the slight electronic activation brought by the phosphonate (Table 1) is compensated by its high steric hindrance. Another observation is the emergence of a regioselectivity for diene **1a** (entry 3), that is not observed for piperylene (entry 2). Despite the low global activation effect of the phosphonate group, comparable regiodiscrimination levels to dienes **1b,c** are computed for diene **1a**. The bulky phosphonate substituent enhances the regiodiscrimination by a direct steric interaction with the nitroso substituent.

Furthermore, nitrosodienophiles of synthetic interest (Figure 3) were considered in order to establish structure reactivity relationships. First, the impact of the nitroso substituent R on the activation barrier was studied for the HDA reaction with **1a**. Next, the impact of the substitution pattern on the *proximal/distal* discrimination was evaluated. The computation of the global electrophilicity (ω) shows that the presence of strong electron-withdrawing substituents on the nitroso dienophile drastically increases its electrophilicity

(Table 3). The acyl nitroso derivatives **d–g** are strong electrophiles and consequently very reactive species (entries 4–7). This is further confirmed by the computation of the activation barriers ($\Delta E^{\neq}$) of their cycloadditions with diene **1a** ranging from 1.5 to 2.1 kcal.mol^{-1} (Figure 3). All these reactions are strongly exothermic (–40 kcal·mol^{-1}<$\Delta H°$<–10 kcal·mol^{-1}).

Table 3.

Entry	Dienophile R-NO	ω (eV)	Regioselectivity *vs* **1a** (kcal·mol^{-1})
1	**a** (R=Me)	2.27	5.8
2	**b** (R=2-Tol)	2.82	8.9
3	**c** (R=Me_2CCl)	2.61	10.2
4	**d** (R=CO_2Me)	3.73	7.3
5	**e** (R=Ac)	4.50	3.8
6	**f** (R=Bz)	3.38	5.9
7	**g** (R=BnCO)	4.41	7.6

Figure 3 indicates that the nitroso dienophiles reactivity *versus* diene **1a** increases from nitrosotoluene **b** and α-chloro nitroso **c** to acyl nitroso compounds **d–g**. The latter particularly low calculated activation barriers have to be related to the *a priori* selection of a *cisoid* conformer of the diene **1a**, which may be experimentally generated by addition of a coreactant such as 9,10-dimethylanthracene. The role of this coreactant has been discussed in a recent publication.[122]

Remarkably, a *proximal/distal* discrimination ranging from 3.8 to 10.2 kcal·mol^{-1} was computed for the reaction of **1a** with the series of R–NO dienophiles (Table 3). This regioselectivity appears to result from a balance between electronic and steric factors.

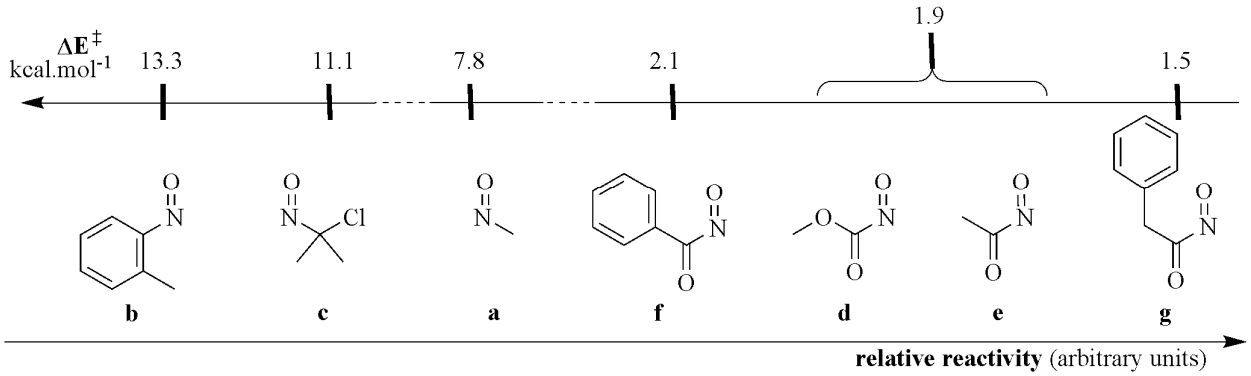


Figure 3

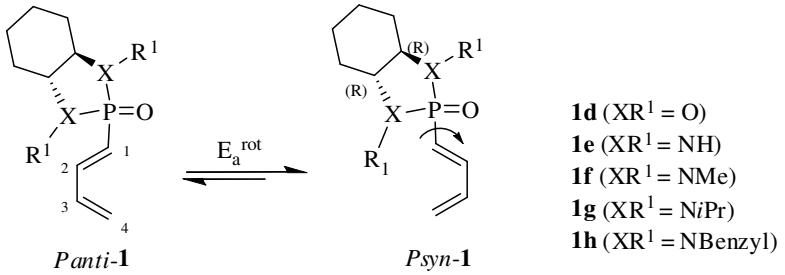
We finally looked at the cycloaddition of an azodicarboxylate dienophile to diene **1a** using dimethylazodicarboxylate (DMAD) as model compound. This reaction is also strongly exothermic ($\Delta H°$=–40 kcal·mol^{-1}) and its activation barrier is comparable to the one computed for the reaction of **1a** and nitrosotoluene ($\Delta E^{\neq}$=12.6 kcal·mol^{-1}).

4.3. Chiral induction

The cycloadditions of O=N and N=N dienophiles proceed *via* very asynchronous TSs. For example, the proximal TS for the reaction of **1a** and Ar–N=O (Figure 2) displays the C_4–N_5 bond length close to the

C–N bond of the final cycloadduct (1.46 Å), while the C_1–O_6 bond remains closer to the sum of the Van der Waals radii for C and O (3.24 Å) than to the length in the final cycloadduct (1.44 Å).[141] This intrinsic asynchronicity should definitely influence the interaction of the dienophile and a chiral auxiliary linked to the diene, hence lowering the induction at C_1, especially for nitroso dienophiles. This assessment prompted us to evaluate the effect of the substituents of the chiral auxiliary and the dienophile on the facial discrimination (chiral induction).[127]

We investigated five different chiral dienes (**1d–h**) having C_2-symmetry auxiliaries and their HDA reactions with nitrosomethane, nitrosotoluene and dimethylazodicarboxylate (DMAD) (Figure 4). For each diene, two reactive *cisoid* conformations have been isolated *in silico*: *Panti* and *Psyn* conformers feature the P=O bond in *anti* and *syn* orientation, respectively, regarding the butadienyl moiety (rotation around the P–C_1 bond). Since the HDA reactions of *Panti* and *Psyn* conformers lead to (*R*)- and (*S*)-cycloadducts, respectively, this conformational equilibrium may be considered as a major factor for stereochemical drifts.[66]



Panti-**1** *Psyn*-**1**

Figure 4

Table 4 gathers the energetic discrimination (ΔE_{conf}=the energy difference between the *Psyn* and the *Panti* conformers) and the rotation activation barrier (E_a^{rot}) for the *Panti* and *Psyn* conformers in the gas phase. The *Psyn* conformer is the most stable in all cases and similar results were obtained in solvents. The nature of XR^1 has a slight incidence on this energetic discrimination. Nevertheless, the diene **1h** shows the highest level of conformational discrimination and rotation activation barrier.

Table 4.

Entry	Diene	E_a^{rot} kcal·mol^{-1}	ΔE_{conf}
1	**1d**	2.1	0.8
2	**1e**	3.8	0.9
3	**1f**	4.0	0.9
4	**1g**	4.9	1.4
5	**1h**	11.7	1.6

The TSs of the cycloadditions of dienes (**1d–h**) and the selected dienophiles have been computed. The energy difference between the TSs related to the *Panti* (**TSan**) and *Psyn* (**TSsy**) conformers gives information in term of stereoselectivitiy. There is clearly a synergy effect when increasing the steric hindrance of both the diene and dienophile substituents: the results of Table 5 show the (**TSan**–**Tsy**) values in kcal·mol^{-1}. The stereoselectivity rises progressively when the size of the XR^1 substituent increases. Diene **1e** is an exception to this general trend with dienophiles since the emergence of a hydrogen bond interaction

lowers the selectivity (entry 2). The selectivities obtained for DMAD and dienes **1f–h** are higher than for the nitroso dienophiles. The interaction between the azodicarboxylate dienophile and the chiral auxiliary of the diene guarantees a stereodiscrimination despite the asynchronicity of the cycloaddition. The highest level of selectivity is obtained for diene **1h** and DMAD (entry 5). A detailed picture of the corresponding cycloaddition is given in Figure 5. Experimentally, the favoured cycloadducts (*S*) has been obtained as major or exclusive diastereoisomer, in agreement with the computations.

Table 5.

Entry	Diene	Dienophiles		
		MeNO	ArNO	DMAD
1	**1d**	1.7	1.7	0.7
2	**1e**	1.8	0.9	0.5
3	**1f**	2.3	1.8	2.6
4	**1g**	2.9	2.0	3.2
5	**1h**	3.1	2.8	5.0

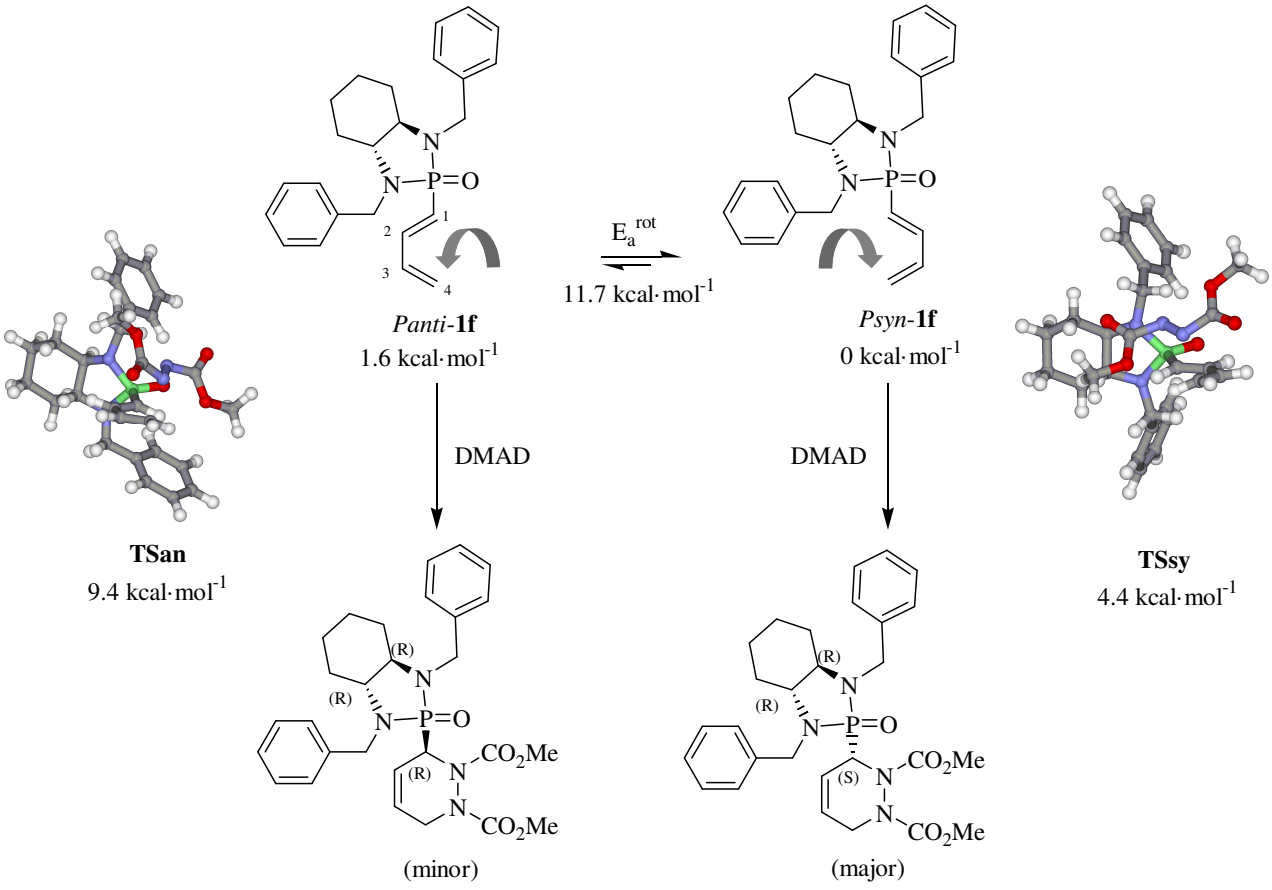


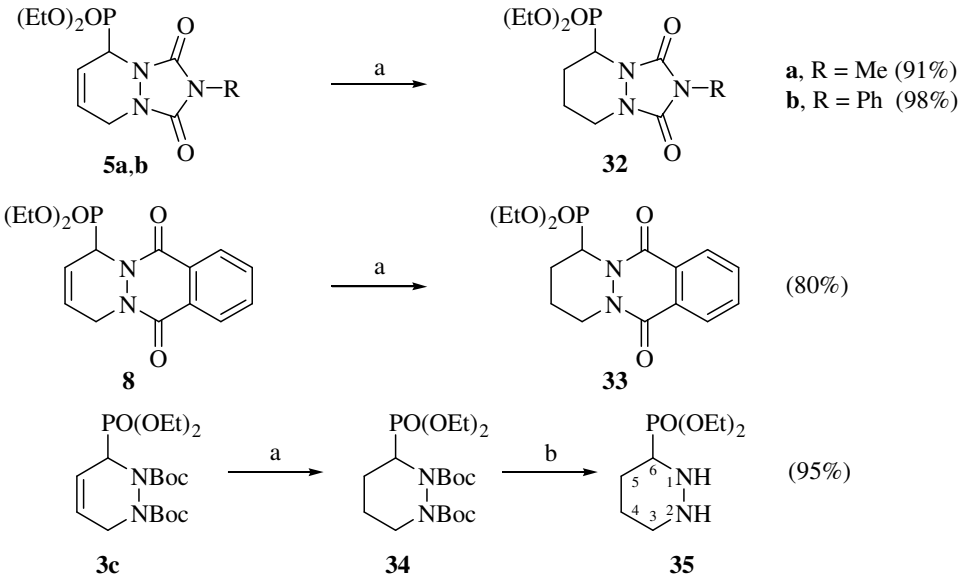
Figure 5

5. Transformations of the pyridazine and oxazine cycloadducts

5.1. Reduction of the C=C double bond

The C=C double bond reduction of the 1,2-pyridazine and 1,2-oxazine cycloadducts offers, in principle, an easy solution to overcome the unwanted retro-Diels-Alder reaction (see Schemes 25 and 31).

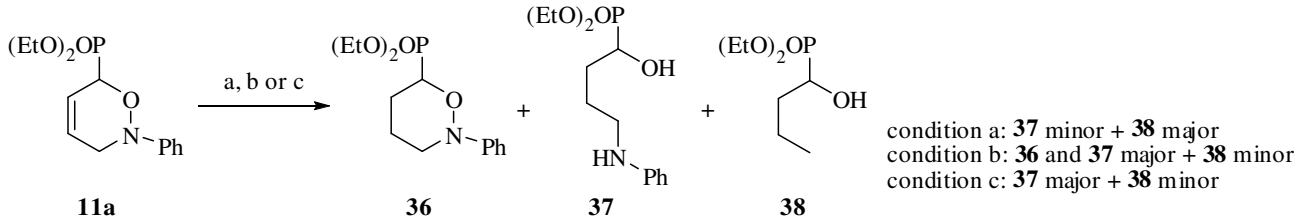
Catalytic hydrogenation of the heteropolycyclic frameworks **5a,b** and **8** led to the corresponding saturated compounds **32a,b** and **33** in high yields, without cleavage of the endocyclic N–N bond.[86] The monocycle **3c** behaved similarly and allowed the almost quantitative recovery of 6-(diethoxyphosphonyl)-hexahydro-1,2-pyridazine (**35**) after Boc deprotection (Scheme 35).[100] The saturated N,N'-unsubstituted framework **35** is thermally stable.



a. H_2, Pd-C (10 mol%), EtOH, 20 °C, 18 h; b. TFA, DCM, 0 °C

Scheme 35

In contrast, for the oxazine series, the selective C=C hydrogenation was not possible because the reductive cleavage of the O–N bond occurs simultaneously and also the loss of the aniline moiety has been observed (Scheme 36).[86] Treatment of **11a** under different hydrogenation conditions gave mixtures of products (**36**, **37**, **38**) with variable ratios. Using Pt on charcoal, Lindlar-Pd or Pd on charcoal as catalysts, we obtained 6-(diethoxyphosphonyl)-tetrahydro-1,2-oxazine (**36**), 1-(diethoxyphosphonyl)-1'-hydroxy-4-aminophenyl-butane (**37**) or 1-(diethoxyphosphonyl)-1'-hydroxybutane (**38**), respectively, as major products. Unfortunately, pure heterocycle **36** could not be isolated.



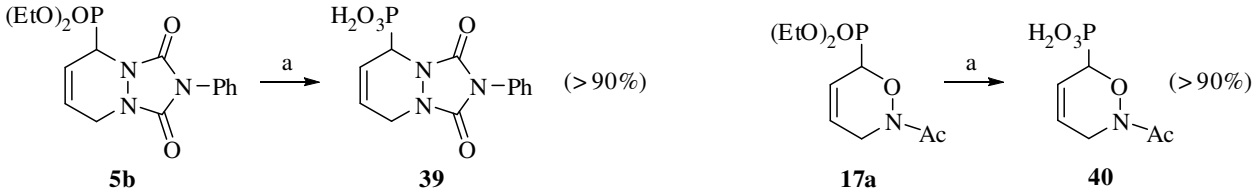
a. H_2, Pd-C (10 mol%), EtOH, 20 °C, 18 h; b. H_2, Pt-C (10 mol%), EtOH, 20 °C, 18 h; c. H_2, Pd-Lindlar (10 mol%), EtOH, 20 °C, 18 h

Scheme 36

5.2. Phosphonate deprotection

The diethoxyphosphonyl group can be transformed into phosphonic acid upon treatment with hot 6 N HCl or trimethylsilylhalides.[143] The use of silyl reagents is a method compatible with a large range of

structures and functionalities.[144,145] Hence, we considered the diethylphosphonate deprotection of our cycloadducts with trimethylsilyl bromide, followed by the *in situ* methanolysis of the silyloxyphosphonate intermediate. Two examples of such deprotection are shown in Scheme 37.[86] The dibenzyloxyphosphonyl ester (see Scheme 32) can be cleaved by catalytic hydrogenation and the chiral phosphonate group introduced with the diene **28** (see Schemes 33 and 34) is removed upon acidic or basic hydrolysis.[146]

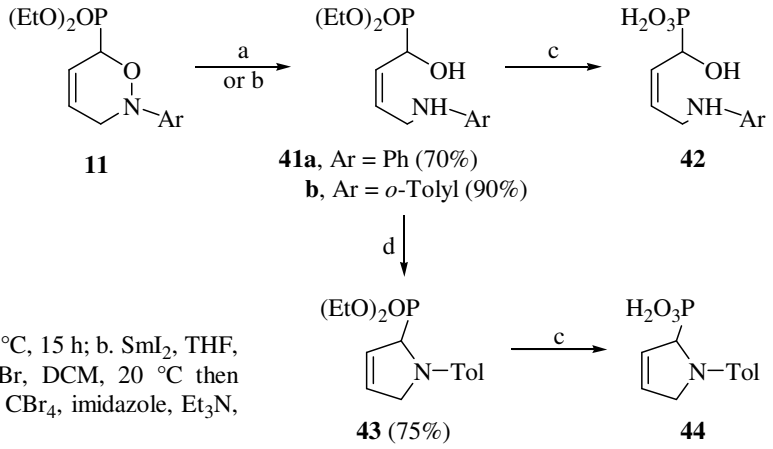


a. TMSBr, DCM, 20 °C then MeOH, 20 °C, 1 h

Scheme 37

5.3. Reductive cleavage of the O–N bond

Two reagents allowed the selective reduction of the O–N bond *versus* the C=C bond of the oxazines cycloadducts: namely zinc dust in acetic acid and samarium iodide in tetrahydrofuran (Scheme 38).[86] As exemplified with the precursors **11a,b** the O–N cleavage yields the (*Z*)-alkenes **41a,b**; the subsequent TMSBr deprotection of the phosphonate group affords the corresponding phosphonic acid **42** (Scheme 38).[114]



a. Zn, AcOH-H_2O, 70 °C, 15 h; b. SmI_2, THF, 20 °C, 1 h; c. TMSBr, DCM, 20 °C then MeOH, 20 °C, 1 h; d. CBr_4, imidazole, Et_3N, PS-PPh_3, DCM, 20 °C

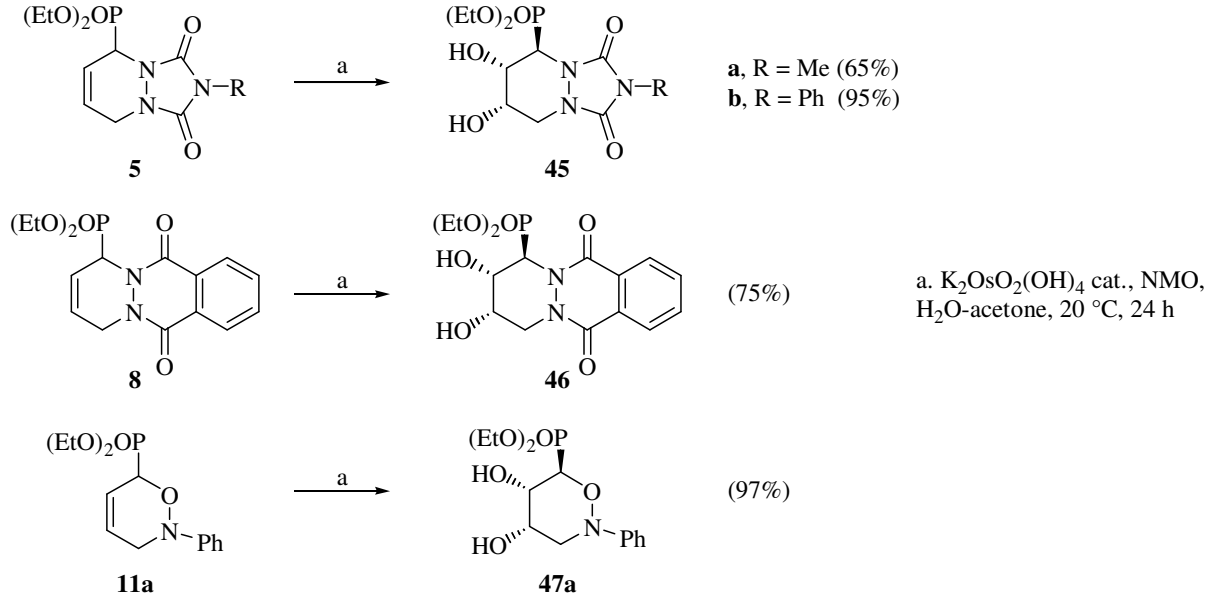
Scheme 38

Taking advantage of the *cis*-stereochemistry of the amino-alcohol **41**, we synthesized, in a one-pot reaction, the pyrrolidine derivative **43** by activation of the hydroxyl function (with tetrabromomethane and polymer supported triphenylphosphine) and intramolecular nucleophilic substitution by the aniline moiety in the presence of imidazole (Scheme 38).[99] Deprotection of the phosphonate ester, giving **44**, is then performed as usual.

5.4. *Syn*-dihydroxylation of the C=C double bond

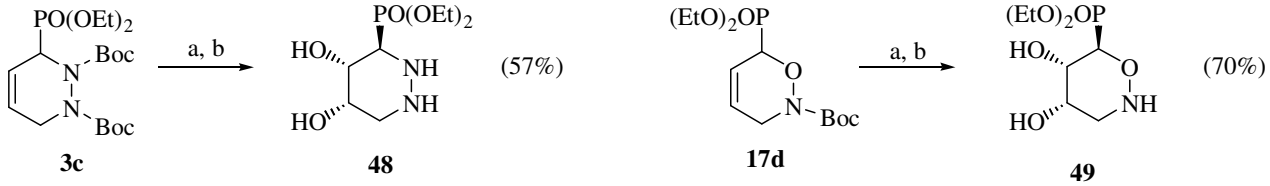
Treatment of the 1,2-pyridazine and 1,2-oxazine cycloadducts with the couple osmium dioxide/ *N*-methyl morpholine oxide (NMO)[147] effected readily the *cis*-dihydroxylation of the C=C double bond, with

a complete stereocontrol induced by the bulky phosphonate group. As shown in Scheme 39,[86] the dihydroxyl derivatives **45–47** feature the phosphonate substituent in *anti* relationship regarding the *syn* OH groups. This relative stereochemistry has been unambiguously established by NMR and X-ray data.[114]



Scheme 39

Interestingly, the saturated heterocycles could be *N*-deprotected to afford stable 4,5-(dihydroxy)-hexahydro-1,2-pyridazine (**48**)[100] and 4,5-(dihydroxy)-1,2-morpholine (**49**)[114] (Scheme 40): obviously, the retro-Diels-Alder degradation is no longer possible.

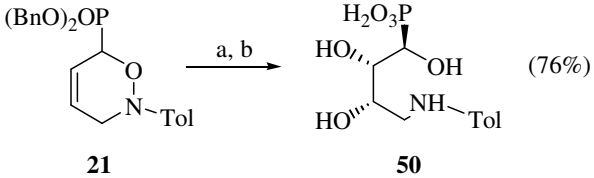


a. $K_2OsO_2(OH)_4$ cat., NMO, H_2O-acetone, 20 °C, 17 h; b. TFA, DCM, 0 °C

Scheme 40

5.5. Sequences of transformations

By combining the previous steps (*i.e.* oxidation, reduction) with functional group interconversions (FGI=deprotection, protection, activation), we have illustrated the potential of our HDA strategy for the stereocontrolled synthesis of highly functionalized δ-aminophosphonic derivatives.[114]

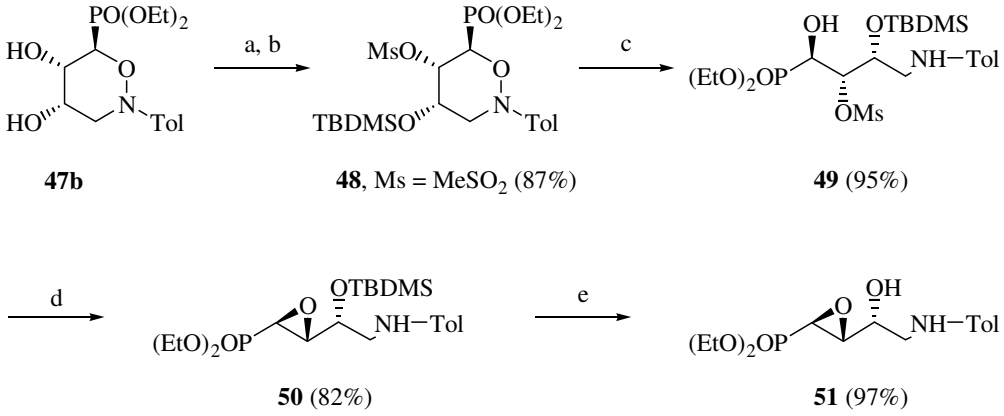


a. $K_2OsO_2(OH)_4$ cat., NMO, H_2O-acetone, 20 °C, 17 h;
b. H_2, $Pd(OH)_2$-C, MeOH, 20 °C

Scheme 41

For instance, dihydroxylation of the cycloadduct **21** followed by hydrogenation (for simultaneous O–N cleavage and benzyloxy group deprotection) gave 1-(dihydroxyphosphonyl)-1,2,3-trihydroxy-4-tolylamino-butane (**50**) in good yield (Scheme 41). This triol is structurally related to xylose[148] and monomers for modified nylons.[149]

In a second example, the phosphonylated oxirane **51** (Scheme 42)[114] has been prepared as an analog of Fosfomycin, an antibiotic which has already stimulated many synthetic efforts.[150,151] Dihydroxylation of the cycloadduct **11b** (see Scheme 27) afforded the *syn* diol **47b** in almost quantitative yield.[99] Treatment with *t*-butyldimethylsilyl (TBDMS) chloride and imidazole led to the protection of the C_4 alcohol with a total chemoselectivity due to the steric effect of the phosphonate group. Then, reaction with mesyl chloride and pyridine, under DMAP catalysis, allowed the activation of the C_5 alcohol. The intermediate **48** was isolated in 87% yield after chromatography; its structural and stereochemical assignment is unambiguous thanks to X-ray diffraction analysis of a monocrystal.[114] The γ-amino-phosphonate derivative **49** was readily obtained by reductive cleavage of the oxazine ring under catalytic hydrogenation conditions. This intermediate cyclized intramolecularly (SN_2i reaction), upon treatment with potassium carbonate in refluxing dichloromethane, to yield the epoxide **50**. Selective deprotection of the silyl ether could be performed with tetrabutylammonium fluoride in tetrahydrofurane (Scheme 42).[114] Thus, after a sequence of five steps, the epoxide **51** was recovered in 66% overall yield, as a single stereoisomer (one signal in ^{31}P NMR).



47b **48**, Ms = $MeSO_2$ (87%) **49** (95%)

50 (82%) **51** (97%)

a. TBDMSCl, imidazole, DCM, 20 °C; b. $MeSO_2Cl$, pyridine, DMAP catal., DCM, 20 °C; c. H_2, $Pd(OH)_2$-C, EtOAC, 20 °C; d. K_2CO_3, DCM, reflux; e. Bu_4NF, THF, 20 °C

Scheme 42

6. Conclusions

The present review highlights the usefulness of phosphono dienes in heterocyclic chemistry. These old reagents have been somewhat neglected by the synthetic organic chemists because of their poor reactivity *versus* carbo-dienophiles and problems linked to their arduous synthesis. Thanks to combined theoretical and experimental approaches, we have successfully revisited the phosphono dienes chemistry and demonstrated their ability to react with azo and nitroso dienophiles, most often under microwave heating.

Pyridazine and oxazine heterocycles bearing a phosphonate substituent have now been made readily accessible by [4+2] cycloadditions of 1-phosphono dienes to azo-dicarbonyl partners, aryl- and acyl-nitroso reagents. The feasibility of asymmetric synthesis by using a C_2-symmetry chiral auxiliary on the P-atom, has been established as well.

The computational results are in agreement with the experimental observations (reactivity, regioselectivity, diastereoselectivity) and allow for rationalization: the polarizing nature of the phosphonate function leads to an activation (but quite low) of the butadienyl system that is compensated by the steric hindrance of the bulky P group at the cycloaddition transition state. Both effects ensure the *proximal* regioselectivity of the cycloadditions on O=N dienophiles and the facial discrimination of the asymmetric cycloadditions on N=N dienophiles.

The cycloadducts of pyridazine-type were further transformed into various phosphonylated 1,2-diaza heterocycles (P and N deprotections, C=C *syn* dihydroxylation); the reduction of the C=C double bond never affects the N–N bond. In contrast, the O–N bond of the cycloadducts of oxazine-type is highly prone to reductive cleavage. Thus, depending on the sequences of reactions performed, the cycloadducts could be transformed into phosphonylated 1,2-morpholine derivatives or into γ-aminophosphonate derivatives in the aliphatic series. Several compounds prepared in this work are structurally related to natural products or analogs of potential biological interest in the field of drug discovery: **41** and **42** (Scheme 38) have the same skeleton as Rhizocticin A antibiotic;[152,153] **43** and **44** (Scheme 38) can be considered as bioisosters of dehydroproline, and after dihydroxylation,[114] as bioisosters of dihydroxyproline;[154] **50** (Scheme 41) is related to aminosugars; **51** (Scheme 42) is similar to Fosfomycin antibiotic;[3] **35** (Scheme 35) is an analog of nonproteogenic cyclic α-hydrazino acids;[155] **48** (Scheme 40) may be considered as a bioisoster of Azafagomine.[156] Hence our HDA methodology towards aminophosphonates, *via* N–N and O–N six-membered heterocyclic intermediates, contributes to the current search of molecular diversity and offers new opportunities for the discovery of original "hits" in medicinal chemistry.

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SYNTHESIS OF PULVINIC ACIDS

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Abstract. *The yellow and red pigmentation of the fruiting bodies of mushrooms of the Boletales order is due in part to the presence of pulvinic acids. Several yellow-coloured and red-coloured lichens also contain such pigments. The aim of this review is to give an overall view on the occurrence, the physical properties and the biological properties of pulvinic acids and to emphasize the different pathways developed to synthesize natural and unnatural members of this family of compounds.*

Contents

1. Introduction

The fruiting bodies of higher fungi are characterized by a variety of colours. Identification of the pigments responsible for these colours has been the subject of many studies. Over the years, chemists have been able, with the help of a growing arsenal of chromatographic and analytical devices, to elucidate the structures of many of them. Pulvinic acids are a family of yellow, orange and red pigments which occur mainly in mushroom of the *Boletales* order. Interestingly, several lichens also contain pulvinic acids, often as their methyl esters.

The occurrence and the properties of pulvinic acids will first be summarized. The different methodologies developed to synthesize these heterocyclic compounds will then be described in details. They will be classified according to the nature of the synthetic step that leads to the completion of the skeleton of the target compound. Indications of the synthetic yields as well as the nature of synthesized compounds, such as natural/unnatural, symmetrical are mentioned. Several previous reviews dealing with pigments of fungi[1] and with tetronic acids[2,3] and butenolides[4] chemistry include some elements about the synthesis of pulvinic acids, but none has recently given a full account on this subject, which has lately seen interesting developments.

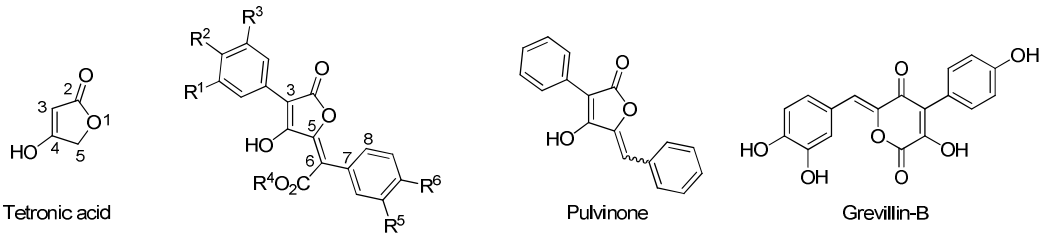
2. Occurrence, physical and biological properties and biosynthesis of pulvinic acid derivatives

2.1. Occurrence and physical properties

Pulvinic acids are pigments isolated from various mushrooms, especially those belonging to the *Boletales* order. The occurrence of these pigments has been used as a taxonomic character and thus helped the classification of mushrooms.[5] They have been found in *Coniophoraceae*, which are assumed to be the most primitive representatives of the *Boletales*. Pulvinic acids are also found in many lichens.[6] The first compound of this family was isolated from *Lichen vulpinus, L.* [corresponding to *Letharia vulpina* (L.) Hue] in 1831 by Bebert[7] and its structure has been elucidated in 1883 through studies by Spiegel.[8] The common structural feature of these compounds is an unsaturated, hydroxylated γ-lactone also referred to as tetronic acid (Figure 1), substituted at the 3-position by an aryl group and at the 5-position by an exocyclic double bond, which is bound to a carboxylic function and to a second aryl group. The most simple member of this family is pulvinic acid itself (**1**, Figure 1). Members bearing the same aromatic groups at the 3-position and on the alkylidene are referred to as symmetrical pulvinic acids. Others bearing different aryl substituents are called unsymmetrical pulvinic acids. The carboxylic function stands generally as the free acid, but in some natural products, such as vulpinic acid **2**, originally named vulpulin by Bebert,[7] it is esterified as a methyl ester (Figure 1). Methyl pulvinates can also be called vulpinic acids. All natural pulvinic acid derivatives possess an *E* configuration of the exocyclic double bond. Structural variations among the members of this class of compounds include the presence of hydroxyl groups (as in atromentic acid **3**, xerocomic acid **4**, variegatic acid **5** and gomphidic acid **7**) or methyl ethers (as in pinastric acid **6**) on the aryl substituents.

While trying to elucidate the structure of vulpinic acid **2**, Spiegel observed that this compound could be saponified to a mixture of a diacid, which was named pulvinic acid **1**.[9] A side-product resulting from a decarboxylation reaction, named pulvinone, was also observed (Figure 1).

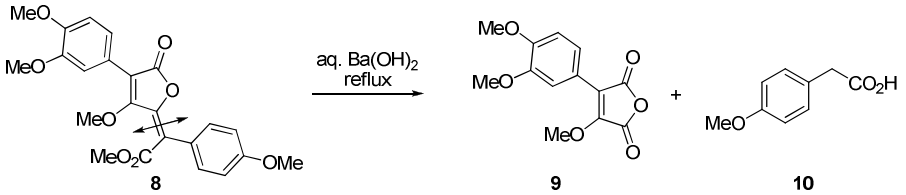
The elucidation of the structures of newly isolated pulvinic acids, especially unsymmetrically substituted ones, was a rather difficult task and several possible methods have been applied. Edwards and Gill reported the alkaline cleavage of permethylated pulvinic acids as a convenient procedure.[10]



	R^1	R^2	R^3	R^4	R^5	R^6
Pulvinic acid (**1**)	H	H	H	H	H	H
Vulpinic acid (**2**)	H	H	H	Me	H	H
Atromentic acid (**3**)	H	OH	H	H	H	OH
Xerocomic acid (**4**)	H	OH	OH	H	H	OH
Variegatic acid (**5**)	H	OH	OH	H	OH	OH
Pinastric acid (**6**)	H	OMe	H	Me	H	H
Gomphidic acid (**7**)	OH	OH	OH	H	H	OH

Figure 1. Chemical structures of tetronic acid, natural pulvinic acids, pulvinone and grevillin-B.

As described in Scheme 1, treatment of permethylated xerocomic acid **8** in a barium hydroxide solution at reflux led to maleic anhydride derivative **9** and 4-methoxyphenylacetic acid **10**. The positions of the two aryl groups in the parent compound were thus ascertained.



Scheme 1. Alkaline cleavage of a permethylated unsymmetrical pulvinic acid.

Unambiguous structure determinations can be obtained owing to X-ray diffraction crystallography. A few X-ray structure analyses of natural methyl pulvinates have been reported. These products are vulpinic acid **2**,[11] a vulpinic acid polymorph,[11b] the pulvinic acid ester derived from 1,6-humuladien-10-ol,[11c] pinastric acid **6**,[12]and the dichloride **11** (Figure 2), which was recently isolated from the fruiting body of a *Scleroderma* sp. originating from Malaysia.[13]

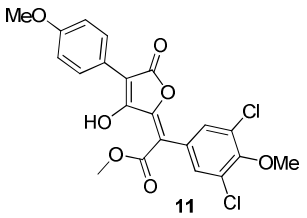


Figure 2. Structure of methyl 3',5'-dichloro-4,4'-di-*O*-methylatromentate **11**.

As expected, several common features were observed for all these compounds. A hydrogen bond takes place between the OH of the 4-enol function and the carbonyl of the ester function. The tetronic ring and the 3-aryl group are nearly coplanar (dihedral angle: 13° in vulpinic acid **2**). The ester carbonyl group linked to the alkylidene is nearly in the same plane than the tetronic ring. On the other hand, the tetronic ring and the aryl ring connected to the exocyclic double bond are not coplanar (dihedral angle: 69° in **2**). The nearly coplanarity of a part of the molecule brings the ester function, the tetronic ring and the 3-aryl group to be

conjugated, thus explaining the intense yellow colour of these compounds. Duncan *et al.* have obtained an X-ray structure of a vulpinic acid polymorph, differing from the structure of **2** by a variation in the rotation of the aromatic ring near the ester function.[11b] The ^{1}H NMR spectra of **2** and of its polymorphic form were also different: for example, the methyl ester chemical shifts are 3.91 and 3.86 ppm (d_6-acetone) for **2** and the polymorphic form, respectively. In the same way, differences are noted for the chemical shifts of aromatic protons.

A characteristic feature in the ^{1}H NMR spectra of pulvinic acid derivatives is that the *ortho*-protons in the aromatic nucleus linked to the butenolide are the most deshielded, much more than the corresponding protons in the nucleus linked to the exocyclic double bond.[1,14] This allowed to distinguish positional isomers. In the infrared spectra of pulvinic and vulpinic acids, a strong band is usually observed near 2400–2500 cm^{-1}; this is due to the enolic hydroxyl, which is strongly chelated by the carbonyl of the acid or ester function.[15,16] On the contrary, in the non natural (*Z*)-isomer, the band of the non-chelated OH appears above 3000 cm^{-1}.[17]

The pK_{a1} values of several natural pulvinic acid derivatives in methanol were recently determined by Hauck *et al.* using a spectrophotometric procedure.[18] Values ranging from 2.8 to 3.4 were obtained for pulvinic acid **1**, pinastric acid **6** and vulpinic acid **2**.

Pulvinic acid derivatives are responsible for the yellow and red colours of numerous species of *Boletus*, *Xerocomus*, *Suillus*. Oxidation of the yellow variegatic acid **5** generates the common red pigment of boletes, variegatorubin (Figure 3).[19] This reaction can be observed when variegatic acid **5** stands in solution with traces of acid or by treatment with hydrogen peroxide in the presence of a copper catalyst.

Interestingly, it was shown that the blue stain, which is produced when the fruit bodies of various boletes are damaged, is due to two hydroxylated pulvinic acids, variegatic acid **5** and xerocomic acid **4**.[15,20] Edwards *et al.* isolated variegatic acid **5** from *Suillus variegatus* (Swartz ex Fr.) and they observed that dilute solutions of **5** rapidly became blue upon addition of a dilute alkali solution. This observation thus invalidated the then accepted idea that an anthraquinone derivative, "boletol", was responsible for such colour change in *Boletaceae*. Indeed, this compound was not detected in the fungus used for this study. Steglich *et al.* then showed that xerocomic acid **4**, isolated from *Xerocomus chrysenteron*, was also a blueing agent and they proposed that the formation of delocalized hydroxyquinone methide anions such as **12**, was responsible for the blue colour.[20b] Aside from pulvinic acids and pulvinones, grevillins (Figure 1) belong to a group of orange and red pyrandione pigments which are also biosynthetically related to pulvinic acids.[21]

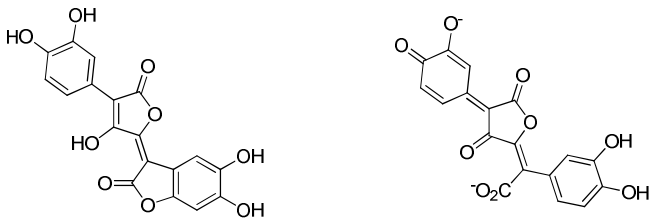


Figure 3. Chemical structures of variegatorobin and dianion **12**.

Several mushroom pigments which result from the dimerization of pulvinic acids have also been isolated (Figure 4). Hence, xerocomic acid dimerization generates norbadione A **13**, badione A **14** and bisnorbadioquinone A **16**, isolated from the cap skin of *Xerocomus badius* by Steglich.[22,23] Badione B **15**,

which is biogenetically derived from variegatic acid **5**, was isolated from *Boletus erythropus*. Compound **13** was also found in high concentration in the gleba of *Pisolithus tinctorius* (or *Pisolithus arhizus*), a gasteromycete of worldwide distribution, by Gill and Lally.[24] Later, the related pisoquinone **17** was found in the white skinned variant of this mushroom by Gill and Kiefel.[25] This suggests, on chemotaxonomic grounds, that a proximity exists between *Pisolithus* and *Boletales*.[26] More recently, Steglich *et al.* isolated two other compounds that also presumably result from the dimerization of xerocomic acid, through different biosynthetic pathways.[27] Thus, sclerocitrin **18** was obtained, along with other pigments, notably norbadione A and xerocomic acid, from the common earthball *Scleroderma citrinum* and from the peppery boletus *Chalciporus piperatus*. Another pulvinic acid dimer, chalcitrin **19**, was also isolated from the latter fungus. The absolute configuration of compound **19** remains to be determined.

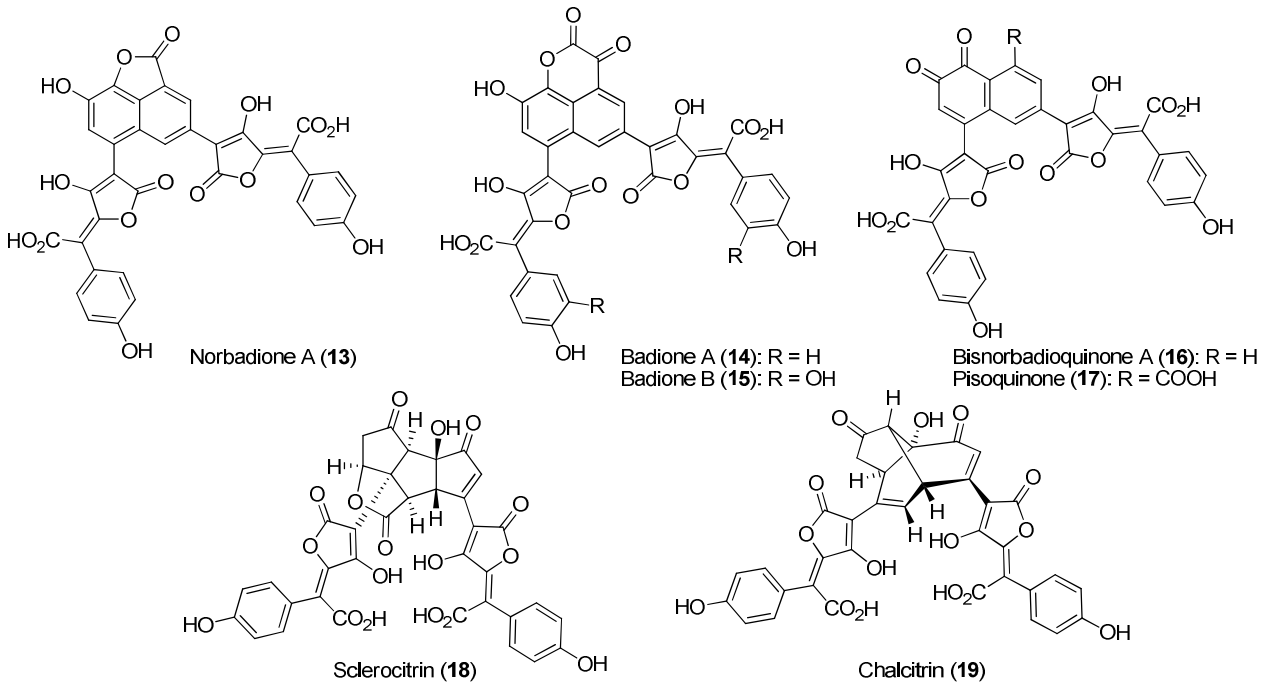


Figure 4. Chemical structures of natural pulvinic acid dimers.

2.2. Biological properties

Many interesting biological properties have been noted for the pulvinic acid derivatives. In the 19th century, lichens containing vulpinic acid **2** were used by Eskimos and people of Northern Europe to poison wolves and foxes.[28] Lichens were used by Arctic and Subarctic people as fodder for reindeer and emergency food,[29] with the exception of two lichens known to be poisonous: *Evernia pulvinia* and *Cetraria pinastri*.[30] The former contains vulpinic acid **2** and the latter contains pinastric acid **6**. In central Europe, members of the genus *Cetraria*, known to produce vulpinic acid **2**, have been used as laxatives and in treatments against cough.[11b] Together with pinastric acid **6**, vulpinic acid **2** showed some activity as repellent for some herbivores.[31] Söderberg described in 1952 several biological properties of vulpinic acid **2**: this compound showed the capacity to induce hyperventilation which in many cases was followed by convulsions and death in laboratory animals.[28a] Since then, various activities have been reported for pulvinic acid derivatives: antibiotic, anti-inflammatory, antiviral, hypotensive, analgesic, antispasmodic and neuromuscular junction blocking properties.[32] In the 1970s, the Smithkline Corporation patented pulvinic acid derivatives displaying anti-arthritic properties measured by their ability to inhibit adjuvant-induced polyarthritis in rats.[33] Besides,

among phenolic compounds extracted from different mushrooms, variegatic acid **5** presents some ability to bind methyl mercaptan (MeSH), responsible for bad odour and could be used in an enzymatic deodorization method.[34]

2.2.1. Anti-inflammatory properties

The anti-inflammatory activity of a series of vulpinic acid derivatives, variously substituted on both aromatic rings, was determined by Foden *et al.* in 1975,[16] by means of an adjuvant-induced arthritis test in rats, as described by Newbould.[35] Rats were treated orally with a range of doses. A minimum active dose, inducing a 30% inhibition of the swelling of the injected foot and a toxic dose were determined. Only products bearing a halogen substituent exhibited higher activities than vulpinic acid itself. The best results were observed with compounds drawn in Figure 5. Although compound **20** was the most active compound, it was abandoned because it induced hyperventilation after oral doses in dogs. With compound **21**, oral treatment did not led to hyperventilation in rats, dogs or monkeys, but gastric damages usually seen with anti-inflammatory agents were observed. Hyperventilation was only noticed after an intravenous injection in both rats and dogs, but at a relatively high level (400 μg/mL, compared with the therapeutic dose of 30 μg/mL).

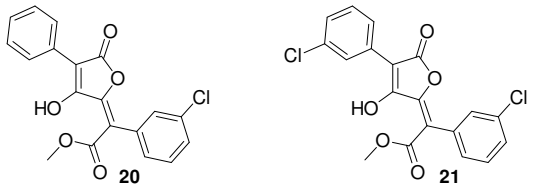


Figure 5. Structures of synthetic vulpinic acid derivatives **20** and **21**.

2.2.2. Antimicrobial, antibacterial and antiviral properties

Considerable efforts have been made by many investigators toward the discovery of valuable properties of pulvinic acid derivatives. Thus, in 1972 Brady evaluated the activity of pulvinic acid **1**, vulpinic acid **2**, atromentic acid **3** and xerocomic acid **4** on *Bacillus subtilis*, *Staphylococcus aureus*, *Mycobacterium smegmatis* and *Enterobacter aerogenes* through various bacterial growth inhibition tests.[36] All of the pulvinic acid derivatives were found to be less potent than usual drugs such as penicillin and tetracyclin (12–50 μg/mL for pulvinic acid derivatives compared with doses of 0.02–2 μg/mL for penicillin and tetracyclin). However, in 2003, Ross and coworkers reported a higher activity of vulpinic acid **2** on *Staphylococcus aureus* than that described by Brady (IC_{50}<2 μg/mL).[11b]

Pinastric acid **6** also showed interesting activities against bacterial and fungal pathogens. It inhibited the growth of *B. subtilis* and *Trichophyton mentagrophytes* at a dose of 300 μg: inhibition zones (radius outside the 6 mm diameter application disc) of 4 and 2 mm, respectively, were observed. It still showed activity against both organisms at 30 μg.[12] The standard agent chloramphenicol had an inhibition zone of 12 mm against *B. subtilis* at 30 μg, while nysatin had an inhibition zone of 6 mm against *T. mentagrophytes* at 100 mg. The dichlorinated pulvinic acid **11** (Figure 2) showed a moderate inhibition of *B. subtilis* (inhibition zone of 4 mm at 40 μg).[13] Pinastric acid **6** revealed a mild activity against the P388 murine leukemia cell line (IC_{50}=7044 ng/mL, compared to 31 ng/mL for the antitumor compound adriamycin, also known as doxorubicin).[12] On the other hand, compound **11** was found to be inactive against the same cell line (IC_{50}=20.6 mg/mL).[13]

Several *in vitro* antiviral activities of pulvinic acids have been reported.[37] Thus, pulvinic acid **1** showed an antiviral activity on an influenza A virus stain (3.9 μg/mL) and on an influenza virus B stain (7.8 μg/mL).[32b] However, no activity has been noticed on two herpes viruses. Pinastric acid **6** was tested against *Herpes simplex* virus and RNA polio virus. A strong activity, without cytotoxicity, was observed against both viruses at 30 μg.[12] When tested at a higher dose of 300 μg on the BSC-1 cells used to grow viruses, toxicity was observed, which made it impossible to ascertain a virus inhibition.

2.2.3. Cesium cation complexation properties

Investigations of the presence of radionuclides in fungi after the Chernobyl accident have repeatedly revealed high amounts of cesium 137 in the bay boletus (*Xerocomus badius*).[38] Steglich *et al.* showed that pileus pigments norbadione A **13** and badione A **14** were able to bind cesium absorbed from the environment. Simple pulvinic acids also present in the mushroom, atromentic acid **3** and xerocomic acid **4**, also associated with cesium, but **13** and **14** were better ligands. It was assumed that their cesium complexation capacity was due to an interaction between the cesium ion and the pulvinic acid moieties of norbadione A. The cation would be held in a pseudo-cavity formed of the two pulvinic acid arms.[39]

2.2.4. Antioxidant properties

Pulvinic acid derivatives have shown antioxidant properties. In 1995, Kasuga observed the antioxidant activity of variegatic acid **5** by studying the peroxidation of methyl linoleate and linoleic acid.[40] Thus, variegatic acid **5** has a far more antioxidant strength compared to 3-*tert*-butyl-4-hydroxyanisole (BHA) and α-tocopherol. However, when tested at low concentrations, variegatic acid **5** seems to have pro-oxidant properties. Recently, the antioxidant properties of dry mushroom extracts from *B. edulis* and *B. auranticus* collected in the Istra region in Croatia, and which both contained variegatic acid **5**, were measured using several tests.[41] Investigation of $DPPH^{\bullet}$, $HO^{\bullet}$, $O_2^{\bullet-}$ scavenging abilities and determination of reducing power and lipid peroxidation were assessed. Overall, the assays suggested that these mushroom extracts might be used as natural source of antioxidant in pharmaceutical and food industry.

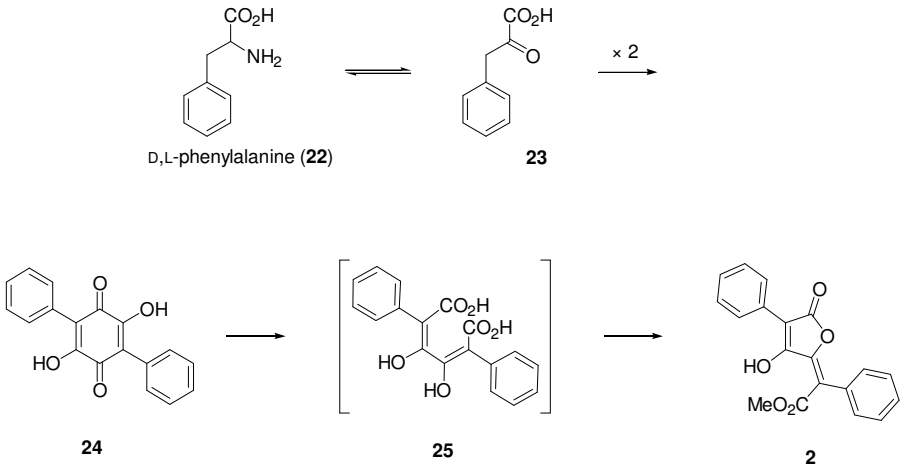
Antioxidant properties of pulvinic acid derivatives have also been evaluated using a thymidine protection assay that employs conventional immunoassay techniques and a DNA protection assay.[42] Several oxidative conditions were applied to the molecules, such as γ-irradiation or Fenton-like conditions (Fe^{3+}/EDTA/H_2O_2). It was shown that norbadione A **13** and pulvinic acid derivatives efficiently protected thymidine and DNA against γ-radiations. However, compound **13** displayed pro-oxidant activity under the Fenton conditions.

Recently, pulvinic acids isolated from the chinese mushrooms *Boletus calopus* and *Suillus bovinus* have shown inhibitory effects on cytochrome P450s (CYPs).[43] Indeed, atromentic acid **3**, xerocomic acid **4** and variegatic acid **5** showed a dose-dependent inhibitory effect on CYP3A4 enzyme activity *in vitro*, with IC_{50} values of 65.1 μM, 2.4 μM and 2.2 μM, respectively. Xerocomic acid **4** and variegatic acid **5** exhibited a stronger inhibitory effect than the positive control uniconazole (IC_{50}=25.1 μM). Both compounds presented a far more inhibitory strength on CYP1A2, CYP2C9 and CYP2D6 enzymes, indicating that they all have an activity on all four CYP isoenzymes and that they act as antioxidants in the mixture. The action of variegatic acid **5** on the ferryl myoglobin reduction was also examined. Addition of compound **5** (10 ng/mL) to ferryl myoglobin induced optical changes of the Soret bands corresponding to the reduction of

ferryl myoglobin (425 nm) to ferric myoglobin (406 nm). These reducing properties of variegatic acid **5** on ferryl heme may be the mode of nonspecific inhibitory action on CYP enzymes. Indeed, when usual antioxidants, such as ascorbic acid and α-tocopherol, and chelating agent EDTA were tested on the four isoenzymes, no inhibitory effect was observed. These observations suggested that the strong inhibition effect of pulvinic acid derivatives was due to their structural properties. Thus, these ferryl reductants have protective activities against *in vivo* oxidative stress.

2.3. Biosynthesis

The biosynthesis of pulvinic acid derivatives isolated either from mushrooms or from lichens follows the same general course.[1] These compounds are formed through the shikimate pathway,[44] which is involved in the synthesis of various products such as aromatic amino acids and aromatic metabolites,[45] alkaloids, tannins, flavonoids and lignins.[46,47] Experiments with ^{14}C-labelled D,L-phenylalanine in the lichen *Evernia vulpina* led to labelled vulpinic acid **2**, which is thus derived from two molecules of phenylpyruvic acid **23** (Scheme 2).[48]



Scheme 2. Biosynthesis of vulpinic acid.

The dimerization of compound **23** generates polyphoric acid **24**, which is then enzymatically oxidized to vulpinic acid **2**. Accordingly, ^{13}C-labelled tyrosine and atromentic acid **3** were converted to variegatic acid **5** by the fungus *Boletus erythropus*.

3. Pulvinic acids synthesis

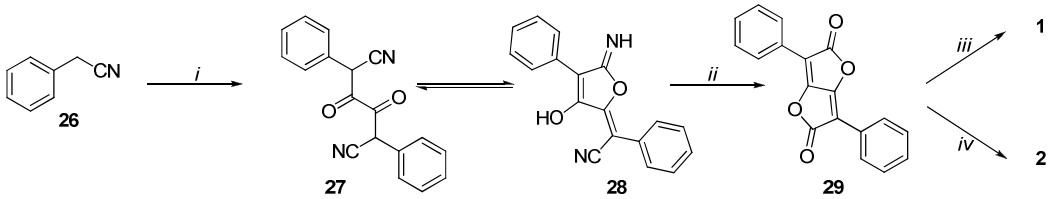
Various synthetic strategies have been published in the literature over the past decades. For a long time, methods that involved the use of anionic chemistry were employed. One of the earlier routes was based on the oxidative rearrangement of 1,4-benzoquinones. More recently, the development of palladium-mediated cross-couplings, particularly useful to create a linkage between an aryl group and a double bond, was beneficial, in particular for the preparation of unsymmetrical pulvinic acids. This improvement allowed the total synthesis of the unusual mushroom pigment norbadione A **13** (Figure 4).

In this part of the review, we wish to detail all these synthetic routes. The different pathways are classified according to the nature of the key step involved in the strategy, *i.e.* the step that leads to the completion of the pulvinic acid skeleton.

3.1. Double anion addition on oxalic acid derivatives

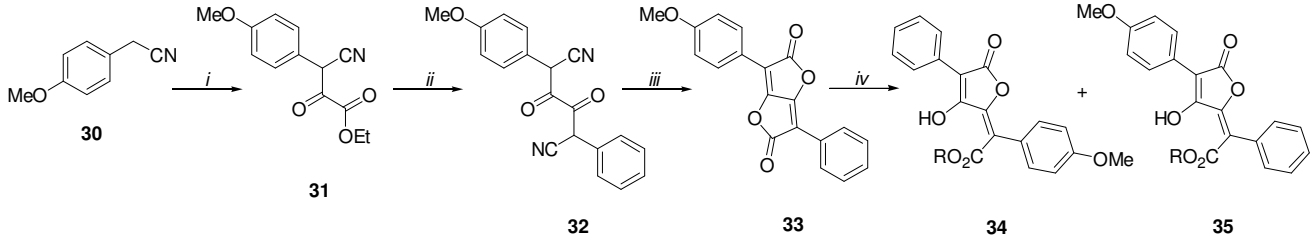
3.1.1. Bis(lactone) as precursor

Volhard reported in 1894 the first synthesis of pulvinic acids.[49] The method started with the condensation of two molecules of phenylacetonitrile **26** on diethyl oxalate in the presence of ethanolic sodium ethoxide (Scheme 3). Treatment of the obtained compound, which is rather the iminolactone **28** than the dinitrile **27**, with 60% sulfuric acid gave the pulvinic bis(lactone) **29**. Hydrolysis or methanolysis of compound **29** then afforded pulvinic acid **1** or vulpinic acid **2**, respectively. This sequence of reactions was notably used to produce ^{14}C-pulvinic acid **1** and other ^{14}C-labelled unnatural pulvinic acid derivatives.[50]



Scheme 3. Synthesis of symmetrical pulvinic acids through the condensation of two molecules of phenylacetonitrile. *i*) EtONa, diethyl oxalate, EtOH, reflux, 73%; *ii*) H_2SO_4, H_2O, reflux, 70%; *iii*) KOH, acetone; *iv*) KOH, MeOH.

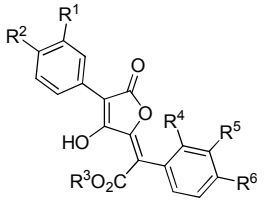
First used to obtain symmetrically substituted pulvinic acids, this strategy has been modified by Asano with the condensation of two variously substituted phenylacetonitriles on diethyl oxalate.[51] The reaction between 4-methoxyphenylacetonitrile **30** on diethyl oxalate in the presence of ethanolic sodium ethoxide generated compound **31** (Scheme 4). The condensation of phenylacetonitrile **27** on compound **31** gave the intermediate **32** (in equilibrium with the corresponding iminolactone), which was cyclized to the unsymmetrical bis(lactone) **33**. Hydrolysis and methanolysis of compound **33** were not regioselective and thus both led to mixtures of isomeric pulvinic acid derivatives **34** and **35**. The overall yields were improved by Äkermark, who used sodium hydride as base during the phenylacetonitrile condensation step.[52] Indeed, sodium hydride allows limiting the retroaldolization reactions observed when sodium ethoxide is used as base. Nevertheless, a mixture of both derivatives **34** and **35** was obtained. In the case where R=Me, compound **35** is similar to pinastric acid **6**.



Scheme 4. Synthesis of unsymmetrically substituted pulvinic acids through the condensation of two molecules of arylacetonitrile: *i*) EtONa, diethyl oxalate, EtOH, rt, 56%; *ii*) **27**, EtONa, EtOH, 70%; *iii*) H_2SO_4, H_2O, reflux; *iv*) hydrolysis or methanolysis.

This methodology has been used for the synthesis of many natural and unnatural pulvinic acid derivatives. Among natural compounds, variegatic acid **5**, methyl variegatate **36** and products **37** and **38** were prepared by Beaumont *et al.* in 11%, 4%, 6% and 12% overall yields, respectively.[15] Xerocomic acid **4**

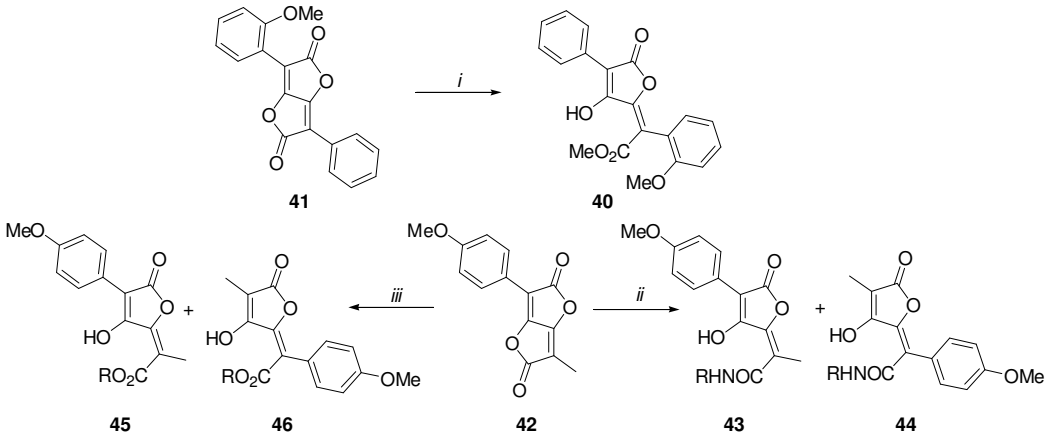
and compound **39** were prepared by Steglich *et al.* in 4% overall yield[20b] and leprapinic acid **40** was synthesized by Mittal[53] (Figure 6). A series of unnatural pulvinic acid derivatives were prepared by Foden *et al.*, such as compounds **20** and **21**, obtained in 29% and 38% overall yields, respectively (Figure 5).[16] Grover *et al.* also employed this method in the synthesis of brominated pulvinic acid derivatives.[54]



	R^1	R^2	R^3	R^4	R^5	R^6
Methyl variegatate (**36**)	OH	OH	Me	H	OH	OH
Methyl 3,4-dihydroxypulvinate (**37**)	OH	OH	Me	H	H	H
Methyl 3',4'-dihydroxypulvinate (**38**)	H	H	Me	H	OH	OH
(**39**)	H	OH	H	H	OH	OH
Leprapinic acid (**40**)	H	H	Me	OMe	H	H

Figure 6. Structure of synthetic pulvinic acid derivatives.

One interesting point was observed by Mittal in the synthesis of leprapinic acid **40**. Indeed, a selectivity was observed during the opening of the bis(lactone) **41** by sodium methoxide (Scheme 5). The two lactone rings are different because of the electronic distribution.[53] The positive charge on the carbonyl carbon atom of the lactone ring closer to the *o*-methoxyphenyl nucleus should be higher; hence this lactone ring is more easily opened. More recently, the opening reaction of an unsymmetrically substituted bis(lactone) has been achieved regioselectively (Scheme 5).[55] Thus, the reaction of the monoaromatic bis(lactone) **42** with various amines and alcohols, using tetrabutylammonium fluoride (TBAF) as an activator, led to the formation of the corresponding amides and esters with excellent regioselectivities, ranging from 85/15 to 99/1 in favour of compounds **43** and **45**, obtained in good yields. A series of variously substituted pulvinamides and pulvinic derivatives were thus prepared.

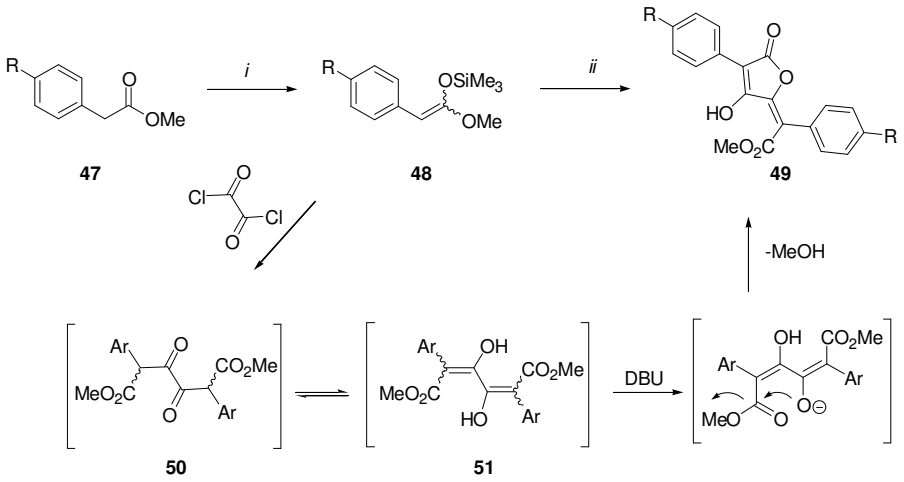


Scheme 5. Regioselective opening of bis(lactone)s: *i*) KOH, MeOH, rt; *ii*) RNH_2, TBAF, THF, −78 °C (80–98%); *iii*) ROH, TBAF, THF, −78 °C or −35 °C (53–83%).

3.1.2. Silyl ketene acetal as precursor

By condensing silyl ketene acetals on oxalyl chloride, various natural symmetrical pulvinic acids were prepared (Scheme 6).[56] Various methyl arylacetates **47** were converted to the corresponding silyl ketene

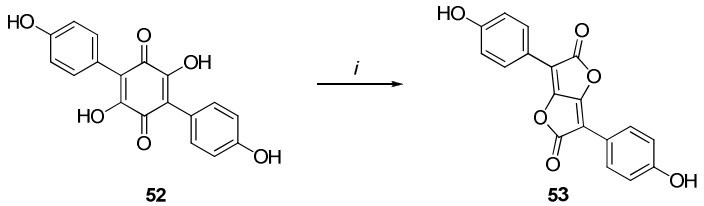
acetals **48**, according to a procedure described by Ainsworth.[57] The condensation of the silyl ketene acetal **48** on oxalyl chloride was first tried in the presence of a Lewis acid ($TiCl_4$, TMSOTf) but complex mixtures of compounds were obtained, presumably resulting from polymerization. Better results were obtained in the absence of any catalyst. Direct treatment of the crude reaction product with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) yielded the pulvinic ester **49**. The preparation of product **49** involves in the first step the formation of diketone **50**. Under basic conditions, it cyclizes to the corresponding pulvinic derivative. Such methodology was used to synthesize, among other compounds, vulpinic acid **2** and methyl atromentate. Saponification of the methyl ester function of these compounds led to pulvinic acid **1** and atromentic acid **3** in 95% and quantitative yields, respectively.



Scheme 6. Preparation of methyl pulvinates: *i*) 1) *i*-Pr_2NLi, THF, −78 °C, 2) Me_3SiCl, −78 °C to rt (quant.); *ii*) 1) oxalyl chloride, CH_2Cl_2, −78 °C, 2) DBU, CH_2Cl_2, rt, 3) conc. HCl/MeOH, 1/1, v/v (60–74%).

3.2. Oxidative quinone rearrangement

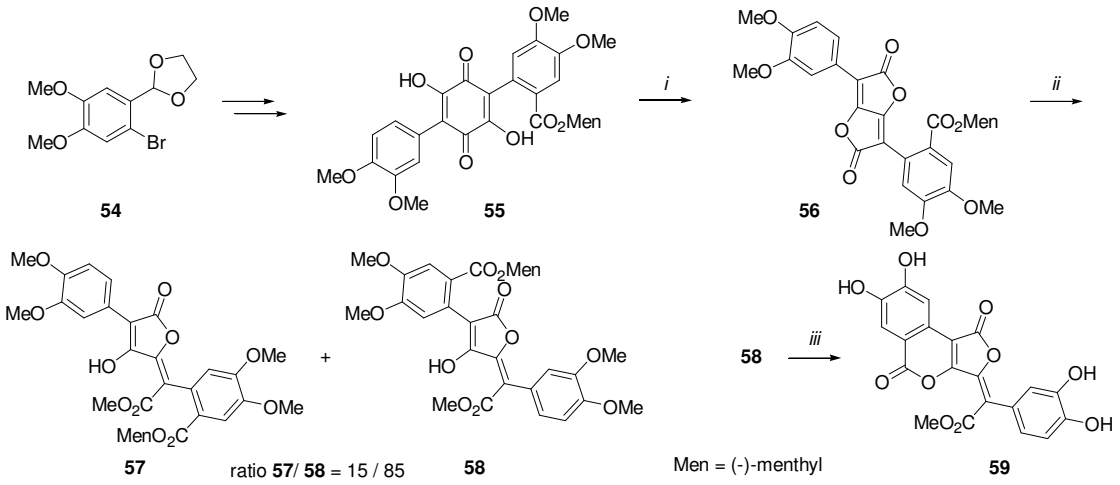
The oxidative quinone rearrangement is an alternative way to prepare pulvinic bis(lactone)s. Thus, conversion of the natural terphenylquinone atromentin **52** in bis(lactone) **53** was achieved by Kögl using hydrogen peroxide and hydrochloric acid in refluxing acetic acid (Scheme 7).[58]



Scheme 7. Conversion of atromentin **52** to bis(lactone) **53**: *i*) H_2O_2, HCl, AcOH, reflux, 77%.

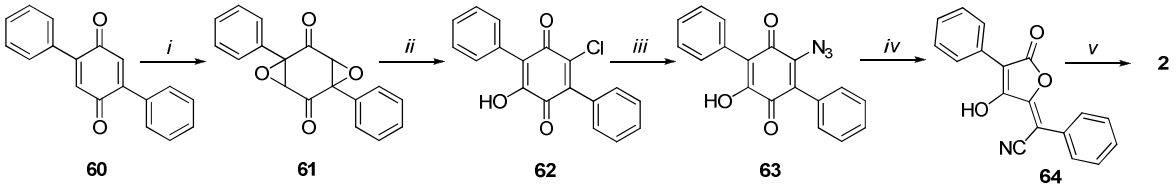
Other oxidative systems have been developed for the transformation of terphenylquinones to bis(lactone)s. Thus, the use of lead tetraacetate has been reported.[59] Several symmetrical bis(lactone)s were prepared using acetic anhydride and DMSO and converted to the corresponding pulvinic acids.[60] This reaction was conveniently used for the preparation of specifically ^{13}C-labelled atromentic acid **3**.[1] The mixture of acetic anhydride and DMSO was also used to transform unsymmetrically substituted terphenylquinones into bis(lactone)s, in order to prepare unsymmetrical pulvinic acid derivatives, including pinastric acid **6**.[61]

This oxidative system was employed by Steglich *et al.* to prepare methyl bovinate **59** (Scheme 8), an orange pigment which was found in the mycelial cultures of *Suillus bovinus*.[62] The structure of this pulvinic acid derivative is unusual, since it contains an additional δ-lactone ring. Acetal **54** prepared from veratraldehyde was transformed into terphenylquinone **55**, which was oxidized to bis(lactone) **56** using a mixture of acetic anhydride and DMSO. Treatment of **56** with KOH in methanol led to the two regioisomeric compounds **57** and **58**, which could be easily separated on a silica gel column, in a 15/85 ratio. Finally, treatment of derivative **58** with BBr_3 resulted in the cleavage of the methyl ethers and the menthyl ester, with concomitant lactone formation, affording methyl bovinate **59**, obtained in 11% overall yield from acetal **54**.



Scheme 8. Synthesis of methyl bovinate **59**: *i*) Ac_2O, DMSO, 60 °C, 82%; *ii*) KOH, MeOH, rt, 99%; *iii*) BBr_3, −78 °C to rt, 69%.

Azido-1,4-benzoquinone **63** has also been used for the formation of bis(lactone)s (Scheme 9).[63] Reaction of 2,5-diphenyl-1,4-benzoquinone **60** with basic 30% hydrogen peroxide in dioxane gave the diepoxide **61**. Treatment of the latter with hydrochloric acid afforded chlorohydroxyquinone **62**, which reacted with ethanolic sodium azide to give azidoquinone **63**. This compound was then converted to the butenolide **64** in refluxing chloroform or ethanol. Finally, the methanolysis of compound **64** afforded vulpinic acid **2**.

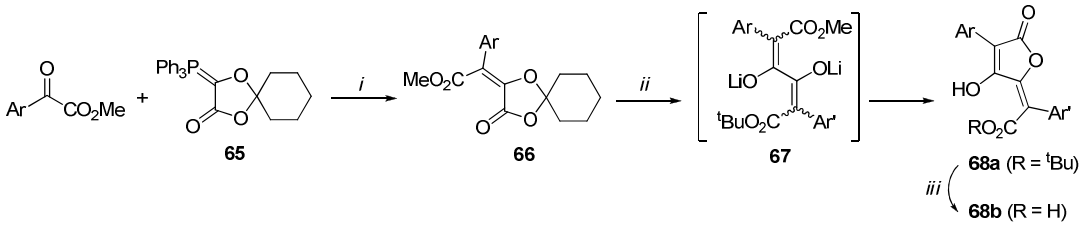


Scheme 9. Synthesis of vulpinic acid **2** from azido-1,4-quinone **63**: *i*) H_2O_2, NaOH, dioxane, Triton B, rt, 75%; *ii*) conc. HCl, dioxane/methanol, 8/2, v/v, reflux, 68%; *iii*) NaN_3, EtOH, reflux, 89%; *iv*) EtOH or $CHCl_3$, reflux, 65%; *v*) HCl, MeOH, reflux, 95%.

3.3. Addition of ester enolate on a dioxolanone

Ramage developed a method for the construction of a tetronic acid ring from a dioxolanone and made use of it to provide a biomimetic synthesis of pulvinic acids, *via* the reaction of 5-(α-methoxycarbonylarylidene)dioxolanone **66** with lithium enolates (Scheme 10).[64] The success of this strategy relied

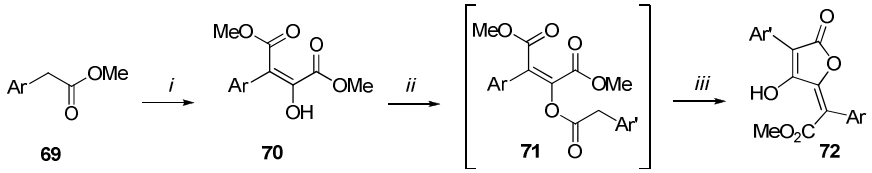
on the facility with which the dioxolanones can undergo a nucleophilic attack at the lactone carbonyl group with extrusion of cyclohexanone. The reaction between methyl arylglyoxylate and phosphorane **65** in toluene at 95 °C gave a mixture of (*E*)- and (*Z*)-dioxolanones **66** which are separated by chromatography on silica gel. The (*E*)-isomer **66** reacted with the lithium enolate of *tert*-butyl arylacetate in THF to give dianion **67**, which cyclized to the corresponding pulvinic acid *tert*-butyl ester **68a**. In some cases, an acyclic adduct was isolated after work-up and the heating of this adduct in THF in the presence of water afforded the cyclized product. Ester was obtained either as a pure (*E*)-isomer or as a mixture of (*E*)- and (*Z*)-isomers, which were easily separated by chromatography. The UV irradiation of the minor (*Z*)-isomer in toluene led quantitatively to the corresponding (*E*)-isomer. Treatment of ester **68a** with trifluoroacetic acid (TFA) afforded the corresponding pulvinic acid **68b**. The natural products pulvinic acid **1**, xerocomic acid **4** and leprapinic acid **40** were prepared according to this method. It is noteworthy that dianion **67** is analogous to intermediate **26** involved in the biosynthesis of pulvinic acids from terphenylquinones (Scheme 2).



Scheme 10. Synthesis of a pulvinic acid **68b** from a dioxolanone **66**: *i*) toluene, 95 °C (72–81%); *ii*) Ar'CH(Li)CO_2Bu^t, THF, −78 °C to rt (74–86%); *iii*) 90% TFA, rt, (76–86%).

3.4. Dieckmann condensation of enol ester

A methodology allowing the preparation of unsymmetrical pulvinic acid derivatives was developed in 1979 by Weinstock,[17] based on Haynes's work on α-acyloxy esters cyclization for tetronic acids preparation.[65] These methods proceeded by a Dieckmann condensation (Scheme 11). Methyl arylacetate **69** and dimethyl oxalate were condensed using sodium methoxide in benzene to afford enol **70**. Reaction of the latter with an arylacetyl chloride using triethylamine (1 equiv.) as base gave the intermediate **71**, which can be either isolated or cyclized using triethylamine (2 equiv.) at 50 °C to give vulpinic acid **72**. Variously substituted vulpinic acids were prepared in 5 to 25% yields for the last two steps. Weinstock succeeded also to prepare derivatives in which the exocyclic double bond was substituted by a non-aromatic substituent.

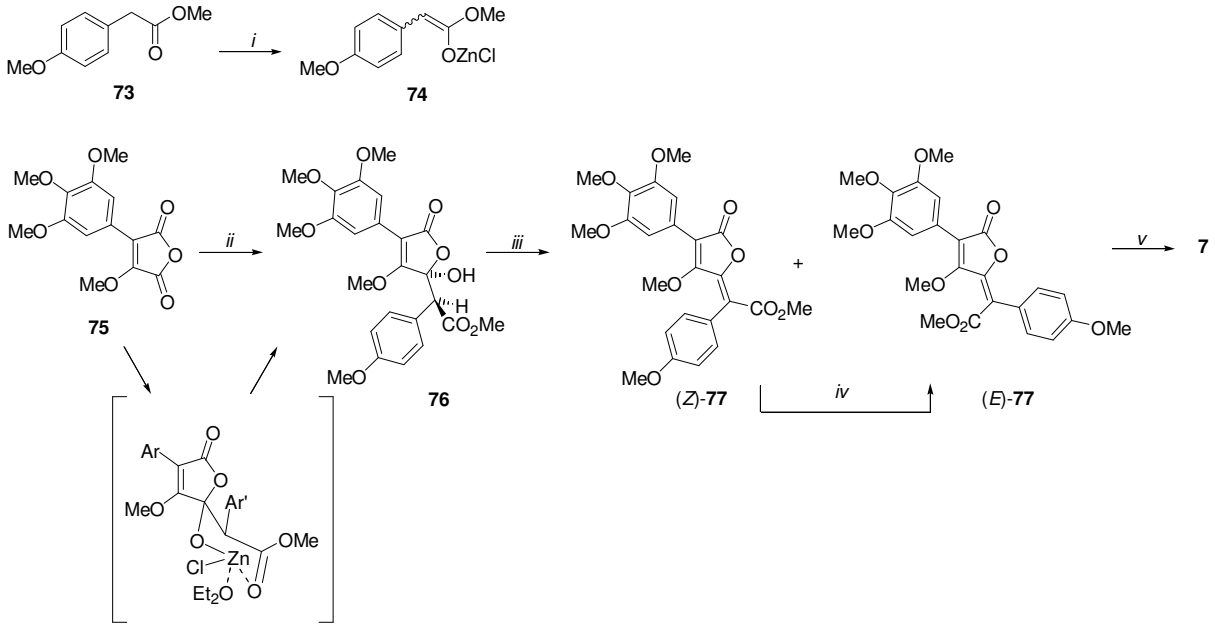


Scheme 11. Synthesis of unsymmetrical vulpinic acids according to Weinstock's methodology: *i*) MeONa, benzene, reflux, 39%; *ii*) Ar'CH_2COCl, NEt_3, acetone, 0 °C to rt; *iii*) NEt_3, 50 °C (5–25% for the last two steps).

3.5. Reformatsky-type reaction

Properties of maleic anhydride derivatives were used by Pattenden and coworkers in several syntheses of pulvinic acids. All these routes have the advantage to allow the formation of unsymmetrical pulvinic acid derivatives.

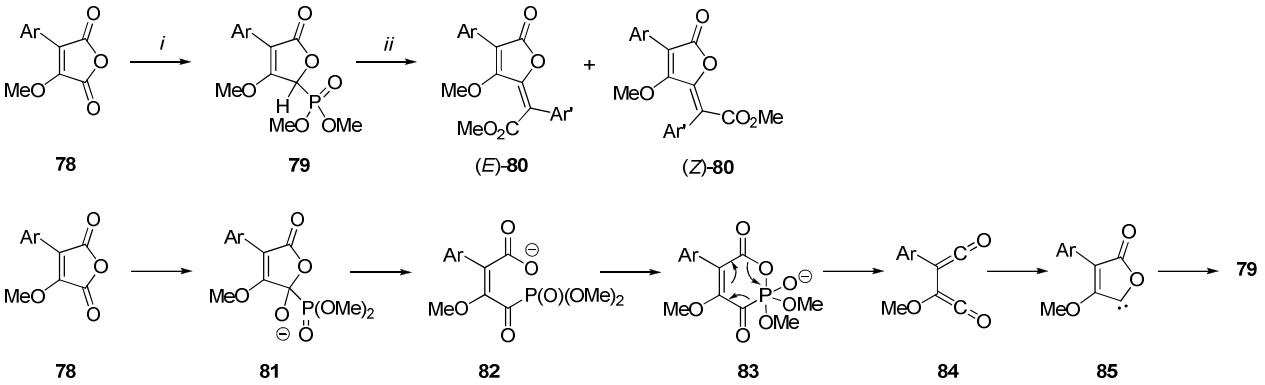
In 1986, Pattenden reported an approach that proceeded *via* a Reformatsky-type condensation reaction between a methyl arylacetate and an arylmethoxymaleic anhydride, as in the preparation of gomphidic acid **7** (Scheme 12).[66] Deprotonation of ester **73** using lithium di-*iso*-propylamide (LDA) at -78 °C, followed by addition of an ether solution of anhydrous zinc chloride afforded the zinc enolate **74**. Compound **74** was then added to anhydride **75**, yielding the tertiary alcohol **76** as a single diastereoisomer. The selectivity observed may be explained by the favourable, chair-like conformation of the zinc chelate intermediate leading to **76**, in which the bulkiest groups stand in equatorial positions. The dehydration of compound **76** leading to the corresponding permethylated pulvinic acid was achieved by treatment with methanesulfonyl chloride followed by 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). A mixture of (*Z*)- and (*E*)-isomers **77** was obtained and was exposed in laboratory to daylight for several days, to yield (*E*)-**77**. Demethylation of compound (*E*)-**77** with trimethylsilyl iodide afforded gomphidic acid **7**. Atromentic acid **3** and pinastric acid **6** were also prepared according to this strategy.



Scheme 12. Synthesis of pulvinic acids through a Reformatsky-type reaction: *i*) 1) LDA, THF, −78 °C, 2) $ZnCl_2$; *ii*) **74**, Et_2O, −60 °C, 27% for the two steps; *iii*) 1) CH_3SO_2Cl, CH_2Cl_2, −10 °C to rt, 2) DBN, THF, 0 °C to rt [57% for (*Z*)-**77** and 18% for (*E*)-**77**]; *iv*) daylight; *v*) Me_3SiI, $CDCl_3$, 55 °C, 65%.

3.6. Horner-Wadsworth-Emmons olefination

The second method developed by Pattenden involved a Horner-Wadsworth-Emmons olefination reaction between a phosphonate such as **79** and a substituted methyl benzoylformate (Scheme 13).[67] The authors assumed that the conversion of maleic anhydride derivative **78** proceeded *via* the corresponding carbene **85**. Thus, reaction of sodium dimethyl phosphite on the more electrophilic carbonyl of anhydride **78** formed the intermediate **81**, which is converted to the carboxylate **82** and then to the cyclic compound **83**. Rearrangement of compound **83** generated the diketene **84**, which then formed the carbene **85**. Condensation between phosphonate ester **79** and substituted methyl benzoylformate in the presence of sodium hydride produced a mixture of (*Z*)- and (*E*)-isomers **80**, which were separated by chromatography. This methodology was used to prepare variously substituted pulvinic acid derivatives. Analogously, pulvinones were obtained from aldehydes.

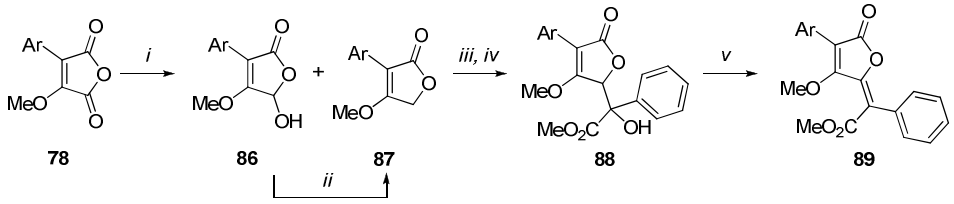


Scheme 13. Synthesis of vulpinic acid derivatives proceeding by a Horner-Wadsworth-Emmons olefination: *i*) NaH, $HP(O)(OMe)_2$, benzene, reflux (21–41%); *ii*) NaH, Ar'C(O)CO_2Me, benzene, 0 °C (45–66%).

3.7. Alkylidenation of tetronic acid derivatives

3.7.1. Maleic anhydride derivatives and methyl 3-aryltetronates as precursors

This pathway proceeded by a regioselective reduction of an unsymmetrically substituted maleic anhydride (Scheme 14) and was developed by Pattenden.[68] Reduction of anhydride **78** with lithium tri-*tert*-butoxyaluminium hydride led to a mixture of lactol **86** and lactone **87**, obtained in a 2:1 ratio. Compound **86** can be further reduced using alkaline sodium borohydride to yield lactone **87** in a 70–90% yield for the two steps. Metallation of compound **87** with lithium *N*-cyclohexyl-*N*-*iso*-propylamide at −78 °C was followed by reaction with methyl benzoylformate, affording the tertiary alcohol **88**. Dehydration of alcohol **88** was obtained with a hot suspension of phosphorus pentoxide in benzene.[69] Vulpinic acid derivatives **89** were thus obtained in 7–18% overall yields. This method was notably used to synthesize permethylated derivatives of pinastric acid **6** and gomphidic acid **7**.



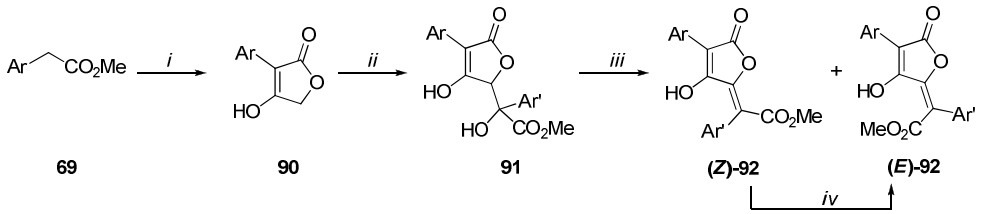
Scheme 14. Synthesis of unsymmetrical pulvinic acid derivatives *via* regioselective reduction of maleic anhydride derivatives and alkylidenation: *i*) $LiAlH[OC(CH_3)_3]_3$, glyme, −30 °C to rt; *ii*) $NaBH_4$, NaOH, H_2O, rt (70–90% for the two steps); *iii*) lithium *N*-cyclohexyl-*N*-*iso*-propylamide, THF, −78 °C; *iv*) PhC(O)CO_2Me, −70 °C to rt; *v*) P_2O_5, benzene, 60 °C (10–20% for the last three steps).

3.7.2. Readily available 3-aryltetronic acids as precursors

The key step of this method is the alkylidenation of an unprotected aryltetronic acid **90**, prepared in one step by treatment of methyl arylacetate **69** and methyl hydroxyacetate with *tert*-butoxide, *via* tandem transesterification/Dieckmann condensation (Scheme 15).[70] The Dieckmann condensation, which was first reported by Lacey for the preparation of 3-acyltetronic acids,[71] has also been used for the synthesis of 3-aryltetronic acids.[72]

Addition of the dianion generated from tetronic acid **90** on a methyl arylglyoxylate afforded alcohol **91**, obtained as a mixture of diastereoisomers.[73] Treatment of **91** with trifluoroacetic anhydride and pyridine in dichloromethane then led to the corresponding alkenes **92**. The mixture of methyl pulvinate stereoisomers

(*Z*)-**92** and (*E*)-**92** obtained was converted selectively to the pure, nature-relevant (*E*)-isomer, thanks to the irradiation of a toluene solution at 254 nm.



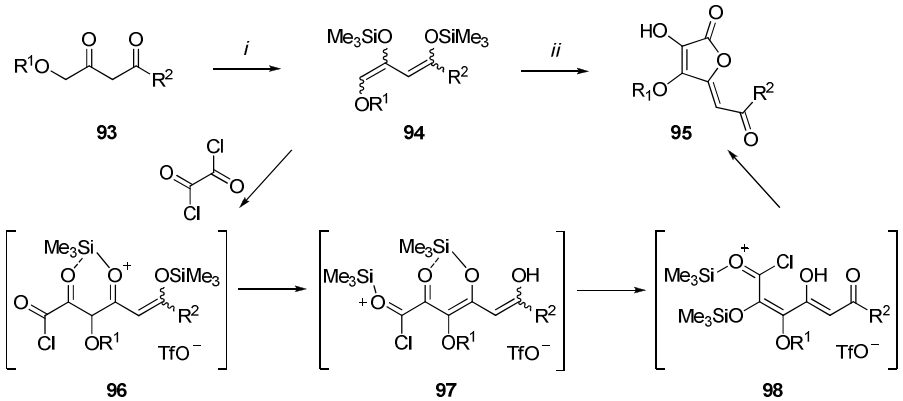
Scheme 15. Alkylidenation of a tetronic acid derivative: *i*) methyl 2-hydroxyacetate, *t*-BuOK, THF, reflux or DMF, rt (85–90%); *ii*) 1) LDA, THF, −78 °C, 2) Ar'C(O)CO_2Me, −78 °C to rt (60–85%); *iii*) $(CF_3CO)_2O$, pyridine, CH_2Cl_2; *iv*) hν, toluene (71–95% for the last two steps).

This methodology was used to prepare three natural methyl pulvinates: pinastric acid **6**, compound **11**[13] and di-*O*-methylatromentate, which was isolated from *Pulveroboletus ravanelii*.[74]

3.8. Suzuki-Miyaura cross-coupling

3.8.1. From arylboron species and triflates of tetronic acid derivatives

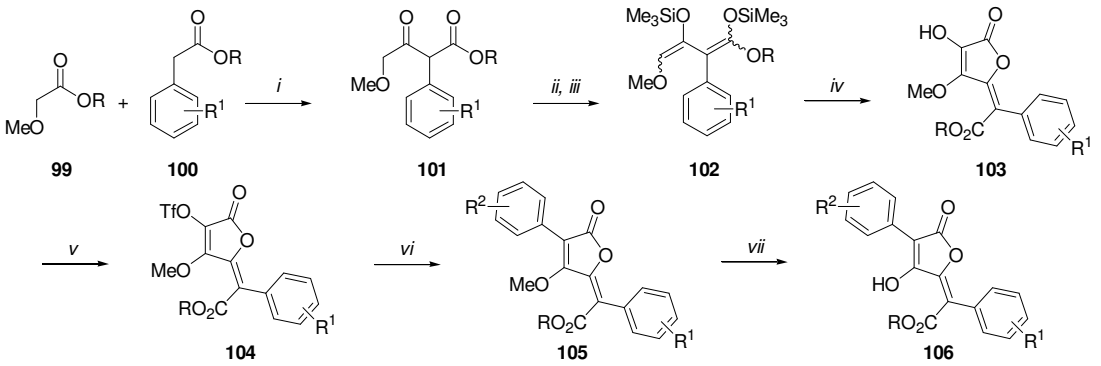
Langer developed methodologies for the preparation of γ-alkylidenebutenolides, including 5-alkylidenetetronic acids, based on the condensation of a 1,3-dicarbonyl compound with an oxalic acid derivative.[75] Thus, the trimethylsilyl triflate-catalyzed reaction of bis(trimethylsilyloxy)buta-1,3-diene **94**, derived from 1,3-dicarbonyl compound **93**, with oxalyl chloride, afforded butenolide **95**, according to the proposed mechanism (Scheme 16). In a first step, the attack of the terminal carbon atom of the 1,3-bis-(trimethylsilyloxy)buta-1,3-diene onto oxalyl chloride activated by TMSOTf would give intermediate **96**. Then, trimethylsilyl group migrations would occur to generate **98**. The attack of the enol oxygen atom onto the activated carboxylic acid chloride, followed by extrusion of TMSCl, would then lead to compound **95** and regeneration of the catalyst. The selective formation of the (*E*)-configured product can be explained by the higher thermodynamic stability of the (*E*)-isomer compared to the (*Z*)-isomer.[75d]



Scheme 16. Condensation of a 1,3-bis(trimethylsilyloxy)buta-1,3-diene on oxalyl chloride: *i*) 1) NEt_3, Me_3SiCl, benzene, rt, 2) LDA, Me_3SiCl, THF, −78 °C (80–90%); *ii*) oxalyl chloride, Me_3SiOTf, CH_2Cl_2, −78 °C (80–90%).

γ-Alkylidenebutenolides related to **95** have been converted *via* Suzuki cross-couplings to pulvinic acid derivatives.[76] As described in Scheme 17, reaction of the enolate derived from methyl methoxyacetate **99**

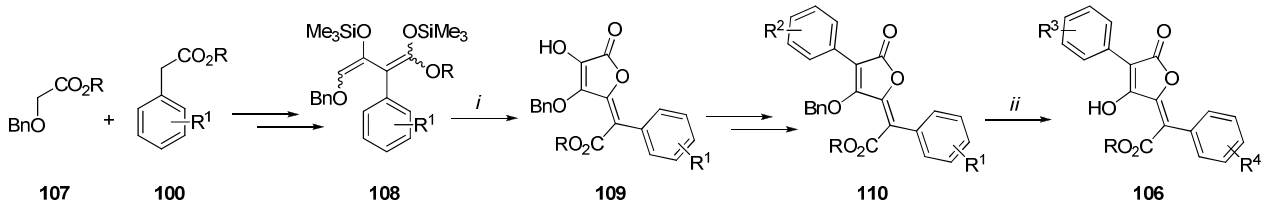
with methyl arylacetate **100** afforded β-ketoester **101**, which was transformed into 1,3-bis(trimethylsilyloxy)buta-1,3-diene **102**. The TMSOTf-catalyzed cyclization of the latter with oxalyl chloride generated the tetronic derivative **103**, which was converted to triflate **104**. The Suzuki coupling of compound **104** with phenylboronic acid afforded compound **105**. The enol ether function was selectively cleaved with BBr_3 to give pulvinic acid derivative **106**.



Scheme 17. Synthesis of pulvinic acid derivatives from 1,3-bis(trimethylsilyloxy)buta-1,3-dienes: *i*) LDA, THF, −78 °C to rt (67−71%); *ii*) NEt_3, Me_3SiCl, THF, rt (80−95%); *iii*) 1) LDA, THF, −78 °C, 2) Me_3SiCl, −78 °C to rt (90−97%); *iv*) oxalyl chloride, Me_3SiOTf, CH_2Cl_2, −78 °C to rt (15−70%); *v*) Tf_2O, pyridine, −78 °C to −10 °C (60−75%); *vi*) R^2-C_6H_4-$B(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, dioxane, reflux (80−95%); *vii*) BBr_3, CH_2Cl_2, 0 °C (14−57%).

The synthesis or the formal synthesis of the following natural products according to this pathway was described: leprapinic acid **40**, atromentic acid **3**, xerocomic acid **4**, variegatic acid **5**, pinastric acid **6**, gomphidic acid **7** and vulpinic acid **2**.

A variant of this pathway, involving compounds such as **109**, in which the enol function is protected as a benzyl ether, has also been used and allowed the formation of pulvinic acids and norbadione A analogues.[77] As described in Scheme 18, reaction of methyl 2-(benzyloxy)acetate **107** with alkyl arylacetate **100** afforded a β-keto ester which was converted into 1,3-bis(trimethylsilyloxy)buta-1,3-diene **108**. The cyclocondensation of **108** with oxalyl chloride led to the tetronic derivative **109**, which was then converted to pulvinic acid derivative **110** through a Suzuki-Miyaura coupling. Treatment with hydrogen over 20% Pd/C led to pulvinic acid derivative **106**. If the aromatic groups are substituted by benzyloxy groups, these ether functions are also cleaved during the final hydrogenolysis step.

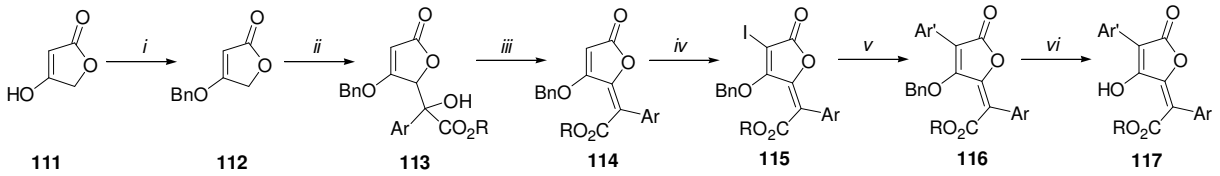


Scheme 18. Synthesis of pulvinic acid derivatives involving the debenzylation of an enol ether: *i*) oxalyl chloride, Me_3SiOTf, CH_2Cl_2, −78 °C to rt (38−53%); *ii*) H_2, 20% Pd/C, CH_2Cl_2 (35−99%).

3.8.2. From arylboronates and 3-iodotetronic acid derivatives

In this pathway, the commercial tetronic acid **111** was converted in a few steps to iodide **115** (Scheme 19).[78] Tetronic acid **111** was alkylated with benzyl bromide to compound **112**. The reaction of the anion

generated by treatment of compound **112** with *n*-butyllithium at −78°C in THF with an α-aryloxoacetate led to the tertiary alcohol **113**, obtained as a mixture of diastereoisomers, which could be partially separated by chromatography on silica gel. However, this separation was not necessary, since the dehydration conditions, using trifluoroacetic anhydride, 4-(dimethylamino)pyridine (DMAP) and triethylamine, were efficiently performed from both isomers. In these conditions, the mixture of diastereoisomers **113** led to alkene **114**, mainly obtained as the (*E*)-isomer. The iodination reaction of compound **114** was performed in good yields using iodine and ceric ammonium nitrate (CAN) at 40 °C in acetonitrile. Thus, 3-iodotetronic acid **115** was obtained in 29–59% overall yield starting from **112**.

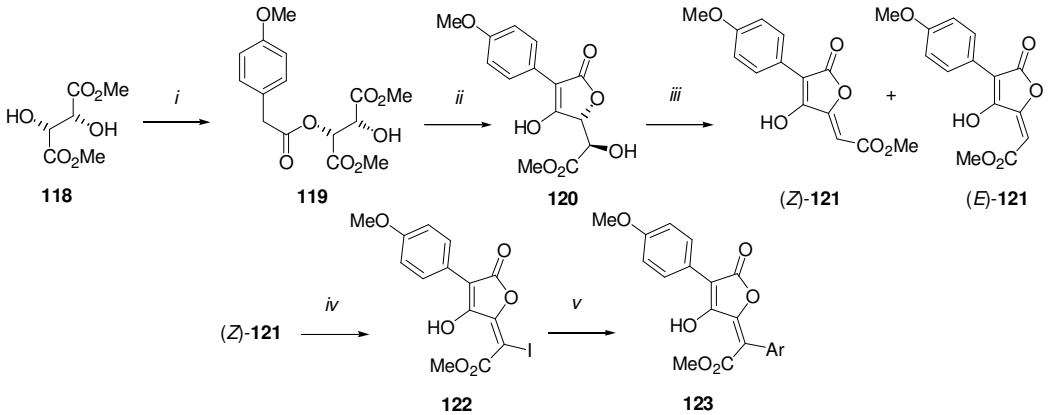


Scheme 19. Synthesis of pulvinic acids from a 3-iodotetronic acid derivative: *i*) BnBr, K_2CO_3, DMF, rt, 75%; *ii*) 1) *n*-BuLi, THF, −78 °C, 2) $ArC(O)CO_2R$, −78 °C to rt; *iii*) $(CF_3CO)_2O$, DMAP, NEt_3, CH_2Cl_2, 0°C to rt (59%–quant. for the last two steps); *iv*) I_2, CAN, CH_3CN, 40 °C (65–78%); *v*) $Ar'B(OR)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3 (2M aq), THF, 80 °C (60–93%); *vi*) H_2, 10% Pd/C, DMF, HCl, (68–90%).

The Suzuki-Miyaura cross-coupling of iodide **115** with various arylboronates was performed in a THF/2 M aqueous Na_2CO_3 mixture using $PdCl_2(PPh_3)_2$ as catalyst, leading to compound **116**. Cleavage of the benzyl ethers (H_2, 10% Pd/C) was performed in DMF in the presence of hydrochloric acid. Various hydroxylated pulvinic acid derivatives **117** were thus synthesized starting from the corresponding benzyl ethers. Different pulvinic and vulpinic acid derivatives, such as vulpinic acid **2**, xerocomic acid **4**, pinastric acid **6**, have been prepared according to this route.

3.8.3. From arylboronates and iodoalkene derivatives

In order to synthesize variously substituted pulvinic acids, another strategy was recently developed, which depended on a Suzuki-Miyaura cross-coupling between an alkenyl iodide **122** and an arylboronate (Scheme 20).[79]



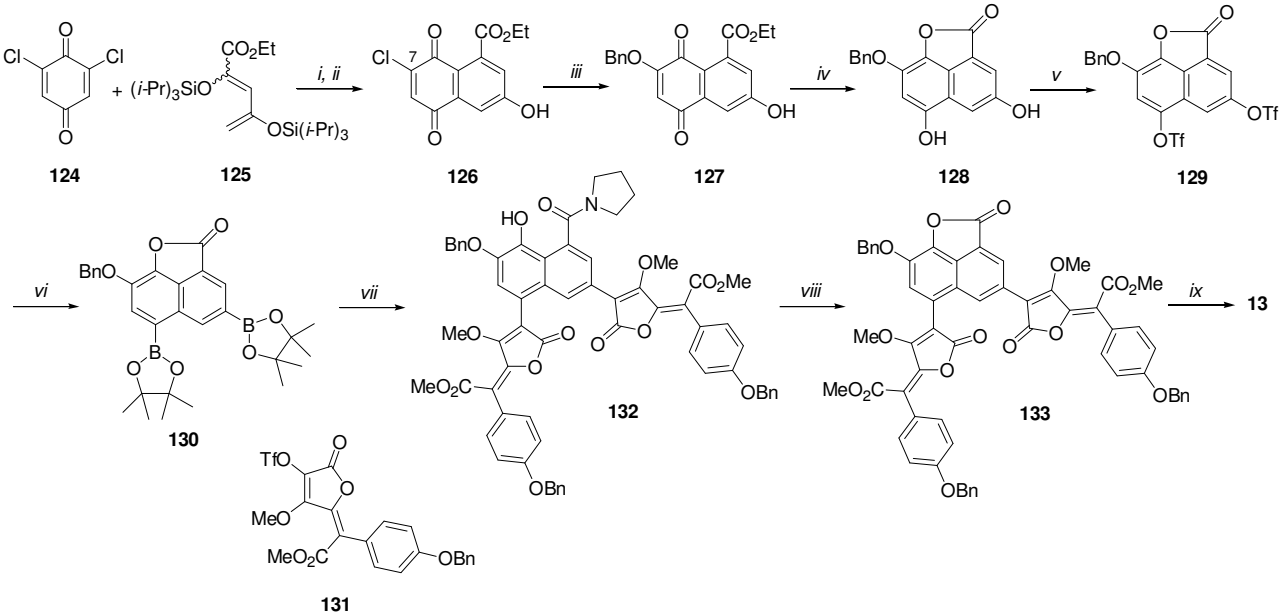
Scheme 20. Synthesis of pulvinic acids from an iodoalkene:
i) 4-methoxyphenylacetic acid, DCC, DMAP, CH_2Cl_2, 65%; *ii*) LiHMDS, THF, −78 °C; *iii*) $(CF_3CO)_2O$, NEt_3, CH_2Cl_2 [81% and 7% for (*Z*)-**121** and (*E*)-**121**, respectively, for the last two steps]; *iv*) 1) 0.5 N NaOH, acetone, H_2O, 2) NIS, AcOH (3 equiv.), THF, 50 °C, 50%; *v*) $ArB(OR)_2$, $PdCl_2(PPh_3)_2$, 2 M aq. Na_2CO_3, THF, reflux (50–81%).

Treatment of (+)-dimethyl L-tartrate **118** with 4-methoxyphenylacetic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) led to a mixture of monoester **119** and the corresponding diester, which are easily separated by chromatography on silica gel. According to the method reported by Brandänge to cyclize the acetate of dimethyl tartrate,[80] reaction of monoester **119** with lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C afforded tetronic acid **120**. Dehydration of **120** led to a mixture of isomers (*Z*)-**121** and (*E*)-**121**, isolated in 81% and 7% yield, respectively, from compound **119**, after chromatography on silica gel. The (*Z*)-isomer was transformed into iodide **122**, using *N*-iodosuccinimide (NIS). This iodination step proceeded with an inversion of the double bond configuration. Suzuki-Miyaura cross-coupling involving iodide **122** and arylboronates were then performed to generate various vulpinic acids **123**.

3.9. Norbadione A synthesis

The unusual pulvinic acid dimer norbadione A is characterized by a naphthofuranone system to which are connected two identical 'pulvinic' moieties. Norbadione A probably biosynthetically derives from badione A, which contains a naphthopyrandione system.[22] The formation of the latter structural feature by oxidative dimerization of 4-methyl-1,2-benzoquinone was demonstrated by Steglich *et al.*[23]

In the course of the total synthesis of norbadione A **13**, that was developed in our laboratory, it was envisioned to introduce simultaneously the two identical 'pulvinic acid' moieties on an appropriately functionalized naphthalene ring. A double Suzuki-Miyaura cross-coupling similar to the one described in Scheme 18 was thus employed for this purpose (Scheme 21).[81]



Scheme 21. Norbadione A synthesis: *i*) toluene, reflux; *ii*) conc. HCl, EtOH, reflux 67%; *iii*) BnOLi, THF, −40 °C to rt, 77%; *iv*) 1) $Na_2S_2O_4$, H_2O, rt, 2) *p*-TsOH, toluene, acetone, reflux 57%; *v*) Tf_2O, pyridine, CH_2Cl_2, −40 °C to rt, quant.; *vi*) bis(pinacolato)diboron, $Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl, *i*-Pr_2NH, dioxane, rt, 59%; *vii*) 1) pyrrolidine, THF, rt, 2) **131** (3 equiv.), $PdCl_2(PPh_3)_2$, THF, 2 M Na_2CO_3, reflux 58%; *viii)* AcOH, reflux, 74%; *ix*) Me_3SiI, $CDCl_3$, 55 °C, 28%.

The Diels-Alder reaction of 2,6-dichloro-1,4-benzoquinone **124** with bis(tri-*iso*-propylsilyloxy)diene **125**, prepared in one step from ethyl 2,4-dioxovalerate, in refluxing toluene, followed by a treatment of the

crude product with hydrochloric acid gave naphthoquinone **126**. A SN_{Ar} substitution of the 7-chlorine was achieved by lithium benzylate in THF and afforded compound **127**. The reduction of naphthoquinone **127** with sodium dithionite was followed by an acid-mediated lactonization which led to precursor **128** in 57% yield. The easy conversion of compound **128** to di-triflate **129** was achieved with triflic anhydride in pyridine and then diboronate **130** was obtained by treatment of compound **129** with bis(pinacolato)diboron under palladium catalysis. First attempts to realize the cross-coupling reaction between diboronate **130** and triflate **131** were unsuccessful. This was attributed to a weak reactivity of the nucleophilic boron species, due to the presence of three electron-withdrawing groups on the naphthalene ring. The lactone might also have reacted with the base necessary for the activation of the boronates. Hence, prior to the cross-coupling, compound **130** was treated with pyrrolidine, so as to allow the boron species to be more nucleophilic. The amide intermediate was then directly treated in the Suzuki-Miyaura conditions with triflate **131**, leading to bis(adduct) **132** in a satisfactory 58% yield. Treatment of the latter in refluxing acetic acid afforded lactone **133** in 74% yield. Final deprotection of compound **133** with iodotrimethylsilane in deuterated chloroform at 55 °C for 11 days allowed cleavage of the seven protecting groups in a single step, leading to norbadione A **13** in 28% yield. Thus, the total synthesis of norbadione A **13** was achieved with a convergent strategy proceeding *via* a Diels-Alder cycloaddition and a double Suzuki-Miyaura cross-coupling in 3% overall yield from 2,6-dichloro-1,4-benzoquinone.

4. Conclusion

The synthesis of pulvinic acids has been the purpose of many studies by chemists interested in mushroom and lichen pigments. Indeed, in many cases, synthesis was used as a mean to prove the actual structure of these heterocyclic natural products. Given the interesting biological properties displayed by pulvinic acid derivatives, innovative synthetic approaches have been regularly designed, following the first synthesis realized by Volhard. While anionic chemistry is still valuable in this context, recent strategies have made use of cross-coupling methods, particularly adapted to the incorporation of aryl groups in the final structure of pulvinic acids.

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INSERTION OF SULFUR ATOMS BY S_2Cl_2 – A CONVENIENT WAY TO SULFUR HETEROCYCLES

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Abstract. *Sulfur heterocycles are important compounds due to their interesting physical properties and significant and versatile biological activity. A novel strategy for insertion of sulfur atoms to readily available organic substrates with the employment of sulfur monochloride is proposed. A synthesis of wide range of heterocyclic systems including thiophenones, 1,2- and 1,4-thiazines, 1,2-dithioles, 1,2,3-dithiazoles, 1,2,3,4,5-pentathiepins, 1,2,3,4,5,6,7-heptathiocanes and others, in a cascade transformations, has been developed.*

Contents

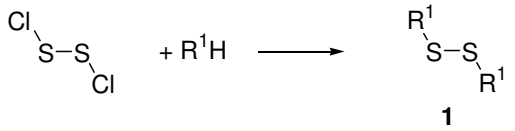
1. Introduction

Sulfur containing heterocyclic compounds have maintained the interest of chemists through decades of historical development of organic chemistry. The reason of this interest is an unique feature of these heterocycles which are considered as promising materials in different areas of pharmaceutical and agrochemical research and also more recently as compounds with interesting physical properties especially for magnetism and conductivity. The preparation of these compounds by conventional ways has usually required many synthetic steps and expensive starting materials. Although there are many methods to introduce sulfur atoms in organic molecules, there is still lack of the methods to construct sulfur heterocycles with inclusion of sulfur atoms in the molecule.

Sulfur chlorides (S_nCl_2) containing two chlorines at the end of polysulfur chain can be considered as excellent reagents for introduction of exact quantity of sulfur atoms into organic molecules. Many of them are known (n=1−12) and some of them can be isolated.[1] But there are only few examples where sulfur chlorides (S_nCl_2), except sulfur dichloride (SCl_2) and sulfur monochloride (S_2Cl_2), inserted *n* sulfur atoms in

the molecule.[2–4] Two sulfur chlorides, SCl_2 and S_2Cl_2, are commercially available and their chemical reactions were investigated more profoundly. However, sulfur dichloride is unstable and has to be purified before the use.[5] Sulfur monochloride is sufficiently stable and can be kept in dark bottles with only slight decomposition giving small amounts of sulfur chloride and sulfur.

Although sulfur monochloride shows complex reactivity (chlorinating, oxidative and sulfurating abilities), it plays an important role with its ability to cyclize organic substances into a heterocyclic ring with insertion of two sulfur atoms.[1] Numerous attempts have been undertaken to prepare a sulfurating reagent with carbon, nitrogen, oxygen or sulfur leaving groups to replace the chlorine atom (Scheme 1).[6] But these disulfides **1** do not substitute for sulfur monochloride and so S_2Cl_2 has ranked among the best sulfur transfer reagent in inorganic and organic chemistry.



R^1 = Ar, NR^2_2, OR^2, SR^2

Scheme 1

About twenty years ago, a novel strategy for activation of the sulfurating ability of S_2Cl_2 by tertiary amines has been proposed by Charles Rees (Imperial College London, UK) and his coworkers. This unexpectedly leads to extensive cascade transformations with the formation of complex heterocyclic compounds. The main feature of activated sulfur monochloride appears to be the addition of two sulfur atoms between carbon-carbon or carbon-heteroatom bonds to produce heterocycles with two bound sulfur atoms. Yet, it was found that often it adds one, three, four, five, six and even more sulfur atoms, sometimes bound together, sometimes not. These syntheses did not have analogs in the literature and this review is devoted to insertion of sulfur atoms by S_2Cl_2 to simple organic substrates with the formation of sulfur heterocycles.

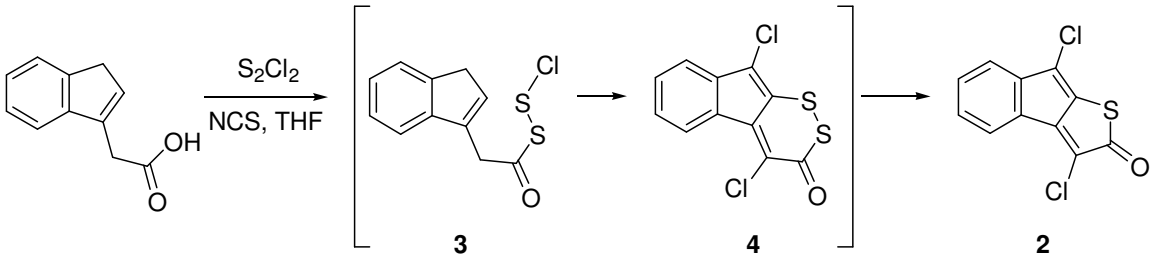
2. Insertion of one sulfur atom

Various heterocyclic compounds with one sulfur atom can be obtained by sulfur monochloride. Sulfur monochloride can add one sulfur atom to a molecule and these transformations usually suggest the extrusion of sulfur dichloride or sulfur atom with contraction of the heterocycle to a more stable (often heteroaromatic) ring. We have discovered few reactions which can be referred to this type.

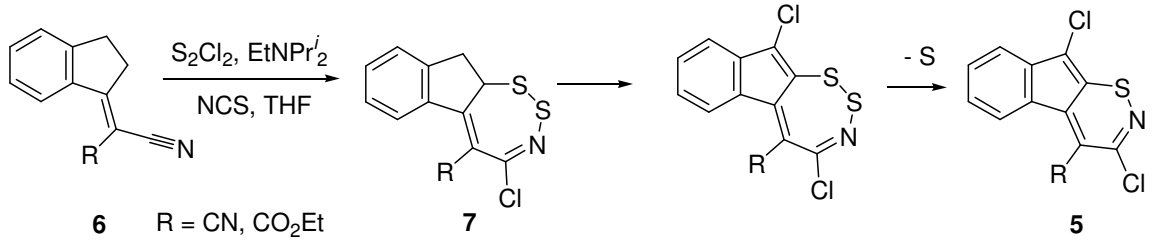
Treatment of inden-3-ylacetic acid with S_2Cl_2, *N*-ethyl di-*iso*-propylamine and NCS gave extensively delocalized 3,8-dichloro-indeno-2*H*-[2,1-*b*]thiophen-2-one **2**, whose structure has been confirmed by X-ray crystallography.[7] Formation of the fused thiophenone **2** is, we believe, unprecedented in S_2Cl_2 reactions. Since S_2Cl_2 has been shown to convert carboxylic acids into acid chlorides,[7] it is possible that some intermediate in this transformation (such as **3**) could be diverted by cyclization ultimately to form thiophene **2** by extrusion of sulfur from intermediate **4** (Scheme 2). The driving force of the last stage is the formation of planar and stable thiophenone ring.

The second example is the formation of 3,9-dichloroindeno-1,2-thiazines **5** from 1-substituted 1-(cyanomethylene)indanes **6**.[7] Treatment of indanes **6** with S_2Cl_2, *N*-ethyl di-*iso*-propylamine and NCS in

THF at 0 °C for three days afforded 1,2-thiazine derivatives **5**. A reasonable pathway for this conversion is given in Scheme 3. Addition of S_2Cl_2 to a nitrile group[8] followed by cyclization onto an activated allylic position would give the dithiazepine **7**; standard chlorination-dehydrochlorination followed by sulfur extrusion (*cf.* ref. [9]) would then give the planar and formally aromatic products **5** isolated.

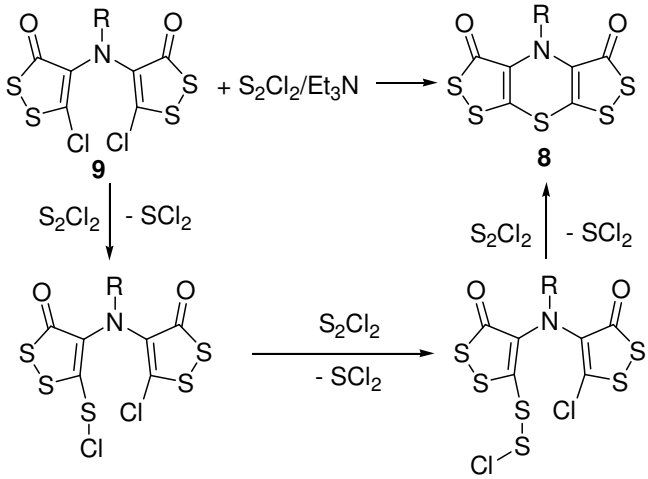


Scheme 2



Scheme 3

Another example is the formation of bisdithiolothiazines **8** from bis(dithiolyl)amines **9**.[10] Investigation of the reaction of *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)-amines **9** with sulfur monochloride and a base showed that DABCO was found to be inert in this reaction, which was not surprising bearing in mind that bicyclic compounds **9** were obtained in the presence of DABCO.[10,11] Treatment of **9** with S_2Cl_2 and triethylamine in chloroform for 3 days at room temperature followed by heating under reflux for 3 hours gave bisdithiolothiazines **8** in high yields (Scheme 4).



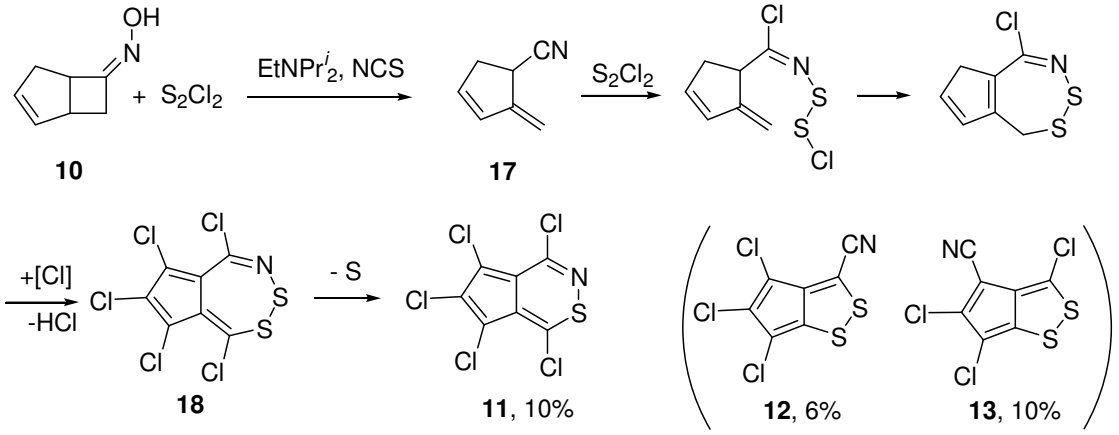
	yield, %
a R = Et	93
b R = CH_2CH_2Phth	95
d R = CH_2CH_2CN	80
e R = $CH_2CH_2CO_2Et$	82
g R = CH_2Ph	79
i R = CH_2CH_2SPh	87

Scheme 4

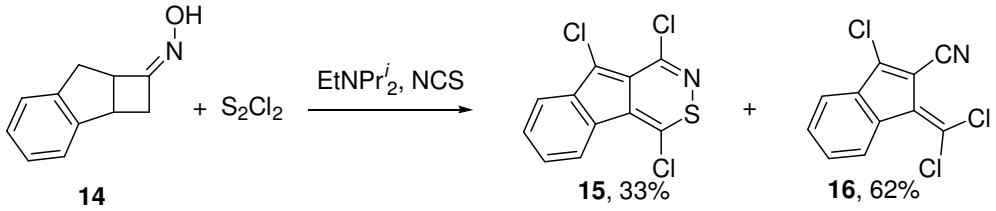
The novelty of these transformations is in replacing chlorines by sulfur in the reaction with electrophilic sulfur monochloride and its mixtures with tertiary amines. The key steps may be explained by

the addition of sulfur monochloride into C–Cl bond with further extrusion of SCl_2 from intermediates (Scheme 4), as explained for polysulfur chain extension in the formation of pentathiepins.[12] The described experimental procedures may serve as an efficient basis for new syntheses of sulfur compounds from readily available chloro-derivatives.

Cyclobutanone oxime **10** reacted with S_2Cl_2, *N*-ethyl di-*iso*-propylamine and NCS in THF to give cyclopenta-1,2-thiazine **11** in low yield together with two other unexpected 10-π pseudoazulenes **12** and **13** (Scheme 5).[13] Benzo-derivative **14** of oxime **10** afforded analogous benzo-product **15** and methylenoindene **16** in high yield (Scheme 6). The simplest mechanism for the conversion of oxime **10** into 1,2-thiazine **11** could involve an initial ketoxime fragmentation of the abnormal (second-order) Beckmann type, presumably induced by sulfur monochloride. Cyclobutane ring opening would give nitrile **17** that could react through the S_2Cl_2 addition to the nitrile with further cyclization and give a seven-membered dithiazepine ring which, by a dehydrogenation and chlorination sequence, would give fully chlorinated product **18**. This is formally a 12-π system that upon the electrocyclization of the seven-membered ring to a fused 6-3 system followed by sulfur loss would give thiazine **11** (Scheme 5).

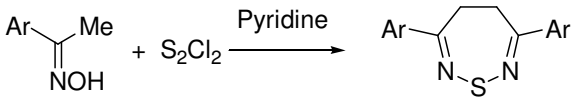


Scheme 5



Scheme 6

Seven-membered dihydro-1,2,7-thiadiazepine **19** was obtained by an unexpected dimerization of acetoxime **20**.[14] Curiously, the reaction of sulfur monochloride containing two sulfur atoms led to the insertion of one sulfur atom to the seven-membered ring, but not two sulfurs (Scheme 7).



Scheme 7

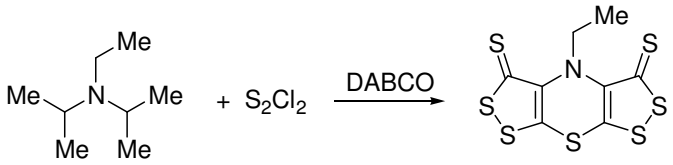
3. Insertion of two sulfur atoms

Heterocycles with two sulfur atoms obtained from sulfur monochloride, *e.g.*, 1,2-dithioles, 1,2,3-dithiazoles and 1,2-dithiines, are most anticipated compounds because they are obtained by a direct insertion of two sulfur atoms during heterocyclic molecule constructing. But even in that case, some unexpected transformations, such as the formation of an adjacent heterocycle, may accompany the main process.

3.1. Synthesis of 1,2-dithioles

3.1.1. From *iso*-propylamines

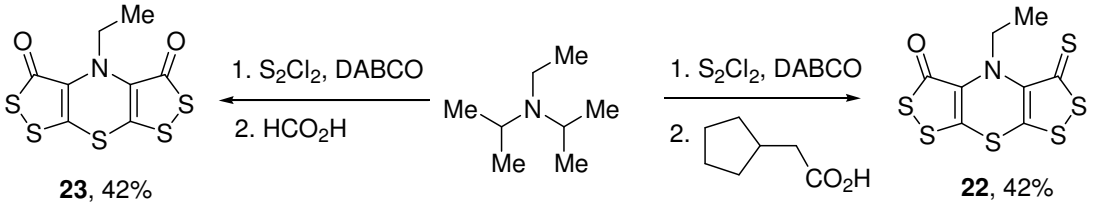
This approach to the synthesis of 1,2-dithioles from tertiary *iso*-propylamines was discovered and elaborated by Charles Rees and co-workers in the late 1990's and in the beginning of this century. These researches commenced when *N*-ethyl di-*iso*-propylamine (Hünig's base), having been initially used as an "inert" base, had been found to react with sulfur monochloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) to give an unexpected and novel multisulfur-nitrogen system, the bis[1,2]dithiolo[1,4]thiazine **21**.[15] In this one-pot conversion of Hünig's base into tricycle **21**, 14 *iso*-propyl C–H bonds were replaced by 10 C–S and two C–C double bonds, whilst the ethyl group remained intact. This is a striking example of high selectivity between primary and secondary *N*-alkyl groups in competitive reactions (Scheme 8).



21, 40%

Scheme 8

Other bis[1,2]dithiolo[1,4]thiazines **22** and **23** can be also selectively obtained by the reaction of Hünig's base with sulfur monochloride through the addition of oxygen donors, such as cyclopentadienylacetic or formic acid (Scheme 9).[16]



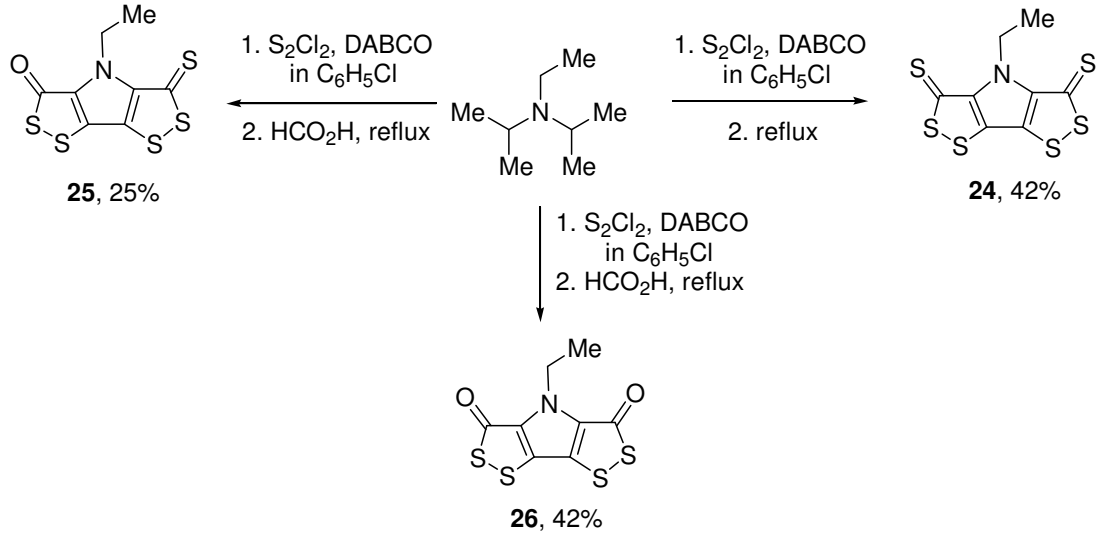
23, 42% **22**, 42%

Scheme 9

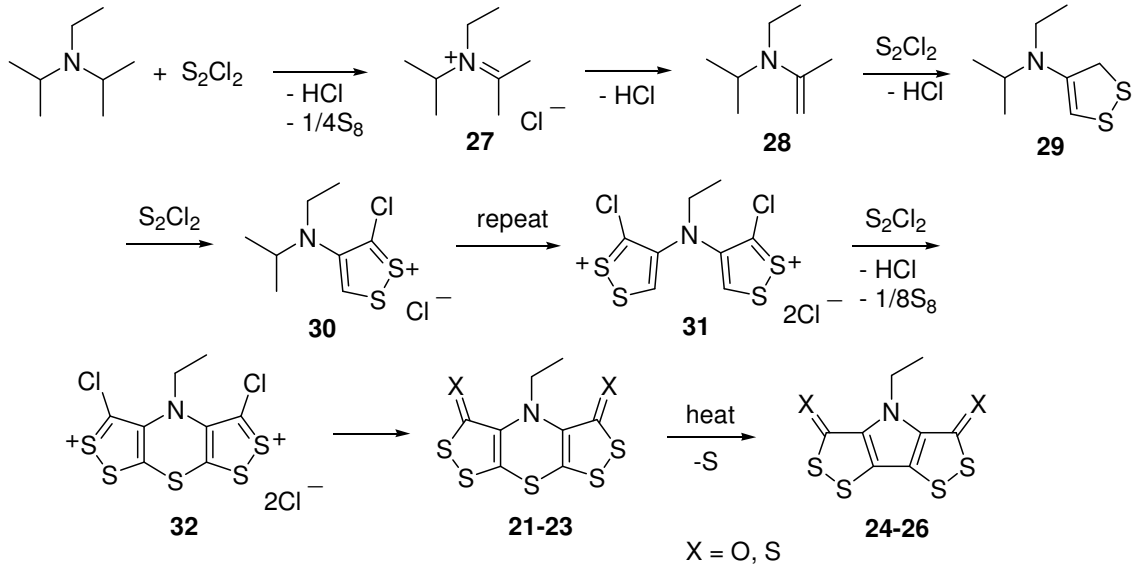
When the reaction of Hünig's base with sulfur monochloride was performed in boiling chlorobenzene, corresponding bis[1,2]dithiolopyrroles **24–26** were formed by the sulfur extrusion from intermediates **21–23** (Scheme 10).[17]

The transformation of Hünig's base into bis[1,2]dithiolo[1,4]thiazines **21–23** and pyrroles **24–26** requires some 15 or so separate reactions and starts, as estimated, from the formation of dithiole rings. A mechanistic pathway for the formation of all products was proposed (Scheme 11).[16] Its first step was the *iso*-propyl group oxidation in Hünig's base by S_2Cl_2 (or its reactive complex with DABCO) to give more stable iminium ion **27**, as generally occurs in the oxidation of tertiary amines. Further deprotonation of **27**

gave enamine **28** which reacted with S_2Cl_2 to give 1,2-dithiole **29** which led to 3-chlorodithiolium salt **30**. The dithiolium ring in this compound is expected to be stable and the whole sequence could then be repeated to transform the other *iso*-propyl group in a similar manner to give dithiolium salt **31**. This could cyclize to tricyclic species **32** by a further reaction with S_2Cl_2 with a loss of sulfur. 3,5-Dichloro-bis-dithiolium salt **32** presumably was the key intermediate and reacted with sulfur and oxygen nucleophiles to give heterocycles **21**–**23**.



Scheme 10

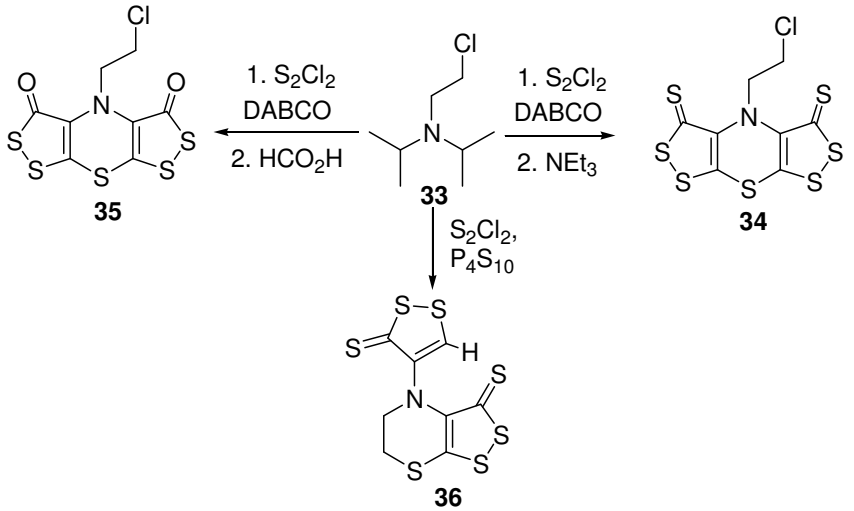


Scheme 11

With a view to furthering the investigations of the substituted di-*iso*-propylamines reaction with sulfur monochloride, Rees and coworkers synthesized a number of tricyclic bisdithiolothiazines, including the parent members.[18–20]

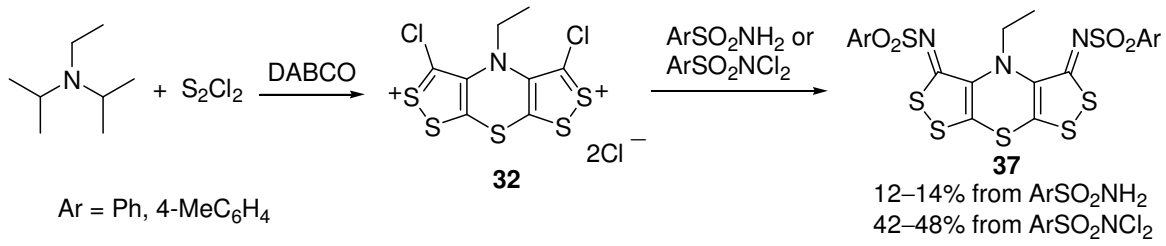
The *N*-(2-chloroethyl) di-*iso*-propylamine **33** constitutes a very special case. Its reaction with sulfur monochloride in the presence of formic acid or triethylamine gave the tricyclic bis[1,2]dithiolo[1,4]thiazine

derivatives **34,35** (Scheme 12).[21] The course of the reaction was completely changed by addition of phosphorus pentasulfide at the last stage of the reaction. In this case, the chlorine atom is replaced by sulfur both in the lateral chain or in the intermediate salt, thus giving a new [1,2]dithiolo[1,4]thiazine ring system **35**.[19] This new compound **36** has shown a notable antitumor activity against breast cancer cells at low concentration (10^{-4} M).



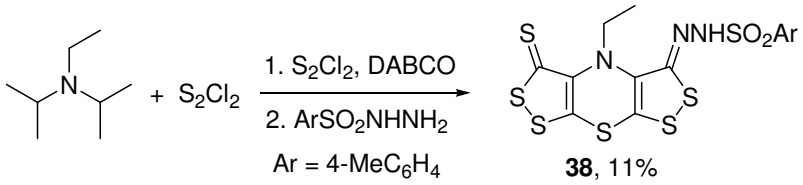
Scheme 12

3,5-Dichloro-bis-dithiolium salt **32** obtained from *N*-ethyl di-*iso*-propylamine, S_2Cl_2 and DABCO in chloroform at room temperature reacted with arenesulfonamides and their *N*,*N*-dichloroderivatives with the formation of *N*,*N*´-bis(arylsulfonyl)dithiolothiazine diimines **37** in modest yields (Scheme 13).[22]



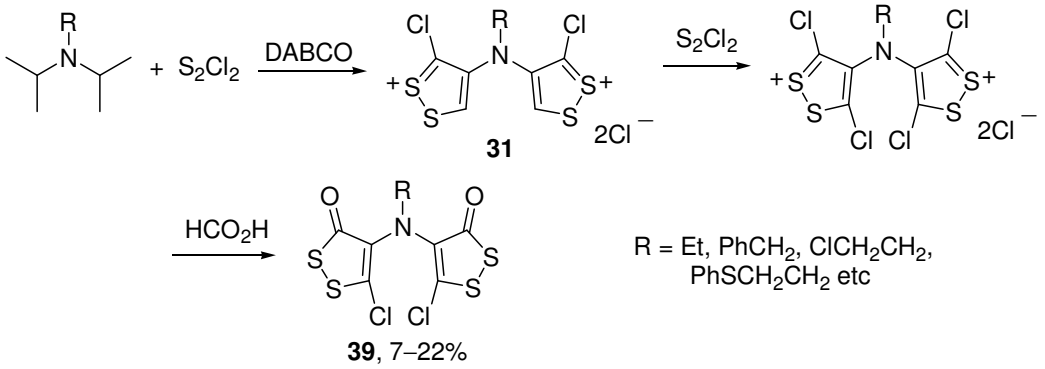
Scheme 13

The reaction of Hünig's base, sulfur monochloride and toluene-*p*-sulfonhydrazide under the same conditions was more complex and gave monohydrazone **38** in low yield (Scheme 14).[22]



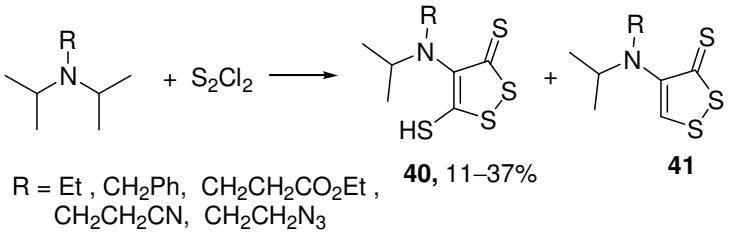
Scheme 14

The reaction of *N*-alkyl di-*iso*-propylamines with sulfur monochloride and DABCO, deficient with the respect to S_2Cl_2, prevented the formation of the 1,4-thiazine ring and led apparently to salts **31** which were then chlorinated by an S_2Cl_2 excess and next treated with formic acid to give *N*,*N*-bis(5-chloro-3-oxo-[1,2]dithiol-4-yl)amines **39** though in low yields (Scheme 15).[11]



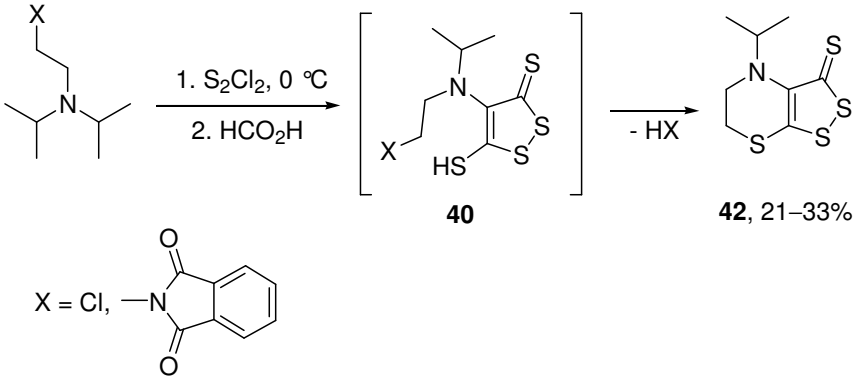
Scheme 15

In all reactions discussed in this Section, both *iso*-propyl groups were transformed into a 1,2-dithiole ring. Going further with the investigation in this area, we demonstrated that the reaction can be stopped at the step of formation of monocyclic 1,2-dithioles. When *N*-alkyl di-*iso*-propylamines and sulfur monochloride were mixed in chloroform in the absence of another base, *i.e.*, DABCO, two monocyclic dithiole-3-thiones **40** and **41** were isolated. 5-Mercapto derivatives **40** were the main products in all the examined cases (Scheme 16).[23,24]



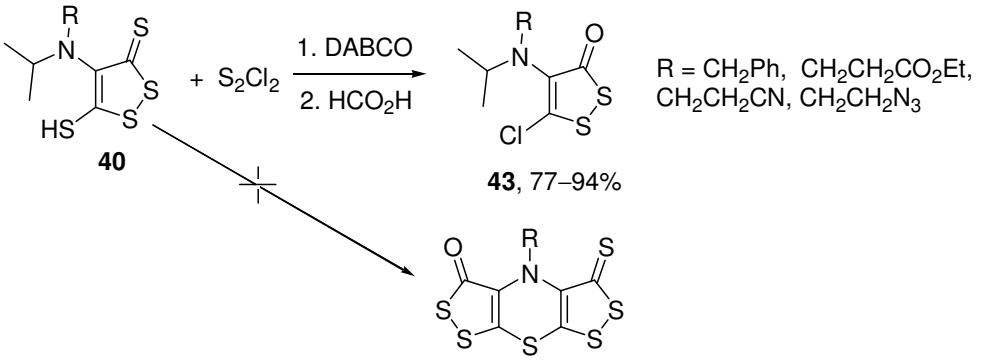
Scheme 16

Two other *N*-substituted di-*iso*-propylamines (R=CH_2CH_2Cl and CH_2CH_2Phth) in the same reaction gave fused dithiolothiazine **42** which had apparently resulted from the HCl or phthalimide extrusion from 5-mercapto-1,2-dithiole-3-thiones **40** (Scheme 17).[24]



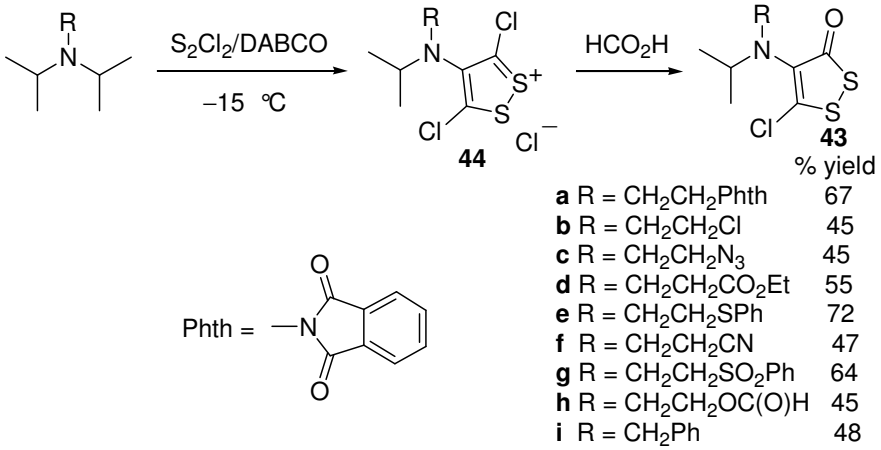
Scheme 17

Treatment of 5-mercaptodithiole thiones **40** with sulfur monochloride and DABCO, in the conditions for the synthesis of tricyclic bis-dithiolothiazines from substituted di-*iso*-propylamines (see Scheme 9), gave unexpectedly 5-chloro-1,2-dithiol-3-ones **43** in high yields (Scheme 18).[24]



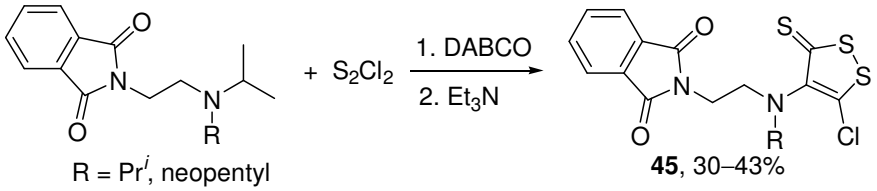
Scheme 18

Going further with the investigation in this area, we demonstrated that dithiolones **43** can be obtained from *N*-substituted di-*iso*-propylamines.[10] The suggested mechanism for all these transformations involves, as a key step, the transformation of *iso*-propyl group into 3-chlorodithiolium salt **30** (Scheme 11). The main condition for the successful synthesis of monodithioles is low temperature (−15 °C). In agreement with the proposed mechanism, the combination of an excess of sulfur monochloride over tertiary amine and DABCO is expected to yield dichlorodithiolium salt **44** from **30** which, in the presence of a oxygen nucleophile (formic acid), gives 5-chloro-dithiol-3-one **43** (Scheme 19). Our syntheses of 1,2-dithiol-3-ones under unusually mild conditions are exclusive among known relevant methods and provides new wide possibilities for the study of this promising chemical class.



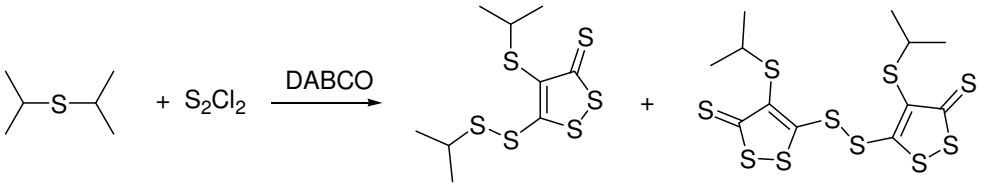
Scheme 19

Structurally similar 5-chloro-1,2-dithiole-3-thiones **45** were obtained upon treatment of *N*-(2-phthalimidoethyl)-*N*-alkyl *iso*-propylamines with sulfur monochloride and DABCO and the final reaction with triethylamine.[25] The stability of thiones **45** is explained by the dipole-dipole interaction between the electron-rich 1,2-dithiole-3-thione ring and electron-poor phthalimido group (Scheme 20).



Scheme 20

A reaction of di-*iso*-propyl sulfide with sulfur monochloride and DABCO afforded 1,2-dithiole-3-thiones **46** and **47**.[26] The dithiole cycle formation had been assumed to be similar to that produced from tertiary di-*iso*-propylamines; however, in the case of di-*iso*-propyl sulfide, only one *iso*-propyl group was activated by the initial sulfide atom; this activation was suppressed where *iso*-propyl sulfide was bound to a dithiolethione group (Scheme 21).

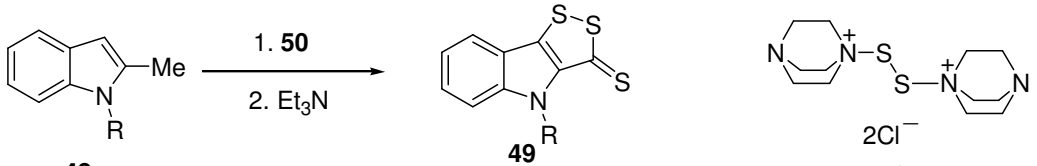


46, 33% **47**, 19%

Scheme 21

3.1.2. From other sources

We have shown (see previous Section) that *N*-*iso*-propyl groups can be converted by S_2Cl_2 into *N*-(1,2-dithiole-3-thiones). Nitrogen heterocycles containing methyl and C–H groups in *ortho*-positions, such as easily available and even commercial 2-methylindoles, are structurally similar to the *iso*-propyl group and may be considered as potential intermediates in the synthesis of dithioloindole thiones. Fused 1,2-dithole-3-thiones have never been generated from methyl heterocycles. We have found that the reaction of *N*-alkyl- and *N*-benzyl-2-methylindoles **48** with a fivefold excess of complex **50** (see below, Scheme 39) in chloroform for 48 hours at room temperature led, after treatment with Et_3N, to dithiolethiones **49** in moderate to high yields (Scheme 22).[27] *N*-Acetyl- and *N*-benzoyl-2-methylindoles did not react with S_2Cl_2 and complex **50**, even under reaction mixtures refluxing for 5 hours in chloroform; starting indoles **48** were isolated from the reaction mixtures. Apparently electron-withdrawing substituents at nitrogen in indole (acetyl or benzoyl groups) suppress the reaction with S_2Cl_2 even under more vigorous conditions.

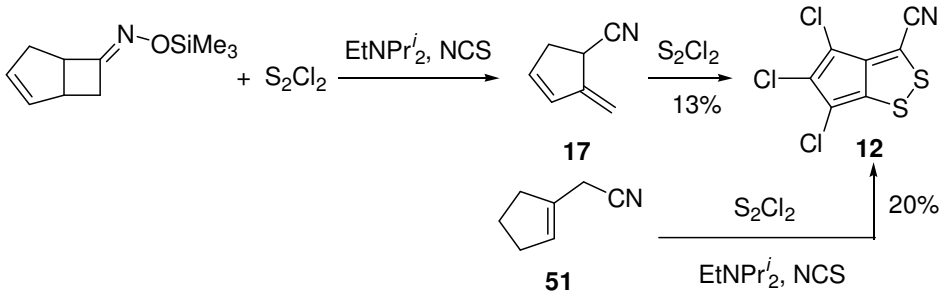


48 **49** **50**

a R = Me, 94%
b R = Et, 56%
c R = Pr^i, 66%
d R = Bn, 70%

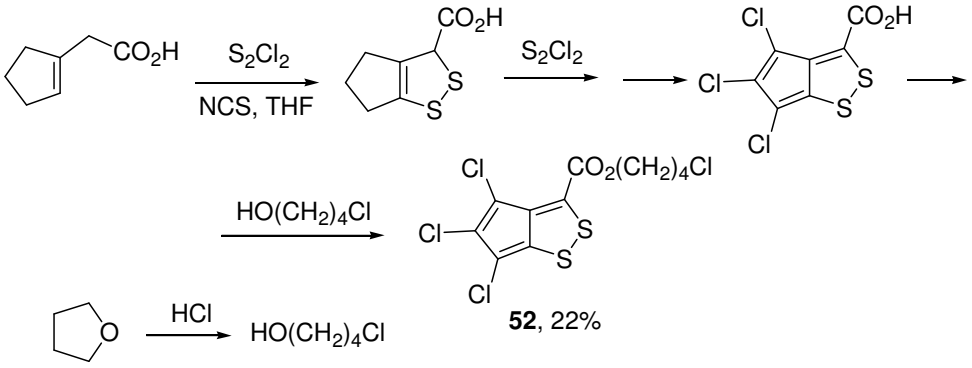
Scheme 22

A general strategy for the synthesis of 1,2-dithioles is the addition of two sulfur atoms to the –CH=C(R)–CH_n– moiety; also, non-ethylenic CH_n groups should be activated. 1-(Cyanomethyl)-cyclopentene **51** reacted with sulfur monochloride, Hünig's base and *N*-chlorosuccinimide to form perchlorinated cyclopenta-1,2-dithiole **12**.[9] The same product was obtained from *cis*-bicyclo[3.2.0]hepten-6-one oxime and, in that case, its formation was explained by the initial abnormal Beckmann rearrangement of the oxime to cyanide **17** (see Scheme 5) followed by cyclization, extensive chlorination and dehydrochlorination (Scheme 23).[9]



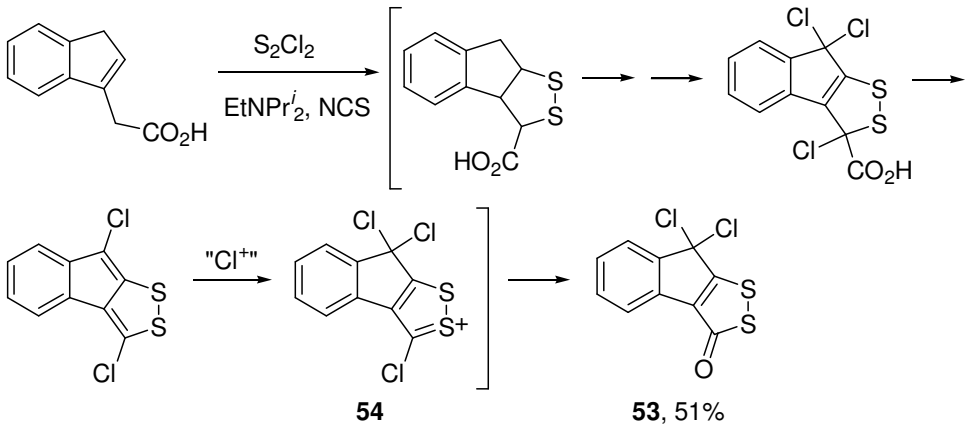
Scheme 23

Cyclopentenylacetic acid, when treated with sulfur monochloride, Hünig's base and *N*-chlorosuccinimide in tetrahydrofuran gave trichlorocyclopenta[1,2]dithiole ester **52**, a product of the heterocyclic ring formation, chlorination and dehydrochlorination and, unexpectedly, the conversion of the acid in THF into its 4-chlorobutyl ester (Scheme 24).[7]



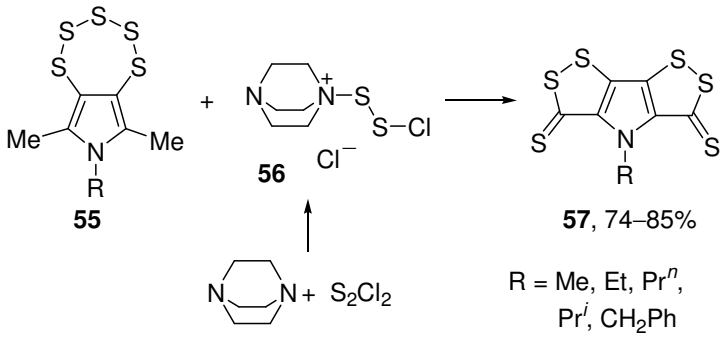
Scheme 24

In the same conditions, indenylacetic acid afforded four crystalline products, one of them (the major product) was tricyclic 1,2-dithiolone **53**.[7] A pathway to **53** can be easily envisaged (Scheme 25) based on the demonstrated propensity of sulfur monochloride, NCS and Hünig's base to form 1,2-dithiole rings with activated allylic systems followed by extensive chlorination-dehydrochlorination that resulted in fully unsaturated and chlorinated products. This suggests an acid group loss caused by the decarboxylation and, probably, the formation of 3-chloro-1,2-dithiolium chloride **54** which then reacts with some external oxygen nucleophile.



Scheme 25

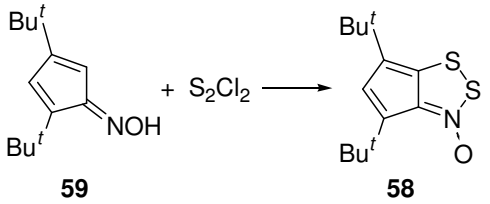
Pentathiepinopyrroles **55** were found to react with complex **56** (see below, Scheme 39) obtained from sulfur monochoride and DABCO, to give bis(dithiolo)pyrroles **57** in high yields.[28] Although pentathiepin rings and methyl groups are normally unreactive toward S_2Cl_2-DABCO at room temperature, pentathiepino-pyrroles **55** react in an extensive cascade sequence. Presumably, electron-releasing pyrrole nitrogen activated **55** to attack either the pentathiepin ring or a methyl group by the electrophilic reagent (Scheme 26).



Scheme 26

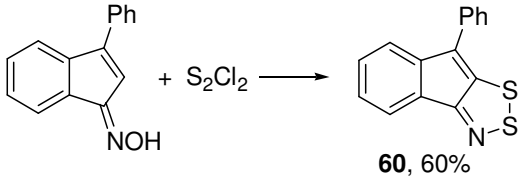
3.2. Synthesis of 1,2,3-dithiazoles

Synthesis of 1,2,3-dithiazoles from oximes is an another example of five-membered heterocycles formation with two sulfurs from sulfur monochloride. The tranformation of cyclic ketone oximes into fused 1,2,3-dithiazoles was actively studied and possibly involves the formation of dithiazole *N*-oxides. However, the only known *N*-oxide **58** was isolated from the reaction of cyclopentadienone oxime **59**, stabilized by two *tert*-butyl groups, with sulfur monochloride in tetrahydrofuran at room temperature (Scheme 27).[29]



Scheme 27

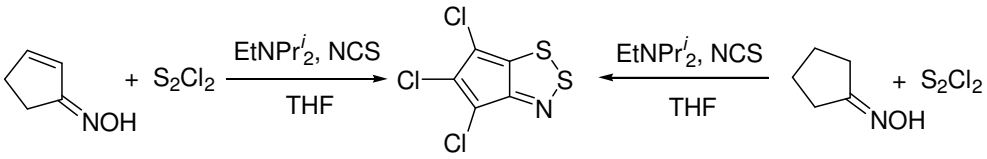
In all other reactions, corresponding 1,2,3-dithiazole *N*-oxides were only proposed as intermediates which had undergone deoxygenation. Thus, 1-oximino-3-phenylindene formed 1,2,3-dithiazole **60** (Scheme 28).[30]



Scheme 28

This reaction was further extended onto cyclopentenone and cyclopentanone oximes (Scheme 29). The greatest improvement in the syntheses was the use of *N*-ethyl di-*iso*-propylamine (Hünig's base) as a base which led to the highest yield of dithiazoles **60** (80%) and **61** (25%). The introduction of chlorine atoms into the five-membered ring, *e.g.*, dithiazole **61**, demonstrated a chlorinating capacity of sulfur monochloride and

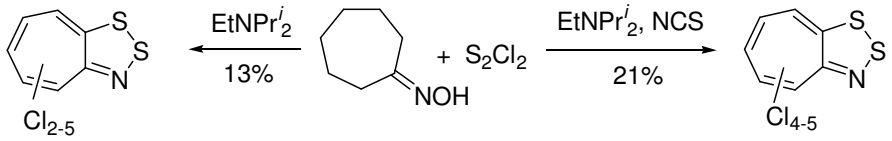
its role as an oxidant in the case of cyclopentanone and cyclopentenone oximes. Multiple chlorination, dehydrochlorination and oxidation steps in the formation of **61** suggest a complex multistage mechanism which makes the reaction sensitive to reaction conditions and may be responsible for lower yields. Where the carbon ring is protected with substituents (see Schemes 27 and 28), chlorination is prevented.



61, 25%

Scheme 29

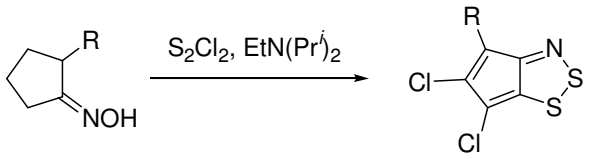
A reaction with seven-membered cyclic oximes proceeded similarly to give 1,2,3-dithiazoles **62** and **63** (Scheme 30).[30] For chlorination, up to 15 equivalents of sulfur monochloride were used and poly-chlorination was assisted by *N*-chlorosuccinimide.



62 **63**

Scheme 30

Cyclopenta-1,2,3-dithiazole system **64** was formed in a reaction of 2-substituted cyclopentanone oximes and S_2Cl_2 (Scheme 31).[31,32] Exhaustive chlorination accompanied this reaction as in the case of other cyclopentadithioles.

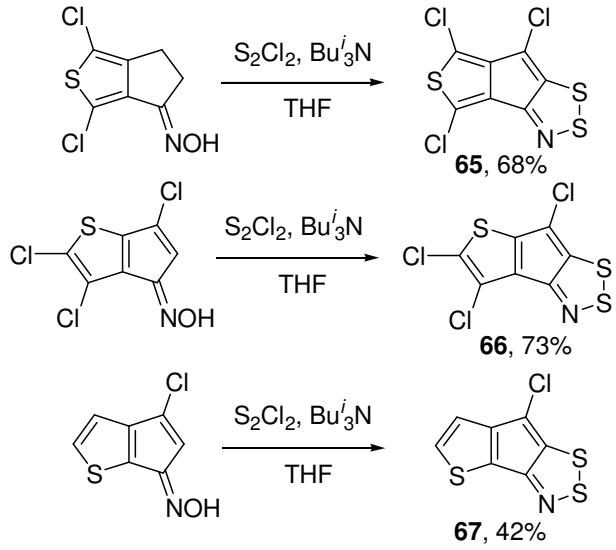


64, R = CH_2CH_2CN, 47%
R = $CH_2CH_2CO_2Et$, 16%
R = CO_2Et, 65%
R = CO_2Me, 67%

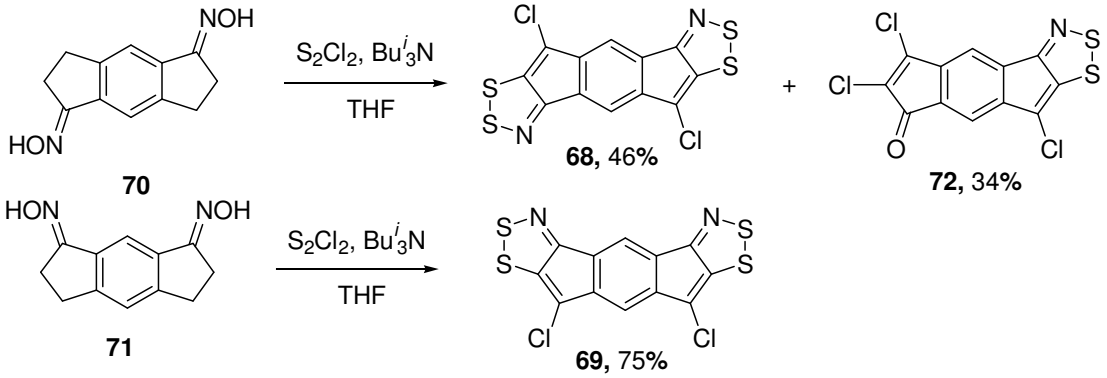
Scheme 31

Chlorine-substituted cyclopentanone oximes fused with the thiophene ring reacted with sulfur monochloride and tri-*iso*-butylamine in tetrahydrofuran at 4 °C for three days.[32] This afforded a number of the corresponding thienocyclopentadithiazoles **65–67** in moderate to high yields (Scheme 32).

The same approach was used for the synthesis of pentacyclic bis(l,2,3-dithiazolo)-*s*-indacenes **68** and **69** from 1,5- and 1,7-hydroindacenedione dioximes **70** and **71**, respectively (Scheme 33).[32] In the former case, the process was complicated by hydrolysis of one of the oxime groups leading to monodithiazole **72**.

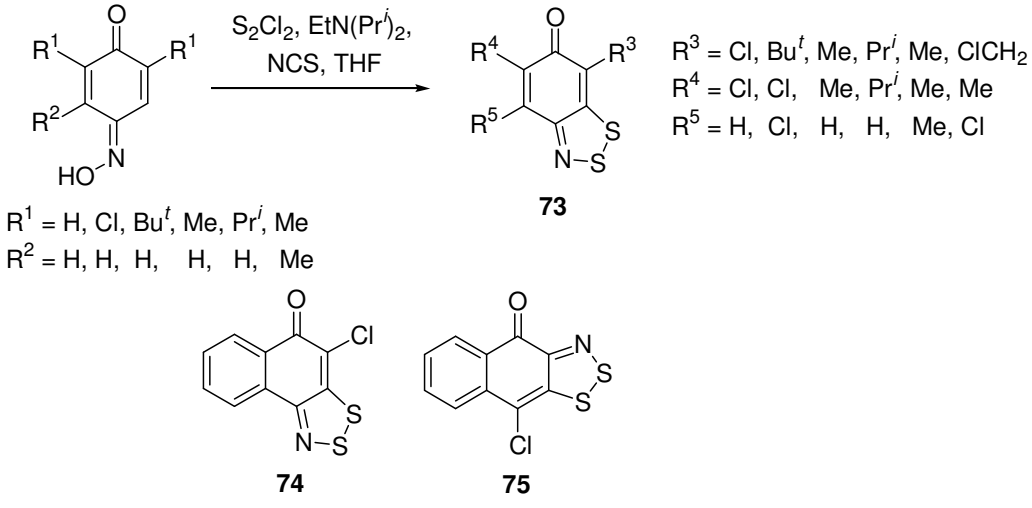


Scheme 32



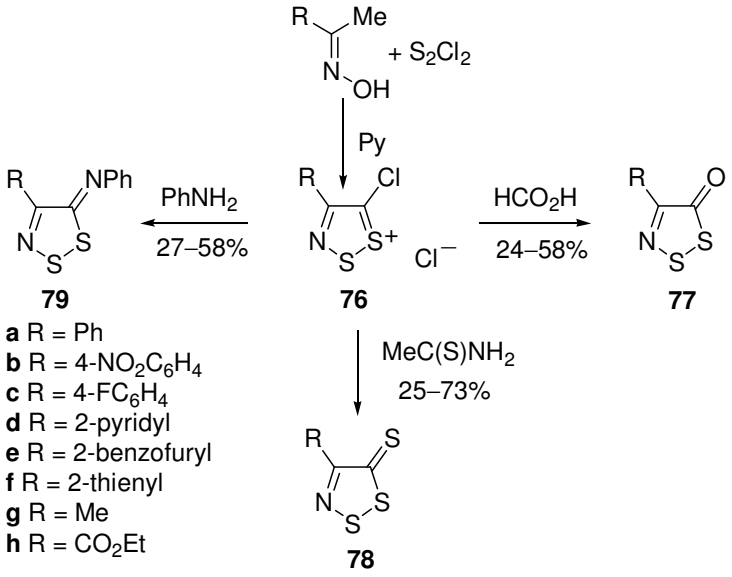
Scheme 33

6*H*-1,2,3-Benzodithiazol-6-ones **73** were prepared from *p*-benzoquinone-4-oximes, S_2Cl_2, *N*-ethyl di-*iso*-propylamine and NCS (Scheme 34).[33] Some ring chlorination occurred whereas 2,6-substituents retained in the products except for the *tert*-butyl group, which was exceptionally replaced by chlorine. 1,4-Naphthoquinone 4-oxime and 1,2-naphthoquinone 2-oxime similarly gave dithiazole derivatives **74** and **75**.[33]



Scheme 34

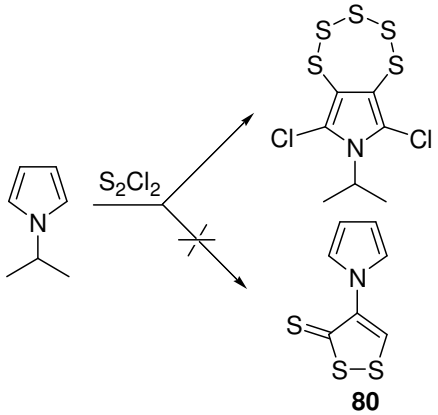
Various 4-substituted 1,2,3-dithiazolium chlorides **76** were synthesized from the reaction of ethanone oximes with sulfur monochloride and pyridine in acetonitrile. These salts were found to be unstable and were converted *in situ* to stable 5-one **77**, 5-thione **78** and 5-phenylimino-1,2,3-dithiazoles **79** by treatment with corresponding nucleophiles (formic acid, thioacetamide and aniline, respectively) in high to moderate yields (Scheme 35).[34]



Scheme 35

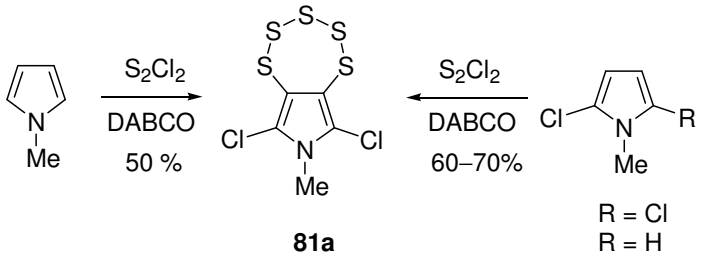
4. Insertion of five sulfur atoms – synthesis of fused 1,2,3,4,5-pentathiepins

If in the reaction with S_2Cl_2 two neighboring carbon atoms were involved, five sulfur atoms have been incorporated in the molecule and fused 1,2,3,4,5-pentathiepins were formed.[35] We have found that the treatment of simple nucleophilic heterocycles like pyrroles and thiophene and their tetrahydro-derivatives with sulfur monochloride and DABCO provided a simple one-pot synthesis of mono and bispentathiepins. Actually this new transformation was discovered by pure accident when we investigated the reaction of *N-iso*-propylpyrrole with sulfur monochloride trying to obtain *N*-1,2-dithiole-3-thione **80**. But pyrrole ring found to be more reactive than the *iso*-propyl group (Scheme 36). This unusual reaction could thus provide an attractive route to fused pentathiepins and we have studied this reaction systematically to find the best reaction conditions and to explore its scope.



Scheme 36

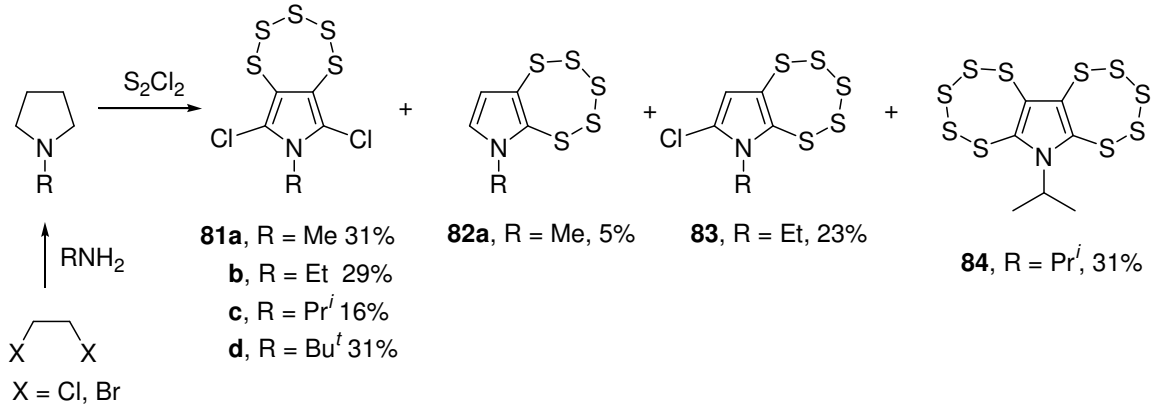
The reaction of *N*-methylpyrrole with sulfur monochloride and DABCO gave dichloropyrrolopentathiepin **81a** in best conditions in 50% yield.[35] In the formation of **81a** from *N*-methylpyrrole, a pentathiepin ring has been fused to the pyrrole ring and both α-positions of pyrrole have been chlorinated. It is not surprising that 2,5-dichloro- and 2-chloropyrroles gave in the same way pyrrolopentathiepin **81a** even in higher yields (Scheme 37).



81a

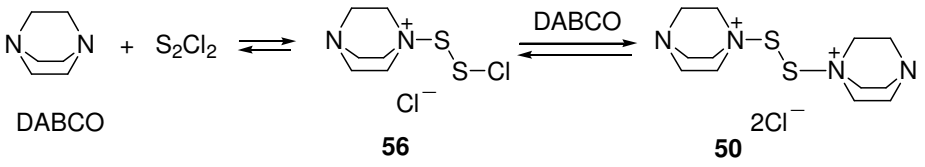
Scheme 37

Since S_2Cl_2 could also, in principle, oxidize the pyrrolidine to pyrrole ring, we studied the same reaction of *N*-alkyl derivatives of pyrrolidine, which are readily available from dichloro- or dibromo-butanes and corresponding amines. *N*-Methyl-, *N*-ethyl, *N*-*iso*-propyl- and *N*-*tert*-butyl-pyrrolidines all gave the corresponding *N*-alkyl dichloropentathiepinopyrroles **81** as the main product in low to moderate yield (16–31%).[12] Additionally, *N*-methylpyrrolidine gave a small amount (5%) of unchlorinated compound **82a** with the pentathiepin ring fused across the 2,3-pyrrole bond, *N*-ethylpyrrolidine - monochlorinated product **83** and *N*-isopropylpyrrolidine - bispentathiepin **84**, which is the first and only known so far bispentathiepin (Scheme 38).



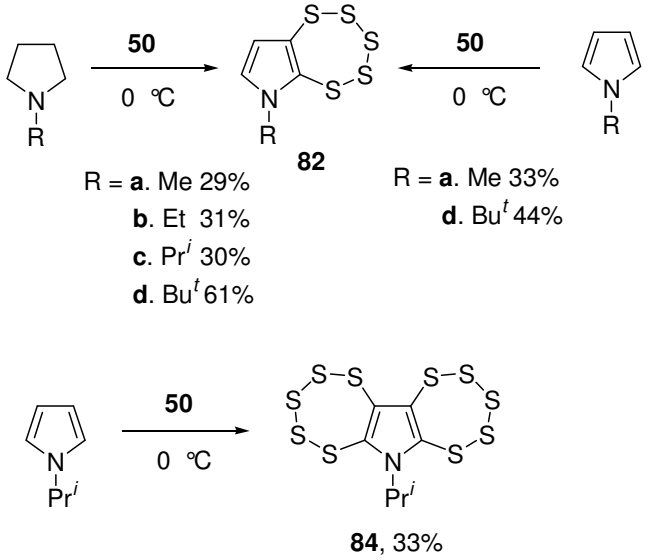
Scheme 38

Sulfur monochloride has acted simultaneously as sulfurating (formation of pentathiepin ring) and chlorinating (chlorination of pyrrole ring) agent. Also, where there was more than one site for fusion of the new polysulfur ring, these reactions were not regioselective and were sensitive to the heterocycle nature and reaction conditions.[12,36] Recently, it was found that a mixture of S_2Cl_2 and DABCO in chloroform, stored for 48 hours at 0 °C or 1 hour at room temperature before use, formed complexes **56** (1:1 mixture of S_2Cl_2 and DABCO) and **50** (1:2 mixture of S_2Cl_2 and DABCO) (Scheme 39).[36] These complexes could exhibit well different reactivities, since **56** is a potential Cl^+ and $^+S–SCl$ source and could be an electrophilic chlorinating and sulfurating agent, whilst **50** should react only as the latter.



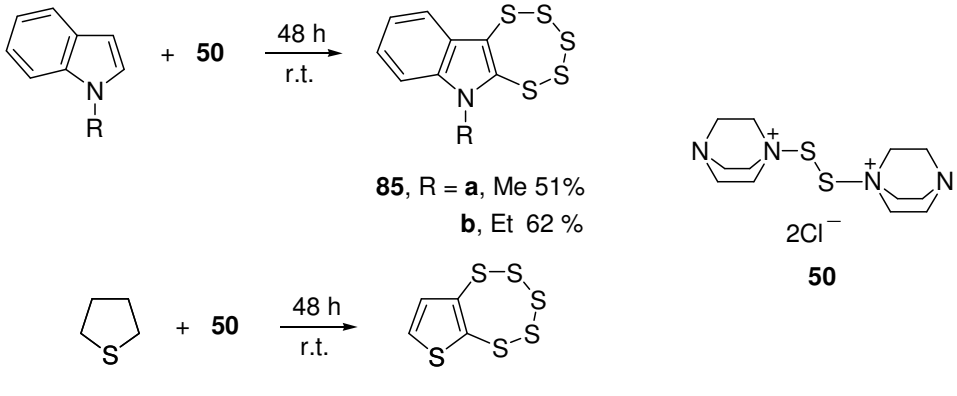
Scheme 39

Indeed, the reaction of *N*-alkylpyrrolidines with complex **50** gave selectively the *N*-alkyl-pentathiepinopyrroles **82** in moderate yields; no chlorinated products were detected in any of these reactions. The same products were obtained from *N*-alkylpyrroles, but in that case it is necessary to use a lower amount of complex **50** to get selective process and the yields of pentathiepins were compatible with those obtained from pyrrolidines. *N-iso*-Propylpyrrole gave selectively bispentathiepin **84** (Scheme 40).[36]



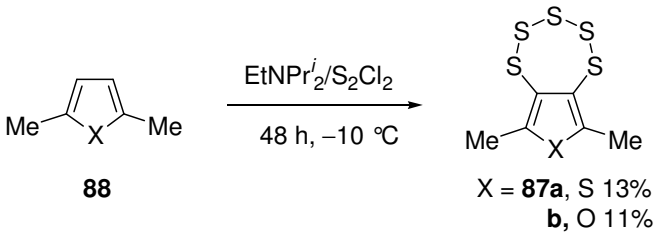
Scheme 40

We tried to spread these reactions to other heterocycles. *N*-Alkylindoles reacted, as pyrroles, to give pentathiepins **85** in moderate yields (Scheme 41). Tetrahydrothiophene also afforded corresponding thienopentathiepin **86** in rather good yield.[36] Unfortunately, more aromatic heterocycles such as thiophene, benzothiophene and furan did not react with complex **50**.



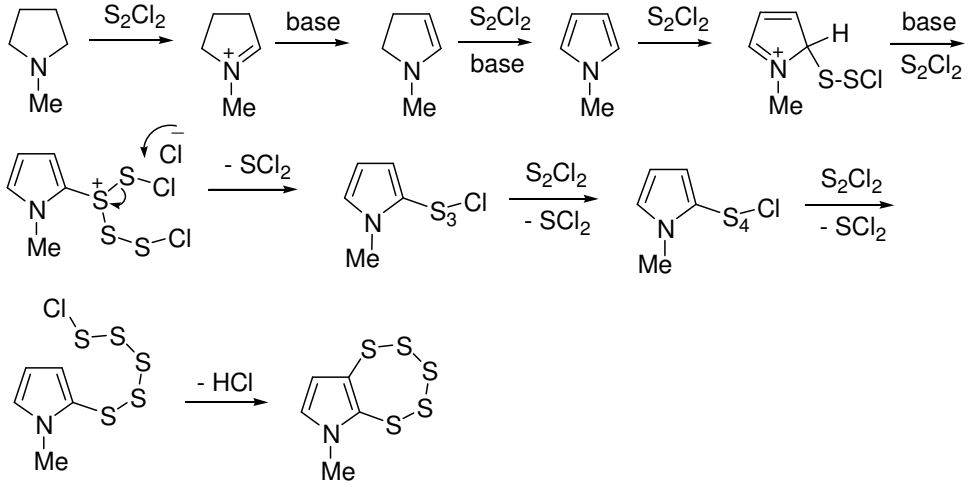
Scheme 41

Even milder conditions were used for the preparation of thienopentathiepin **87a** and pentathiepinofuran **87b** from corresponding heterocycles **88**.[37] A reaction of these heterocycles with the mixture of sulfur monochloride and *N*-ethyl di-*iso*-propylamine at low (−10 °C) temperature gave pentathiepins **87** although in low yields (Scheme 42).



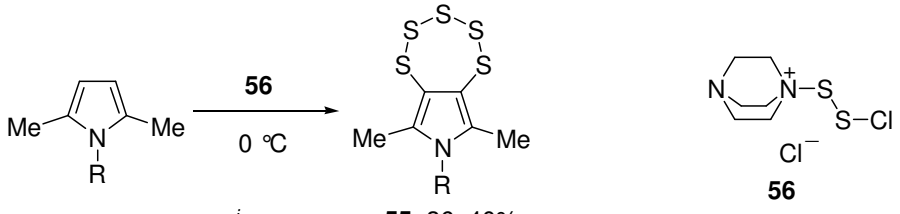
Scheme 42

Various, fairly complex, cascade reactions described above converted simple saturated and aromatic heterocycles into polycyclic pentathiepins and their chlorinated derivatives; this fact strikingly illustrates extensive reactivity of S_2Cl_2 and its complexes with bases, particularly DABCO. This reactivity includes dehydrogenation of tetrahydroaromatics, chlorination, sulfuration and pentathiepin ring formation. It was proposed that $-S_nCl$ chains could be extended to give $-S_{(n+1)}Cl$ chains by the S_2Cl_2 addition and SCl_2 loss and, ultimately, the thermodynamically stable[38] pentathiepin ring. A typical mechanism is presented in Scheme 43.[12]



Scheme 43

If the α-positions of pyrrole are substituted by methyl groups, the pentathiepin ring is fused across the 3,4-pyrrole bond to give pentathiepinopyrroles **55** in moderate yield.

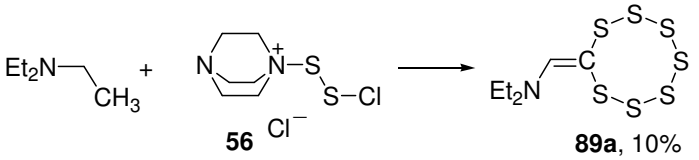


Scheme 44

We have investigated the synthesis of pentathiepinopyrroles from 2,5-dimethylpyrroles, which are readily available from acetonylacetone and amine, and found that the best yields were obtained if we used as a reagent complex **56** at low temperature (0 °C).[28] The pentathiepins **55** were isolated in moderate yields (Scheme 44).

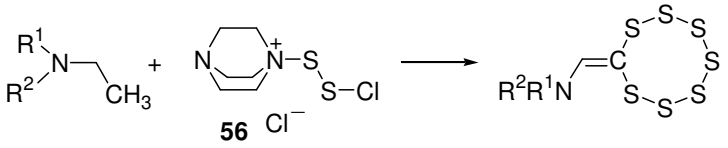
5. Insertion of seven sulfur atoms – synthesis of 1,2,3,4,5,6,7-heptathiocanes

As a rule, usually more than one carbon atom in substrate is included in the transformation. The only known example is the reaction of tertiary *N*-ethylamines with complex **56** produced from S_2Cl_2 and DABCO. If triethylamine was treated with this complex, heptathiocane **89a** was isolated in 10% yield (Scheme 45).[39] The structure of **89a** was confirmed by X-ray analysis. The heptathiocane ring has the expected crown conformation close to the conformation of stable elemental sulfur.



Scheme 45

Given that these are reactions of the ethyl group, Et_3N should be a favoured substrate; the same reactions were observed with other tertiary *N*-ethylamines but in lower yields. Diethyl *n*-propylamine, ethyl-di-*iso*-propylamine, benzyldiethylamine, dibenzylethylamine and *N*-ethylpiperidine all gave corresponding heptathiocanes **89** in low yields 3–10% (Scheme 46). Whilst the yields of heptathiocanes **89** were mostly low, they are readily prepared in one pot from cheap starting materials.[39]



R^1 = Et, R^2 = Pr; R^1 = R^2 = Pr^i; R^1 = Et, R^2 = Bn
R^1 = R^2 = Bn; R^1, R^2 = -$(CH_2)_4$-

Scheme 46

6. Conclusions

The reactions described show that sulfur monochloride is an important reagent for the synthesis of heterocyclic systems with various number of sulfur atoms which in many cases are not easy, or impossible to obtain by conventional ways. The interesting characteristics found in many of these heterocycles, rapid synthetic methods from easily available materials and the huge variety of products obtained by these methods looks very promising for further development of this chemistry. The limit of this chemistry is difficult to foresee.

Acknowledgments

We gratefully acknowledge financial support from the Royal Society, the Russian Foundation for Basic Research (grants No. 99-03-32984, 05-03-32032, 08-03-00003-a) and the Royal Society of Chemistry (Research Fund Grants).

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INTRAMOLECULAR CARBOLITHIATION REACTIONS OF ARYLLITHIUMS IN THE SYNTHESIS OF CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS

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Abstract. *The intramolecular carbolithiation of alkenes and alkynes has become an interesting approach for the synthesis of functionalized carbocyclic and heterocyclic systems due to the high regio- and stereoselectivity when a carbon-carbon bond is formed and to the possibility of trapping the resulting cyclized organolithium with various electrophiles to introduce diverse functionality into the cyclized products. Synthetic applications of cycloisomerization of alkenyl and alkynyl substituted aryl- or heteroaryl-lithiums generated by metal-halogen exchange are surveyed.*

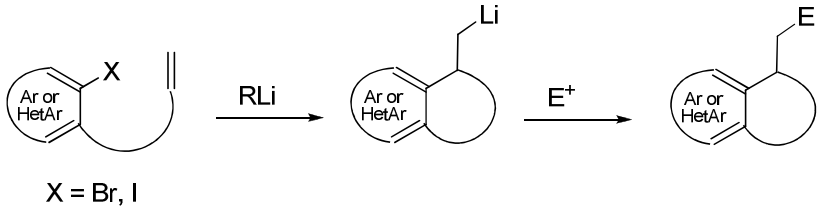
Contents

1. Introduction

The synthetic utility of lithium-halogen exchange reaction[1] for the metalation of aromatic substrates, though mechanistically controversial,[2] has been shown in the facile construction of benzo-fused cyclic ring systems *via* intramolecular reaction of the so-generated aryllithium compounds with internal electrophiles,[3] a metalation-cyclization process known as Parham cyclization.[4] In addition to the carbon-carbon bond formation, the halogen-lithium exchange reaction allows the preparation of highly functionalized aryl- or heteroaryllithiums, so polysubstituted aromatic compounds can be prepared in a single step.

On the other hand, the intramolecular carbolithiation of alkenes and alkynes has recently emerged as an interesting approach for the synthesis of functionalized carbocyclic and heterocyclic systems. The attraction of this methodology lies in the high regio- and stereoselectivity when a carbon-carbon bond is formed and in the possibility of trapping the resulting cyclized organolithium with various electrophiles to introduce diverse functionality into the cyclized products.[5] To generate the organolithium in the presence of the internal alkene or alkyne, different approaches have been used, as deprotonation, tin-lithium exchange, selenium-lithium exchange[6] or reductive lithiation.[7] Although many of these carbolithiations involve alkyl or alkenyllithiums,[8] there are also some examples of cycloisomerization of alkenyl-substituted aryl- or heteroaryllithiums generated by metal-halogen exchange. Thus, these carbolithiation reactions could be viewed as a type of

Parham cyclization. The combination of the versatility of the halogen-lithium exchange reaction and the possibility of further functionalization and stereoselectivity associated with the carbolithiation reactions opens new strategies that can play a crucial role in natural products synthesis (Scheme 1). This anionic cyclization represents an interesting alternative to radical ones, as allows an easier functionalization after cyclization and generally higher stereochemical control.

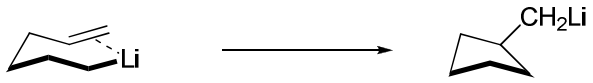


Scheme 1

The present review will survey some recent advances in the application of intramolecular carbolithiation reactions of aryl- and heteroaryllithiums generated by halogen-lithium exchange.[9] The review will not attempt to provide exhaustive coverage of the literature, but it is intended to focus on the most interesting developments in its application to the synthesis of heterocyclic systems, including our results on the subject.

2. Synthetic applications of the intramolecular carbolithiation reaction of aryllithiums

The cycloisomerization of an olefinic organolithium can be modeled by the cyclization of 1-hex-5-enyllithium to generate cyclopentylmethyllithium (Scheme 2). Mechanistic studies[10] indicate that the stereochemical outcome of these reactions is related to a rigid chair-like transition state, in which the lithium atom is coordinated to the π-bond.[11] According to this proposal, the cycloisomerization would occur with retention of configuration at C-1, through a *syn* addition to the π-bond.[12]



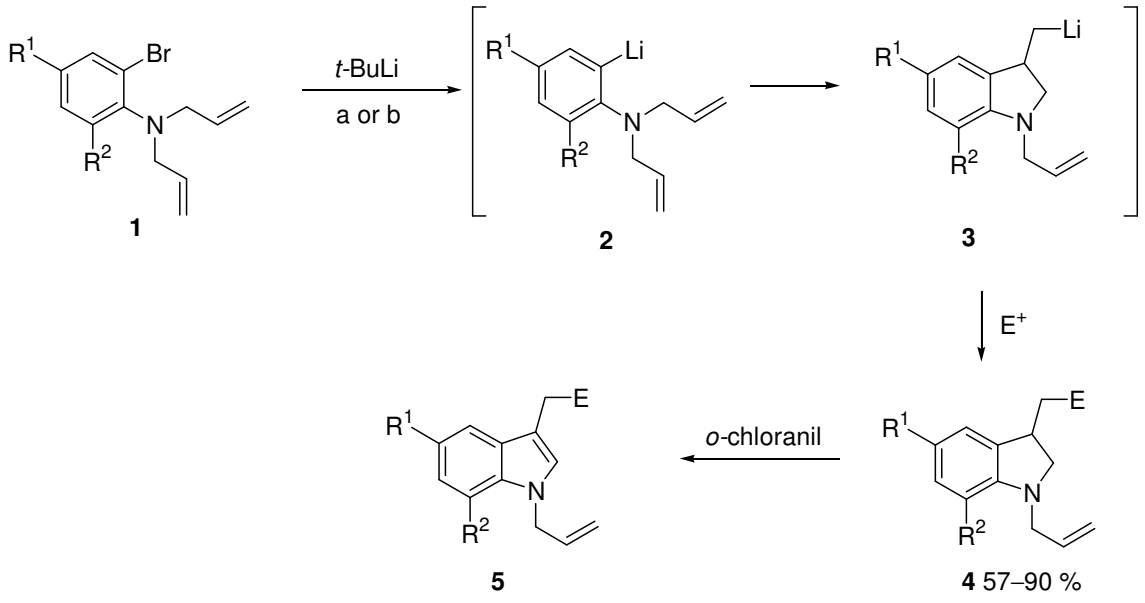
Scheme 2

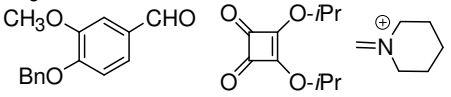
Intramolecular carbolithiation reaction of unsaturated aryllithiums is particularly well suited for the construction of five-membered rings through a 5-*exo*-trig or 5-*exo*-dig cyclization process, depending on the character of the unsaturation (double or triple bond), as it has been shown in the synthesis of carbocyclic and heterocyclic compounds, even in a diastereoselective or enantioselective fashion. However, some limitations have precluded the general applicability of this method as it remains unclear whether cyclization to six-membered cycles would provide the same degree of stereo- and regiochemical efficiency. Thus, some recent interesting examples will be discussed according to the size of the ring formed, and paying special attention to the stereoselectivity.

2.1. Formation of five-membered rings

Liebeskind[13] and Bailey[14] showed independently that *N*-allylindolines possessing a variety of substitution patterns can be rapidly constructed by an anionic cyclization of readily available *o*-bromo-*N,N*-

diallylanilines. Thus, anilines **1** were treated with 2 equivalents of *t*-BuLi in *t*-butyl methyl ether (TBME) at −78 °C. Protonation or electrophile trapping of the intermediate 3-(lithiomethyl)indolines **3** provided a variety of 3-methylindolines **4** in good to high yields. The indolines were carried forward to their respective 3-methylindoles **5** by treatment with *o*-chloranil. Deallylation of the nitrogen atom on various indolines **4** was also performed with catalytic $Pd_2(dba)_3$/dppb.[13]



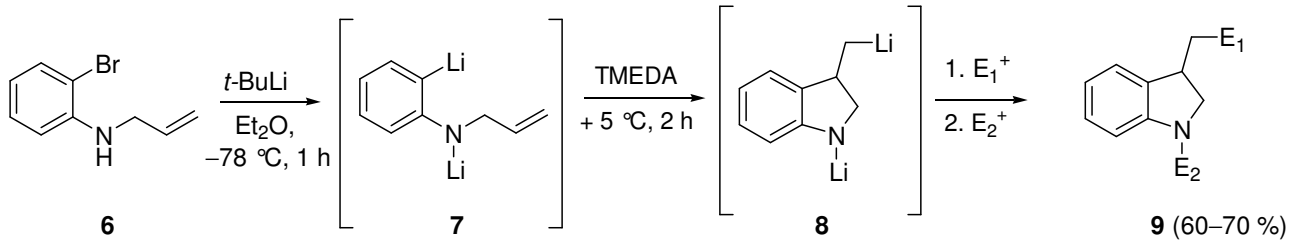
a: (Ref 13) 1. *t*-BuLi, *t*-BuOMe, −78 °C to rt
2. E^+
R^1 = H, CH_3, OCH_3, N(allyl)$_2$
R^2 = H, OCH_3
E^+ = H_2O, 

b: (Ref 14) 1. *t*-BuLi, pentane/Et_2O, −78 °C
2. TMEDA, −78 °C to 0 °C
3. E^+
R^1 = H, CH_3
R^2 = H
E^+ = CH_3OH, CH_3OD, $(CH_3)_3SiCl$, Bu_3SnCl, $(CH_3)_2NCHO$, $(CH_3)_3CCHO$, $Br(CH_2)_2Br$ $(CH_2O)_n$, $ClCO_2Et$

Scheme 3

Bailey[14] has shown that the 5-*exo* cyclization of the aryllithium **2**, generated by bromine-lithium exchange with *t*-BuLi, is a facile process that does not require the presence of TMEDA. Indeed, substituted indolines were prepared in the absence of the additive, with some loss of yield, by allowing solutions of the aryllithium in *n*-pentane-diethyl ether to warm and stand at room temperature for 1 hour prior to the addition of the electrophile. The use of TMEDA to facilitate the isomerization is, however, the recommended procedure. Otherwise, a portion of the organolithium product **3** may be quenched by proton abstraction from the solvent at the high temperatures needed to effect cyclization of **2** in the absence of the additive.

The possibility of functionalization both at 1- and 3- positions of the indoline nucleus after cyclization has led to a more versatile route to these heterocycles.[15] Thus, treatment of **6** with 3 equivalents of *t*-BuLi at –78 ºC provided a dilithium species **7**, whose cyclization was accomplished by addition of TMEDA and warming to +5 ºC. Differential functionalization of **8** was achieved in high overall yields (60–70%) by sequential addition of two electrophiles ($E^1 \neq E^2$) (Scheme 4).



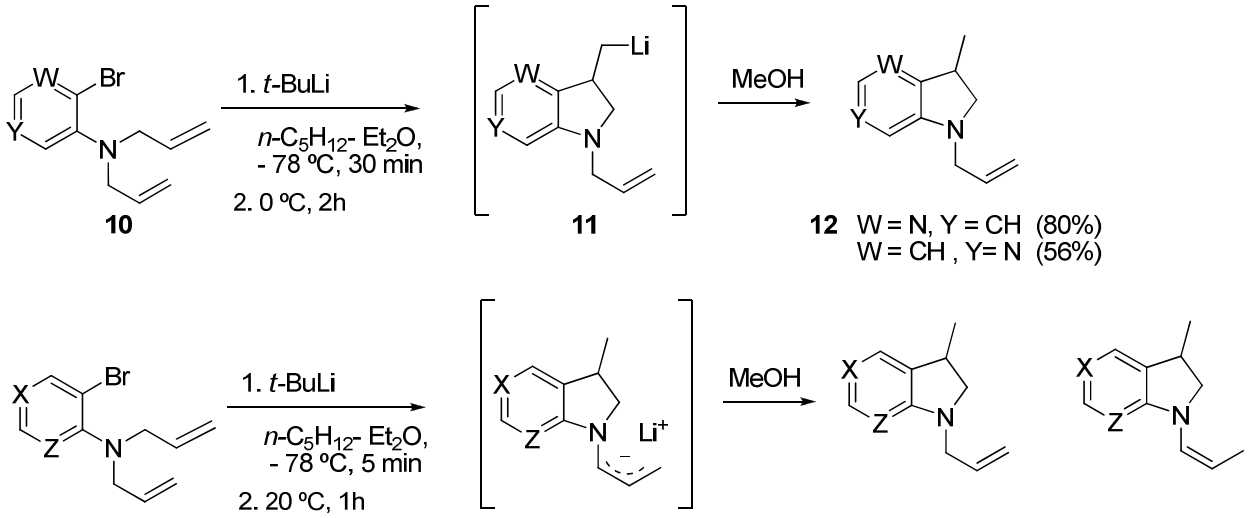
6 **7** **8** **9** (60–70 %)

E_1^+= MeOH, $(MeO)_2SO_2$, AllylBr, EtOH, TMSCl

E_2^+= MeOH, $(MeO)_2SO_2$, AllylBr, EtOAc, EtOBz, $(Boc)_2O$

Scheme 4

The procedure has been extended to heteroaryllithiums, providing access to 3-substituted 4-, 5-, 6- and 7-azaindolines (Scheme 5).[16] While cyclization of anilines **10** proceeded as expected to give 1-allyl-3-methyl indolines **12** in reasonable yields, after protonation of **11**, the cyclization of anilines **13** followed an unanticipated course. As shown, two isomeric azaindolines were isolated: the expected 1-allylazaindolines **15** were the minor products and enamines **16**, largely the *Z*-isomers. A series of experiments showed that, although the ring closure of the aryllithium derived from **13** was accelerated in the presence of TMEDA, the enamines **16** were the major products under all conditions. Both **15** and **16** are supposed to derive from a common precursor, a *Z*-configured allylic anion **14**, generated from the initial cyclization product *via* proton transfer.



10 **11** **12** W = N, Y = CH (80%); W = CH , Y= N (56%)

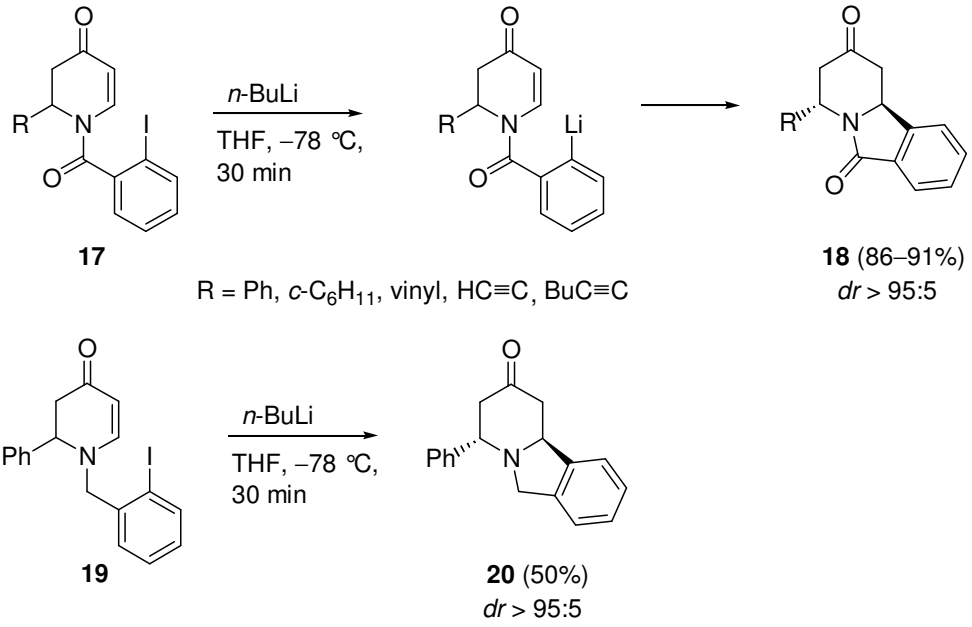
13 **14**

	15	**16**
a X = N, Z = CH	27%	43%
b X = CH , Z= N	22%	70%

Scheme 5

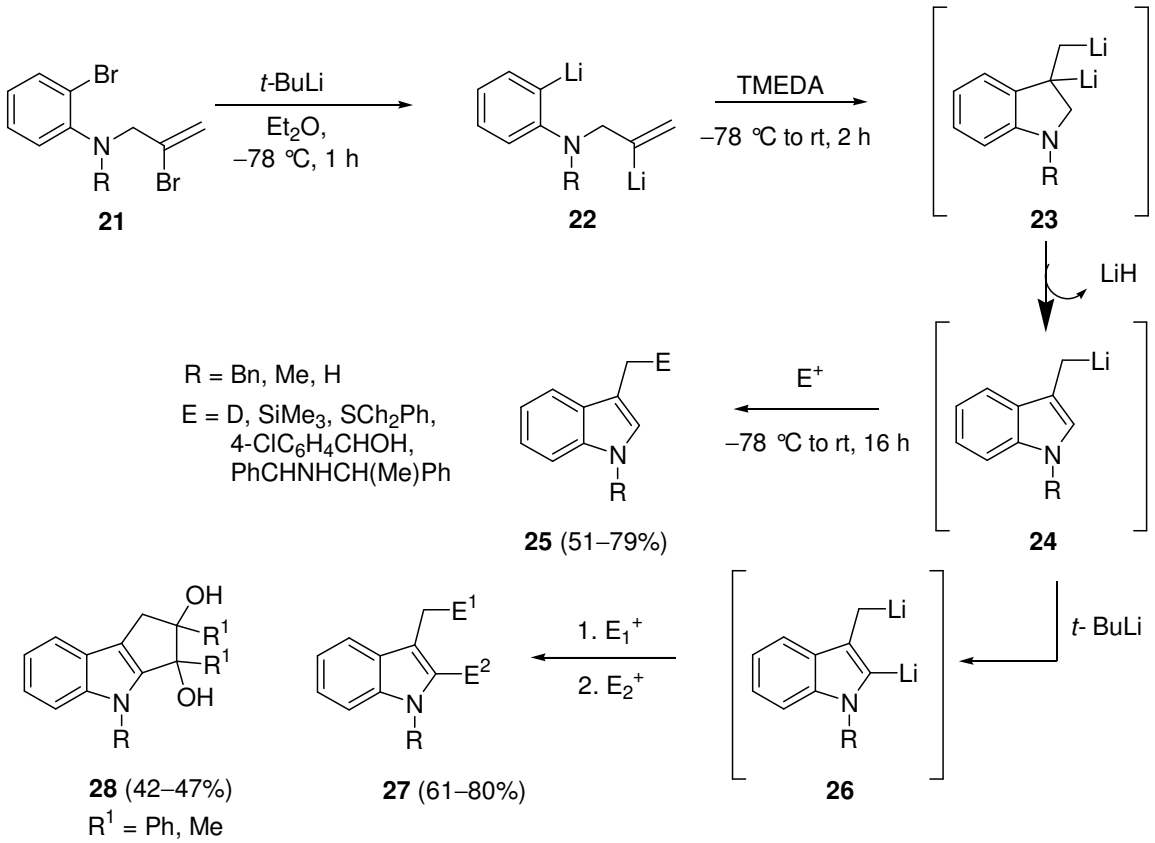
When the alkene was substituted by an electron withdrawing group, the cyclization was faster even at low temperature (Scheme 6). Thus, fast lithium-iodine exchange in the presence of an enaminone moiety occurred when *N*-acyl-2,3-dihydro-4-pyridones **17** were treated with *n*-BuLi at –78 °C. The subsequent cyclization occurred at the same temperature in only 30 minutes, with complete control of the stereochemistry, to give pyrido[2,1-*a*]isoindolediones **18** as single *trans* diastereomers. The same reaction could be applied to the corresponding benzyl derivative **19**, although it took place in lower yield. It is

noteworthy that, under radical cyclization conditions, **20** was obtained as a mixture of diastereomers 3:1 in favour of **20**.[17]



Scheme 6

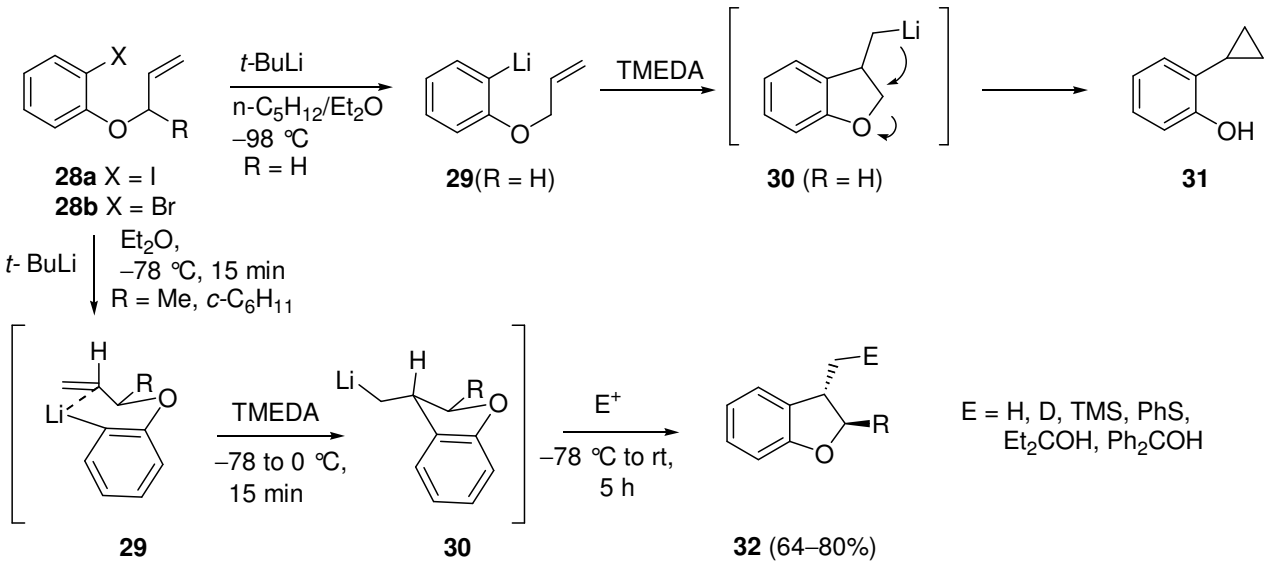
Barluenga[18] has shown that it is also possible to carry out the carbometalation of lithiated double bonds promoted by TMEDA (Scheme 7).



Scheme 7

Thus, bromine-lithium exchange on bromoanilines **21** afforded a dianion **22**, which, under treatment with TMEDA, underwent intramolecular carbometalation of the vinyllithium moiety by the aryllithium to afford dilithiated indolines **23**. Subsequent elimination of LiH generated 3-lithiomethylindoles **24**, which were reacted with different electrophiles to obtain functionalized indole derivatives **25**. The procedure can also be applied to the synthesis of *N*-unsubstituted indoles. Thus, treatment of the secondary amine **21** (R=H) with *t*-BuLi gave the corresponding trianion **22** (R=Li). Cyclization of this trianion required refluxing for 3 hours to obtain the indole derivatives **25** in good yields. When **21** was treated with an excess of *t*-BuLi (5 equivalents), lithiation of the 2-position was also observed leading to dianions **26**, that could be trapped sequentially with different electrophiles. Treatment of **26** with 1,2-diketones afforded cyclopent[*b*]indole derivatives **24** as single diastereomers.

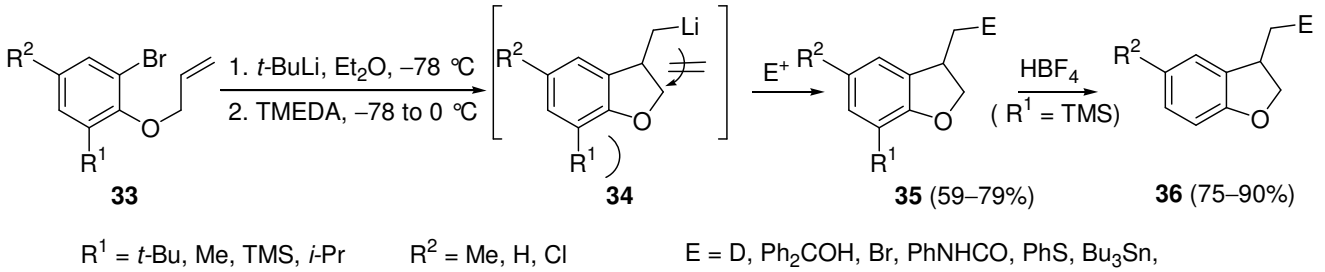
Carbolithiation is also useful for the synthesis of fused furan systems, though the substitution pattern of the allyl ether precursor is determinant. As shown on Scheme 8, aryllithium **29**, obtained by iodine lithium exchange on **28a** (R=H), underwent a 5-*exo* cyclization, to afford the 3-lithiomethyl-2,3-dihydrofuran **30**. This organolithium, however, in the presence of TMEDA was not stable enough to be trapped by electrophiles and rapidly isomerized *via* a cyclization-elimination sequence, yielding 2-cyclopropylphenol **31**.[19] This elimination process could be avoided in the presence of a substituent in the α-position of the allyl moiety.[20] Thus, treatment of **28b** (R=Me, cyclohexyl) with *t*-BuLi in Et_2O at –78 ºC, followed by TMEDA and warming to 0 ºC, afforded, after treatment with different electrophiles, the corresponding *trans*-2,3-dihydrobenzofurans **32**, with total diastereoselectivity. This fact could be explained assuming that the cyclization took place *via* a chair-like transition state that resembles the geometric disposition depicted for intermediate aryllithium **29**, in which the substituent preferentially occupies the pseudoequatorial position. When the reaction was applied to enantiomerically pure (*R*)-**28b** (R=Me), the corresponding (2*R*,3*S*)-dihydrobenzofurans were obtained in good yield and high *ee* (96%).



Scheme 8

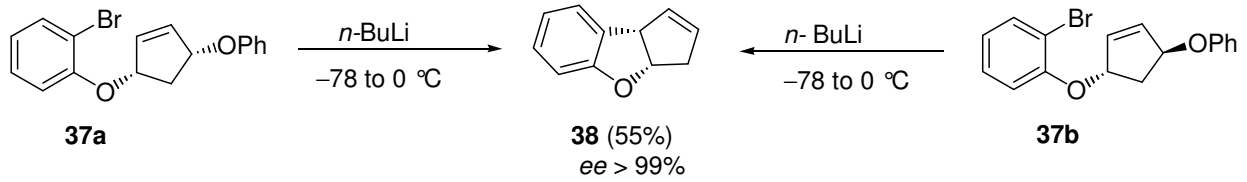
Substitution at the 6-position of the aromatic ring also prevents the isomerization of the lithiomethyldihydrofuran and functionalized 2,3-dihydrobenzofurans could be prepared from simple 2-propenyl ethers **33** (Scheme 9). Thus, the substituent at the 6-position could exert a stereoelectronic effect

that inhibits the 1,3-elimination in the intermediate organolithium **34**. The TMS group could be removed under mild conditions, leading to benzofurans **36** with no substituent at 2- and 7-positions.[20]



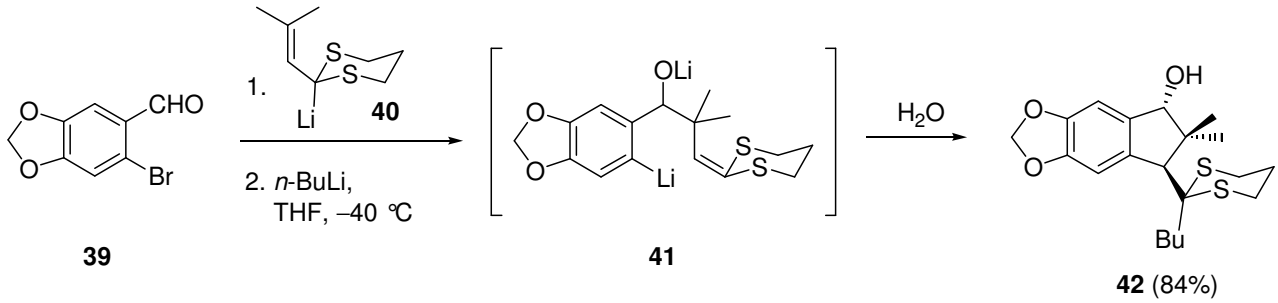
Scheme 9

As shown in the previous examples, the generally high stereocontrol of the carbolithiation reactions allowed the preparation of enantiomerically pure products when chiral non-racemic precursors were used. Thus, ciclopenta[*b*]benzofurans **38** were obtained in moderate yield and high *ee*. The intermediate aryllithium cyclized through an S_N2' pathway with complete diastereoselectivity (Scheme 10), regardless the C-4 configuration of the cyclopentane.[21]



Scheme 10

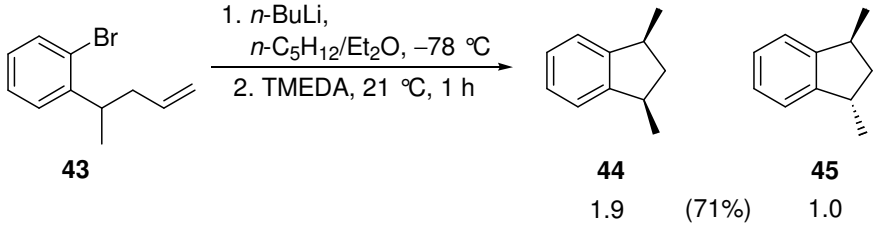
Fused cyclopentane systems have been efficiently prepared by this anionic cyclization, also in a stereoselective fashion. Harrowven reported the addition of a 2-lithio-2-vinyl-1,3-dithiane **40** to a bromo-benzaldehyde **39**, leading to a ketenedithioacetal (Scheme 11). Addition of *n*-BuLi effected the bromine-lithium exchange reaction, followed by an intramolecular 5-*exo*-trig cyclization onto the ketenethioacetal moiety, leading to an indane. Subsequent *in situ* alkylation of this intermediate with the alkylbromide, generated as a consequence of transmetalation, then completed the sequence to the *trans* substituted indane **42**.[22]



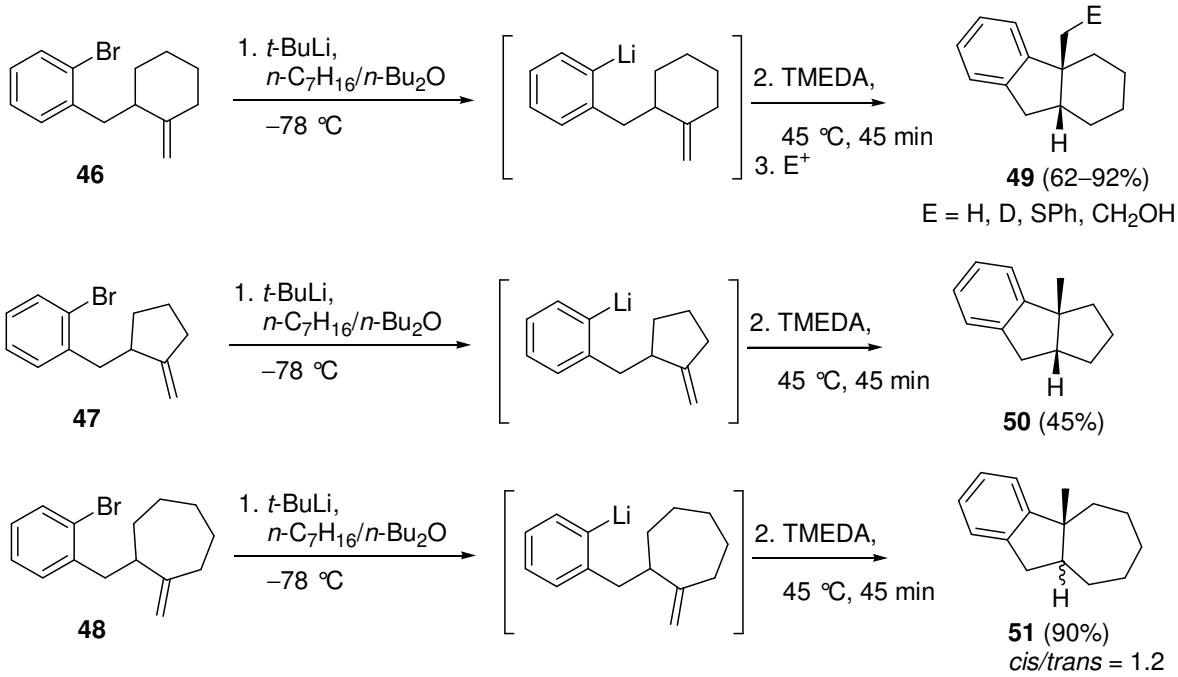
Scheme 11

The preparation of 1,3-dimethylindanes has been achieved with modest diastereoselectivity from 4-(2-bromophenyl)-1-pentene. The aryllithium cyclized cleanly in the presence of TMEDA upon warming to

room temperature (Scheme 12).[23] On the other hand, the cyclization of an aryllithium tethered to a methylenecycloalkane, generated from 2-(*o*-bromobenzyl)-1-methylenecycloalkanes **46**, **47** and **48** by low-temperature lithium-bromine exchange, has been found to be a kinetically slow but thermodynamically favourable process that proceeds at a convenient rate in an exclusively 5-*exo* fashion, when solutions of the aryllithium in *n*-heptane/di-*n*-butyl ether (9:1 v/v) were warmed to 45 °C. The use of this mixture of solvents is important to minimize proton abstraction due to the high temperature required for the cyclization. The resulting organolithium could be trapped with different electrophiles to obtain 4*a*-substituted *cis*-hexahydrofluorenes **49** in high yield (Scheme 13).[24]

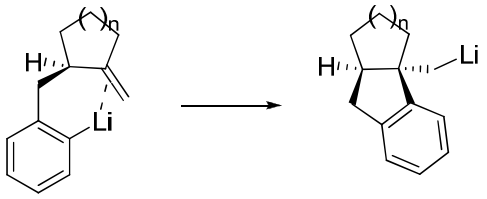


Scheme 12



Scheme 13

As shown on Scheme 13, pure *cis*-fused products **49** and **50** were obtained when the methylene-cycloalkane is five- or six-membered but it is less stereoselective when the methylenecycloalkane is seven-membered. As stated before, this stereochemical outcome is due to the fairly rigid geometry of the transition state for the ring closure and the conformational constraints of these substrates. Thus, coordination of the lithium atom with the methylene π-bond exocyclic to a cyclopentane or a cyclohexane ring can only occur on the face that is *syn* disposed to the aryl substituent, leading to *cis* isomers. The conformational flexibility of the methylenecycloheptane substrate **48** would account for the loss of diastereoselectivity in this cyclization (Scheme 14).

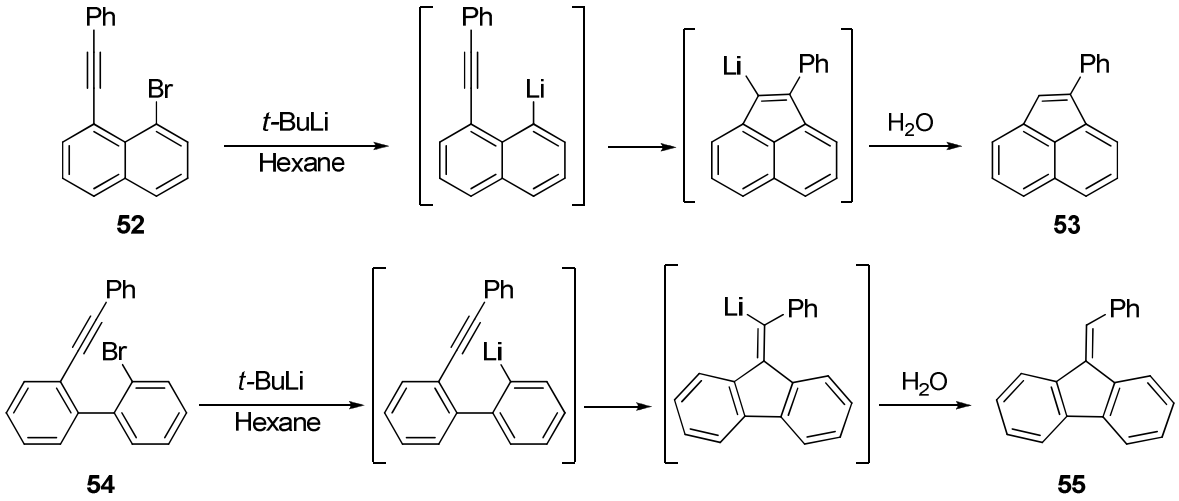


Scheme 14

Addition of an organolithium to a carbon-carbon triple bond has also been investigated, but the chemistry of such acetylenic systems is less well developed than that of their olefinic counterparts.[5] Although carbometalation of alkynes is recognized to be useful in the preparation of stereochemically defined tri- and tetrasubstituted alkenes, in some cases the regioselectivity becomes the principal problem.[25] Thus, the deprotonation of not only acetylenic protons but also propargylic ones generally predominates over addition.[26] Carbolithiation of alkynes having propargylic protons is possible when the addition is accelerated through intramolecular reaction or by the introduction of a heteroatom directing group (such as an alkoxy or amino group) or an electron-withdrawing group in the alkynes, but simple alkyl groups on alkynes are prone to suffer deprotonation. Therefore, the carbolithiation of alkynes has limited synthetic use because only particularly kinds of alkynes can be used and as for the stereochemistry, the vinyllithium intermediates tend to isomerize with ease.[27] In this context, improvements can be achieved by the use of an iron or iron-copper catalyst, as it has been showed in the regio- and stereoselective carbolithiation reactions of alkynes bearing an alkoxy or amino group[28] or even having no heteroatoms.[29]

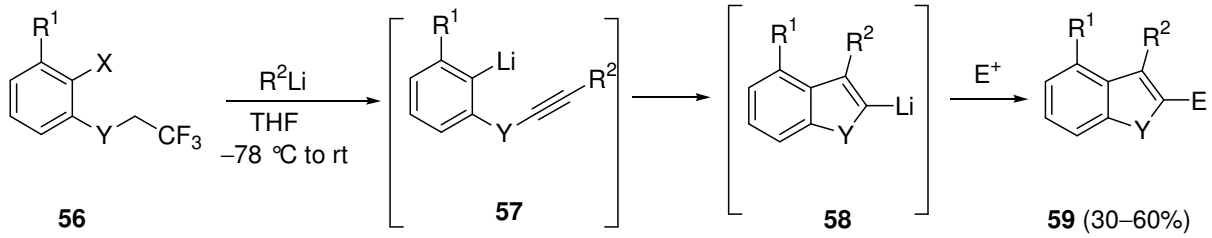
Nevertheless, in the case of intramolecular carbolithiation reactions, studies of acetylenic alkyl-[30] and vinyl-lithiums[31] have established that the ring closure can proceed with excellent regio- and stereocontrol. 5-*Exo*-cyclizations of vinyl lithiums onto phenyl substituted alkynes are *syn* stereospecific and give the sort of stereodefined dienes of value in Diels-Alder reactions. 6-*Exo* cyclizations are also possible but they are much slower.

However, only a few examples of carbolithiation of alkynes using aryllithiums have been reported in the literature, since the first results described in 1967 by Kandil[32] on the synthesis of benzylidenefluorene and related systems (Scheme 15).



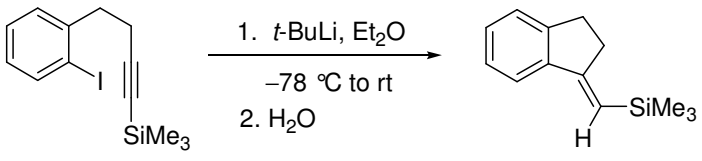
Scheme 15

It should also be mentioned the early work reported by Johnson[33] who opened a route to benzofurans, indoles and benzothiophenes, through a 5-*endo*-dig process, though the intermediate aryllithiums were not always prepared by halogen-lithium exchange (Scheme 16). Thus, treatment of 2,2,2-trifluoroethyl phenyl ethers **56** (Y=O, X=H, R^1=H), of the related thioethers (Y=S; X=Br, R^1=H) or of the amines (Y=NMe; X=H, R^1=MeO) with four equivalents of an aryl or alkyl lithium reagent (R^2Li) caused in almost all cases complete dehalogenation of the trifluoroethyl side chain with the concomitant introduction of an alkyl or aryl group (R^2) at the acetylenic 2-position. This was followed apparently by aromatic lithiation to give the lithio intermediates **57**, which then spontaneously cyclized to the 2-lithioheterocyles **58**. Electrophilic quenching then led to the corresponding heterocycles **59**.



Scheme 16

On the other hand, a silyl or aryl anion-stabilizing group at the terminus of the alkyne is essential for rapid *exo*-dig cyclizations. Thus, aryllithiums cyclized onto alkynes bearing alkyl substituents only very slowly even in the presence of TMEDA.[34] Negishi[35] has extended the intramolecular carbolithiation reactions to the use of trialkylsilylalkynes as internal electrophiles. Lithiation in the δ position of (trimethylsilyl)alkyne derivatives with *t*-BuLi led to the stereoselective formation of exocyclic alkenes containing five-membered carbocycles in high yields. Thus, cyclization of aryllithiums, generated by halogen-lithium exchange of (4-(2-iodophenyl)but-1-ynyl)trimethylsilane **60**, gave the corresponding indane derivatives **61** in high yields (95%), even in the absence of TMEDA (Scheme 17).

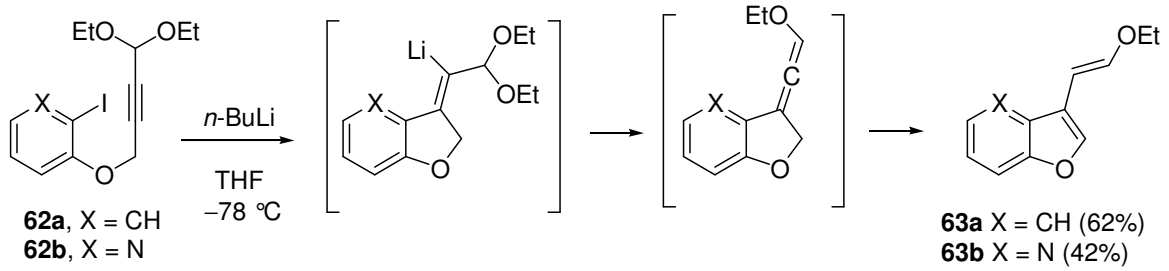


60 **61** (95 %)

Scheme 17

In relation to their work on conjugated elimination reactions involving acetals and propargylic systems,[36] Maddaluno developed a new route to 3-vinyl-benzofurans, furopiridines and indoles based on intramolecular carbolithiation of acetylenic precursors.[37] Treatment of iodinated aryl ether **62a** or the iodopyridine **62b** under standard halogen-lithium exchange with *n*-BuLi led to the corresponding aryllithium intermediate. An anionic cascade then ensued, started by a 5-*exo*-dig addition of the aryllithium on the triple bond, followed by lithium ethoxide elimination. A final isomerization of the exocyclic allene provided the

1,3-dienic systems **63** with total *E*-selectivity (Scheme 18). Interestingly, the preliminary isomerization of the triple bond into the corresponding allene, followed by the iodine-lithium exchange led to the same products in higher yields, but as a *E*/*Z* mixture (86:14).

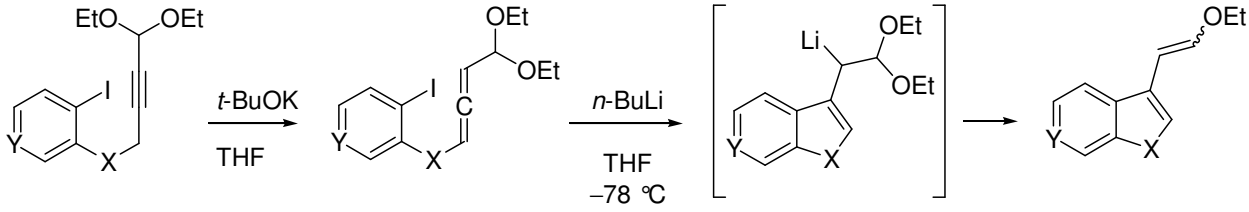


62a, X = CH
62b, X = N

63a X = CH (62%)
63b X = N (42%)

Scheme 18

Neither *n*- nor *t*-BuLi induced lithium iodine exchange worked properly in the case of iodinated aniline **64a**. However, by first isomerizing the triple bond into the allene (using *t*-BuOK in THF), the desired ring-closure could be effected by action of *t*-BuLi leading to the indole nucleus as a 77:23 mixture of *E* and *Z* isomers (Scheme 19). This procedure of intramolecular carbolithiation of allenes was later extended to the synthesis of other furopyridines **65b**.[38]



64a X = NBoc, Y = CH
64b X = O, Y = N

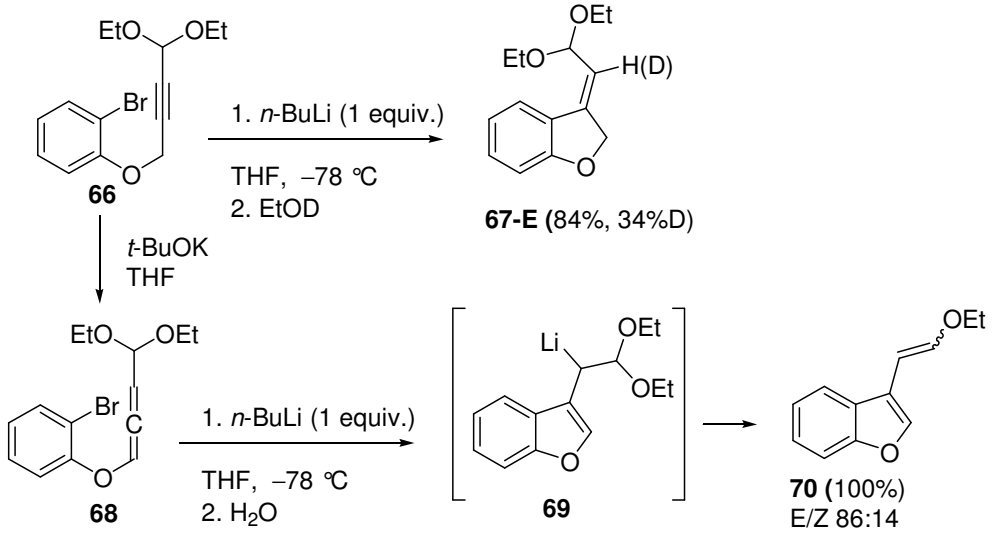
65a (75%) E/Z 77:23
65b (44%) E/Z 90:10

Scheme 19

Later, Maddaluno[39] has reinvestigated the mechanism of intramolecular carbolithiation of lithiated propargylic ether **66** both experimentally and theoretically (DFT calculations). The results showed that the action of one equivalent of *n*-BuLi is sufficient to trigger halogen-lithium exchange and the subsequent heterocyclization, but the reaction stopped at the stage of dihydrobenzofuran **67**; no spontaneous elimination of lithium ethoxide was observed. The fact that the *E* configuration of this adduct was exclusively produced suggested that the reaction proceeded by following an unprecedented *anti* addition on the alkyne. DFT calculations showed that this fact is related to the intramolecular coordination of the lithium atom by one oxygen atom of the terminal acetal. The experiments repeated on allene **68** showed that in this case one equivalent of *n*-BuLi sufficed to trigger not only halogen-lithium exchange and cyclization, but also the elimination of lithium ethoxide. DFT calculations indicated that the intramolecular addition of the aryllithium on the central carbon of the allene led to the benzofuran **69**, which bore a lithiated lateral chain at the 3 position that was ready for a β-elimination process, leading to **70** (Scheme 20).

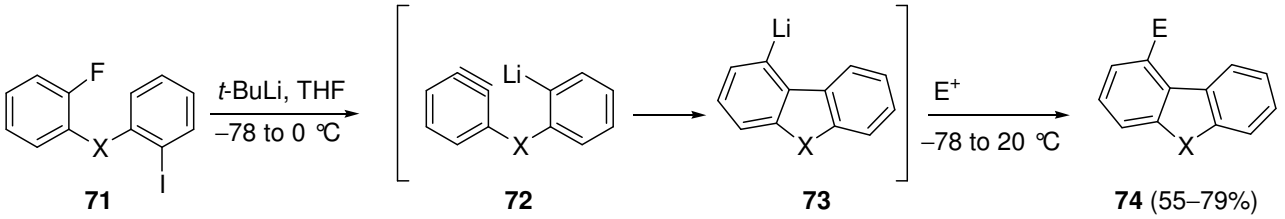
Complementary calculations showed that, in the absence of this coordination, the *Z* olefin, that results from a classical *syn* addition, should be obtained *via* transition state with a higher energy barrier. Overall the

data suggest that the stereochemical outcome of such carbolithiation reactions could be controlled through appropriate design of the substrate.[40] These authors have also proposed a possible mechanism for the last step of the cascade transformation in which lithiated propargyl ether is converted into the 3-vinyl-benzofuran.[41]



Scheme 20

Finally, arynes have also been used as internal electrophiles in what could be considered as a type of benzyne cyclization. The generation and cyclization of benzyne-tethered organolithiums has been only scarcely reported using alkyllithiums[42] or vinyllithiums.[43] As shown on Scheme 21, the treatment of 2-fluorophenyl 2-iodophenylamines, ether and thioether **71**, with 3.3 equivalents of *t*-BuLi and further reaction with selected electrophiles gave rise to functionalized carbazole, dibenzofuran and dibenzo-thiophene derivatives **74** in a direct and regioselective manner. The process involves an anionic cyclization on a benzyne-tethered aryllithium intermediate **72**, which is generated by consecutive halogen-lithium exchange, abstraction of the *ortho* proton to the fluorine atom and elimination of lithium fluoride, affording a regioselectively lithiated intermediate **73**, which could be trapped with selected electrophiles (Scheme 21).[44]

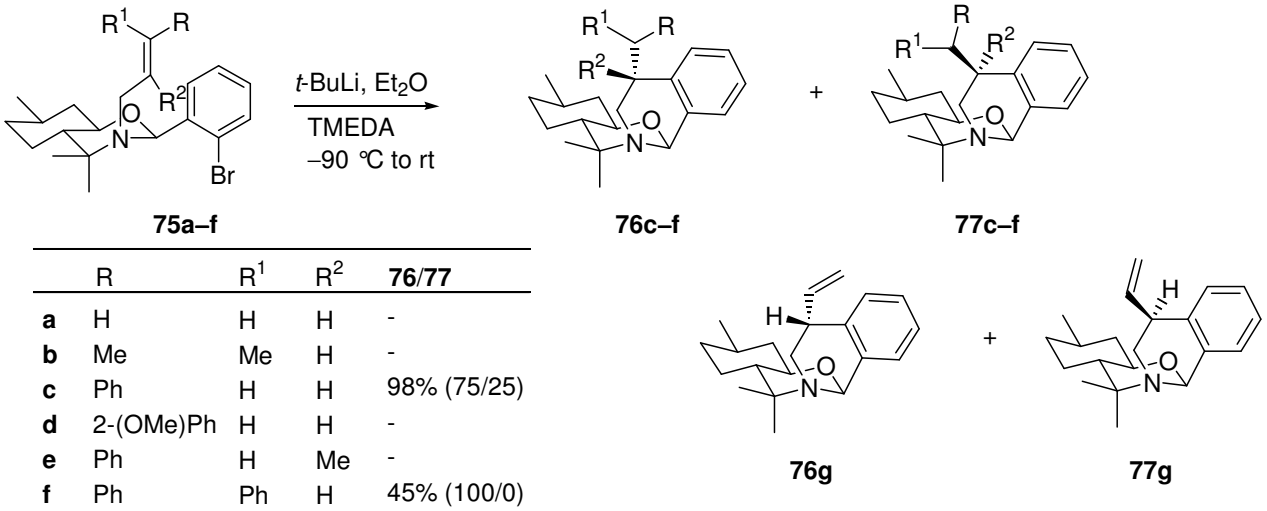


Scheme 21

2.2. Formation of six-membered rings

As it has been shown in the examples presented, intramolecular carbolithiation reaction of unsaturated aryllithiums is particularly well suited for the construction of five-membered rings. However, there are few precedents on the preparation of six-membered rings by carbocyclization of unactivated double bonds, as the

6-*exo* cyclization is slower than the 5-*exo*.[45] For instance, although intramolecular cyclization of vinyllithiums obtained by *t*-BuLi treatment of *N*-allyl-*N*-(2-bromoallyl)amines was initially reported to proceed through a 6-*endo* ring closure, it was later demonstrated that these processes start with a 5-*exo* cylization.[45]



75a–f **76c–f** **77c–f**

	R	R^1	R^2	**76/77**
a	H	H	H	-
b	Me	Me	H	-
c	Ph	H	H	98% (75/25)
d	2-(OMe)Ph	H	H	-
e	Ph	H	Me	-
f	Ph	Ph	H	45% (100/0)
g	CH_2OBn	H	H	66% (75/25)

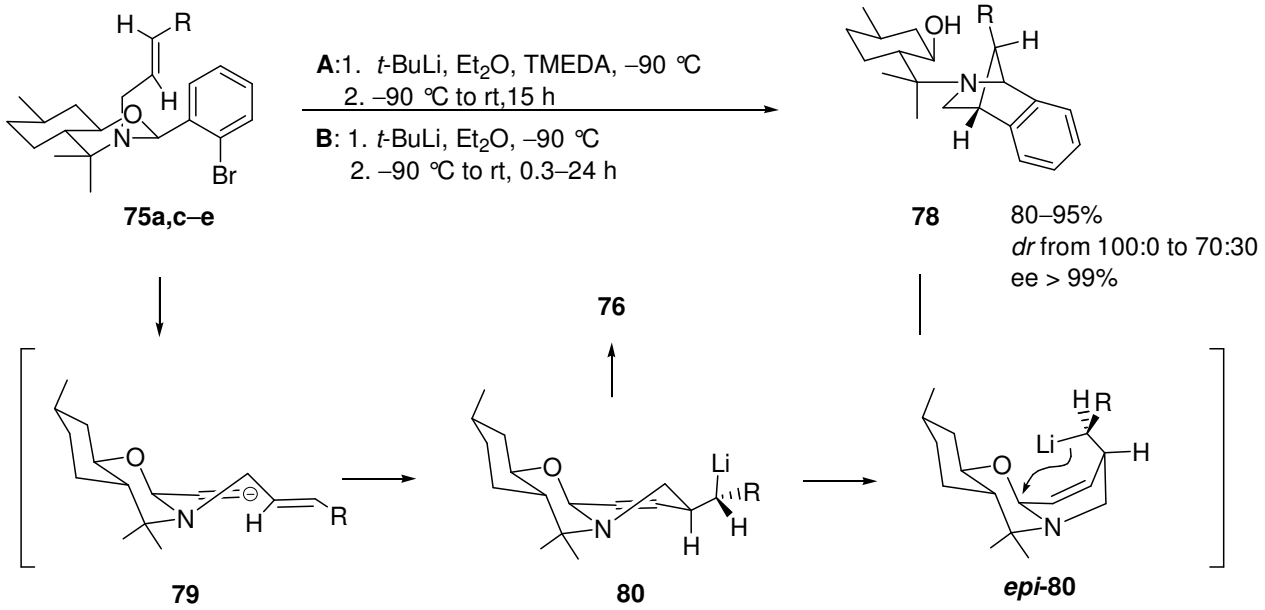
76g **77g**

Scheme 22

Aryllithiums prepared by bromine-lithium interchange in chiral 2-(*o*-bromophenyl)-substituted perhydro-1,3-benzoxazines **75** participate in the intramolecular 6-*exo* carbolithiation.[47] Thus, when benzoxazines **75** were treated with *t*-BuLi at –90 °C for 5 minutes, TMEDA was added and the mixture was allowed to reach room temperature, isoquinolines were obtained. As shown on Scheme 22, the formation of the six membered ring did not occur onto an unsubstituted alkene (**75a**), obtaining only the proton-quench product, after bromine-lithium exchange in the presence of TMEDA or extending the reaction time to 5 hours at –90 ºC. However, the presence of a phenyl group to stabilize the resulting organolithium triggered the cyclization, obtaining the diastereomeric benzo[5,6][1,3]oxazino[2,3-*a*]isoquinolines **76c/77c** in almost quantitative yield and in enantiomerically pure form (ee>99%). Interestingly, the introduction of a donor group on the phenyl ring (**75d**) or substitution on the alkene moiety (**75e**) precluded cyclization. The introduction of an additional phenyl group (**75f**) resulted in a lower yield of cyclization due to competitive metalation of one of the phenyl groups. The introduction of a leaving group α to the double bond (**75g**) also favoured the cyclization, in this case trough an S_N2' pathway, leading to **76g/77g**.

Interestingly, when the reaction time was extended (Scheme 23, conditions A) or no TMEDA was used (conditions B), the cyclized lithium intermediates **80** reacted intramolecularly with the *N,O*-acetal system leading to 2-azabenzonorbornane derivatives **78** in good yield and high stereoselectivity, even for the non-substituted alkene. In this case, the driving force for the initial cyclization could be the second nucleophilic reaction leading to the 2-azabenzonorbornane system. The stereochemical results have been explained assuming that the major or single isomer is formed from the initial coordination of the lithium atom to the alkene π-bond, followed by *syn* insertion across the double bond in a chair-like transition state formed from **79** (Scheme 23), where the double bond is in the pseudoequatorial disposition. In this way, alkyllithium intermediate **80** would be formed, leading to the major diastereomers of tetrahydro-isoquinolines **76** after

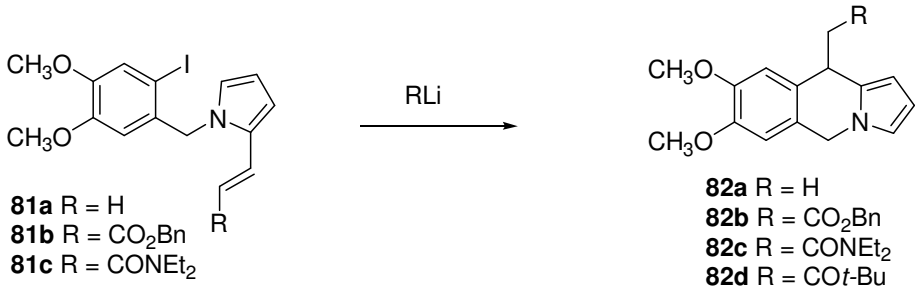
hydrolysis. The formation of the azabicyclic system **78** occurs from alkyllithium **80**, by intramolecular attack of the lithium alkyl to the early iminium ion (**C**) formed during the *N*,*O*-acetal opening. This reaction could occur with inversion of configuration at the organolithium centre or, most probably, through *epi*-**80**, as a result of a previous epimerization of this carbon due to its benzylic character.



Scheme 23

In connection with our work in this area,[48] our group has also shown that the 6-*exo* carbolithiation reaction for the synthesis of isoquinoline systems required the use of electron deficient alkenes (Scheme 24), although the introduction of electron withdrawing groups may result in undesired direct addition of the organolithium reagent.[49] Thus, although iodine-lithium occurred efficiently on *N*-(o-iodobenzyl)pyrrole **81a** (R=H) using *t*-BuLi/TMEDA, under various conditions, no cyclization product was isolated and addition of *t*-BuLi to the unsubstituted alkene was competitive with cyclization. The use of equimolecular amounts of *t*-BuLi/TMEDA resulted in a low conversion and the isolation of deiodinated **81**. Cyclization was achieved in low yield by the introduction of an electron withdrawing group (R=CO_2Bn), as the direct addition of *t*-BuLi to both the alkene and the ester moieties was competitive in the presence of TMEDA. The addition of *t*-BuLi to the ester moiety could not be avoided under various conditions, isolating pyrroloisoquinoline **82b**, together with **82d** as a by-product (20–25%) in all cases. When an amide was used as electron withdrawing group (**81c**, R=$CONEt_2$), pyrroloisoquinoline **82d** was obtained, although in low yield, due to competitive direct conjugate addition of *t*-BuLi at –78 ºC, that could not be avoided at lower temperatures. Some of the conditions used are shown on Scheme 24.

The use of a more bulky and less nucleophilic reagent for the iodine-lithium exchange reaction, as mesityllithium (MesLi), avoided the addition side reactions.[50] Thus lithium-iodine exchange was performed efficiently with MesLi, although the unsubstituted alkene **81a** was also unreactive under various conditions, isolating the non-iodinated benzylpyrrole, but avoiding the direct addition of the organolithium reagent to the alkene. On the other hand, cyclization of **81b** and **81c** took place smoothly at low temperature and in only 5 minutes to afford pyrroloisoquinolines **82b–c** in high yields and avoiding side reactions.



RLi = *t*-BuLi/TMEDA

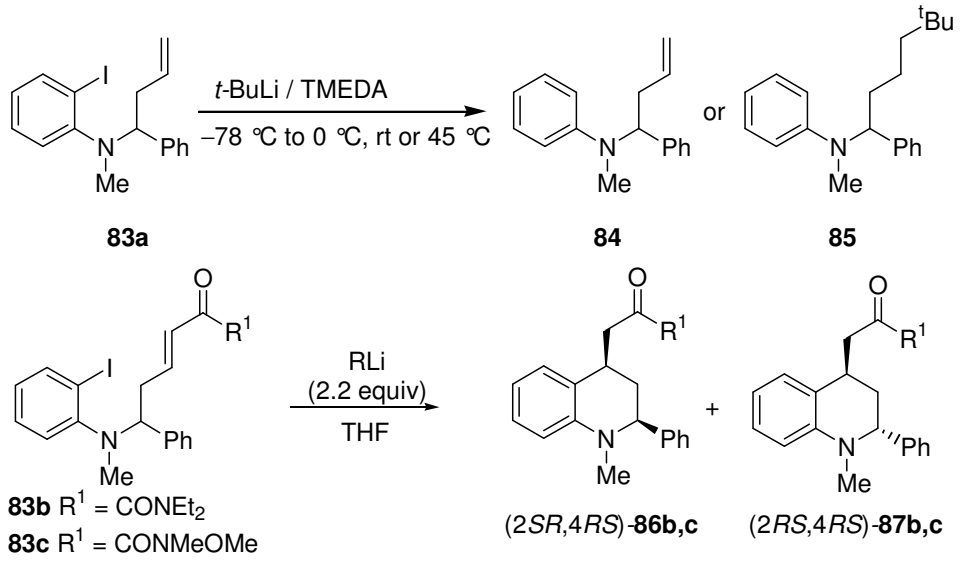
R	conditions	**82** Yield (%)
H	–78 °C, 3h	-
CO_2Bn	– 90 °C, 10 min	40%
$CONEt_2$	– 78 °C, 10 min	41%
$CONEt_2$	– 105 °C, 10 min	31%

RLi = MesLi

R	conditions	**82** Yield (%)
H	– 78 °C, 3 h	-
CO_2Bn	– 105 °C, 5 min	92%
$CONEt_2$	– 78 °C, 5 min	83%
$CONEt_2$	– 105 °C, 5 min	90%

Scheme 24

The 6-*exo* carbolithiation of *N*-butenyl substituted 2-iodoanilines **83** has allowed the diastereoselective synthesis of 4-substituted 2-phenyltetrahydroquinolines **86/87** (Scheme 25).[51]



R^1	RLi	additive	Yield	*dr* **86:87**
NEt_2	*n*-BuLi	-	80%	58:42
NEt_2	*n*-BuLi	TMEDA	81%	77:23
NEt_2	*t*-BuLi	-	81%	56:44
NEt_2	*t*-BuLi	TMEDA	64%	61:39
NMe(OMe)	*n*-BuLi	-	68%	40:60
NMe(OMe)	*n*-BuLi	TMEDA	74%	59:41
NMe(OMe)	*t*-BuLi	-	76%	29:71
NMe(OMe)	*t*-BuLi	TMEDA	-	-

Scheme 25

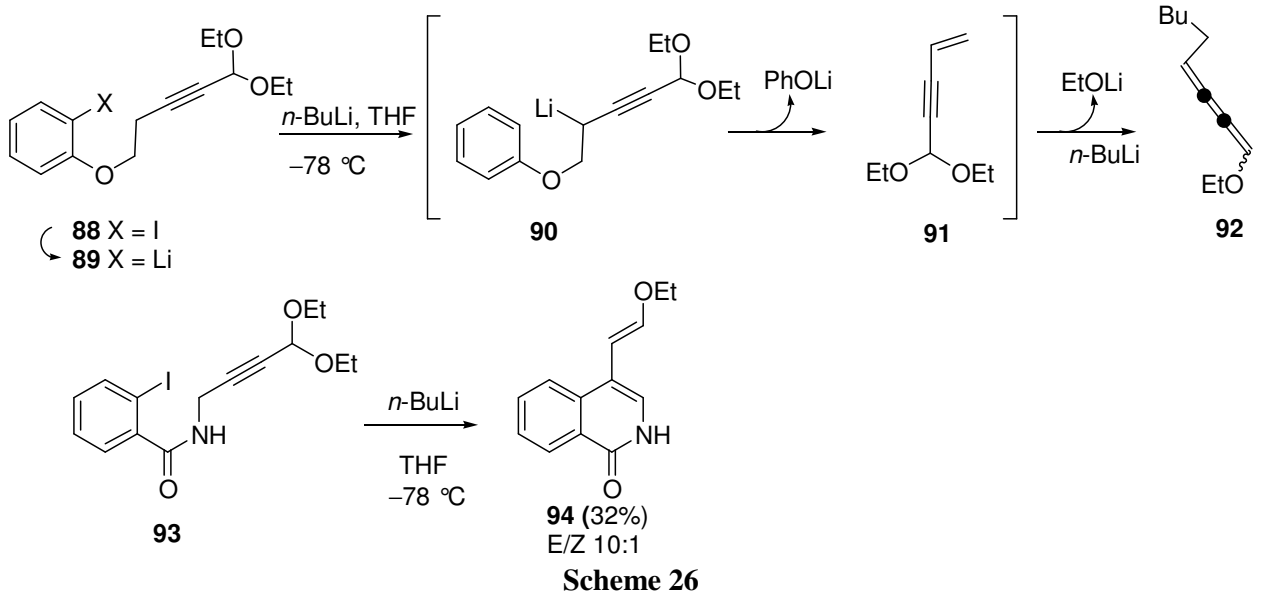
Once again, as shown on Scheme 25, the unsubstituted alkene was not reactive enough to participate in the cyclization and reduction product **84** was the only product isolated (60–80%) under various conditions

using *t*-BuLi/TMEDA. When the conditions were forced warming the mixture from −78 ºC to +45 ºC, intermolecular addition of the organolithium to the alkene was observed, isolating **85** (80%).

The introduction of an electron withdrawing group on the alkene favoured the cyclization and the stereochemical outcome of the carbolithiation reactions depended on the nature of organolithium employed to perform the lithium-halogen exchange, the solvent or the use of additives. Thus, treatment of **83b** (R^1=$CONEt_2$) with *n*-BuLi afforded the corresponding tetrahydroquinolines **86b** and **87b** at –78 ºC, although with almost no diastereoselectivity (73%, 58:42). The addition of TMEDA did not improve the results.[52] Different reaction conditions were tested in order to improve the yield and the stereoselectivity, some of which are shown on Scheme 25. The cyclization turned out to be fast even at –105 ºC and the best results were obtained using *n*-BuLi/TMEDA as metalating agent, yielding **86b** with a reasonable diastereoselectivity (77:23). A change in the solvent to Et_2O resulted in lower yield and loss of diastereoselectivity.

When the amide **83c** was used as substrate, the cyclization took place efficiently at –105 ºC, even in the absence of TMEDA, although with opposite diastereoselectivity, obtaining mainly the *trans* product **87c**. In the presence of TMEDA, the reaction did not take place under various conditions. When *n*-BuLi was used, an increased formation of the *cis* product **86b** was observed, which was the major product in the presence of TMEDA, although with almost no diastereoselectivity (59:41). Thus, the use of TMEDA as additive not only increases the rate of the cyclization, but also favours the formation of the *cis* adducts **86**.

The formation of 6-membered rings through 6-*exo*-dig carbolithiation of alkynes has also met with limited success.[38] Although the formation of five member rings from propargylic acetals has been successful (Schemes 19 and 20), the homologous propargylic ether **88** gave cumulene **92** instead, as a 1:1 mixture of diastereomers in 89% yield (Scheme 26). Lithium-halogen exchange took place, but an intramolecular deprotonation at the propargylic position to afford **90** facilitated the elimination of lithium phenoxide. Excess of BuLi adds to the double bond, triggering the elimination of lithium ethoxide.



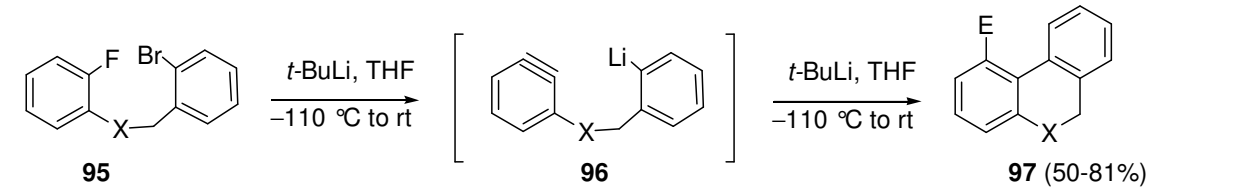
Scheme 26

Various propargylic amines were tested as substrates for the synthesis of quinolines, but only amide **93** gave the desired isoquinoline system, although in low yields (13−32%) depending on the reaction conditions.

The authors, however, assume that the reaction does not proceed *via* carbolithiation of an initially formed aryllithium, but through nitrogen deprotonation, allene isomerization and electrocyclization.

It has also been shown that the benzyne cyclization of an aryllithium can be accomplished also in a 6-*exo* mode to afford dihydrophenanthridines, dibenzopyrans and dibenzothiopyrans in moderate to good yields.[43b]

The reaction of compounds **95** with 3.5 equivalents of *t*-BuLi in THF at −110 to 20 ºC, and further treatment with different electrophiles afforded the corresponding six-member benzofused *N*-, *O*-, or *S*-heterocycles **97** in moderate to good yields *via* the benzyne intermediate **96** (Scheme 27).

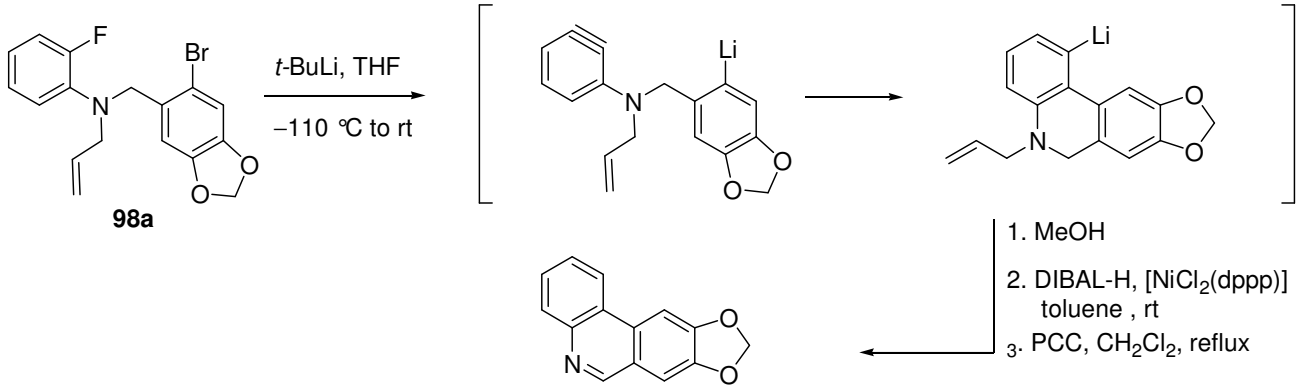


95 **96** **97** (50-81%)

X = NMe, N(allyl), O, S

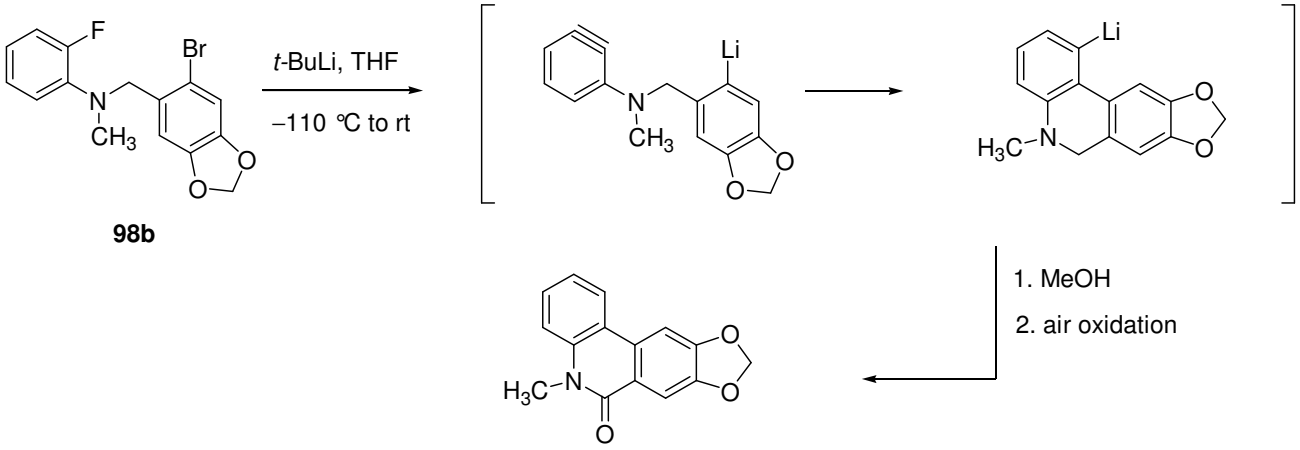
E = H, Br, SPh, CO_2Et, $SnBu_3$, PhCH(OH)

Scheme 27



98a

99 (48%) trisphaeridine



98b

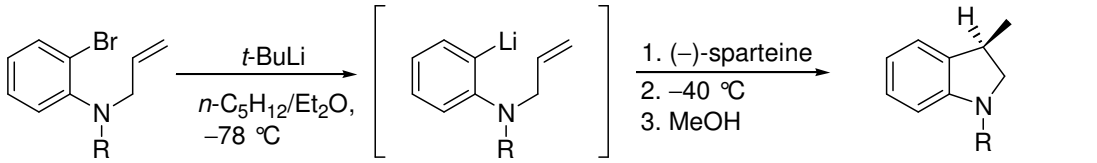
100 (65%)
N-methylcrinasiadine

Scheme 28

This type of cyclization has been applied to the synthesis of phenanthridine natural products, as *Ammaryllidaceae* alkaloids trisphaeridine (**99**) and *N*-methylcrinasiadine (**100**) (Scheme 28).[53]

2.3. Enantioselective carbolithiation reactions

Enantioselective versions of intramolecular carbolithiation reactions can be carried out under the influence of a chiral ligand for lithium, which would promote face selection on C=C bond. The stereochemical course of these anionic cyclizations is a consequence of a rigid transition state in which the lithium atom is coordinated to the remote π-bond (Scheme 2).[11] Assuming that the internally coordinated organolithium has two additional sites available for ligation, an enantioselective cycloisomerization of an achiral olefinic organolithium could be performed conducting the reaction in the presence of chiral bidentate ligands, such as (–)-sparteine.[54] This naturally occurring alkaloid, which is inexpensive and available in large quantities, has proved to be very efficient for these processes. Thus, Bailey has extended intramolecular carbolithiation reactions to the enantioselective synthesis of indolines.[55]

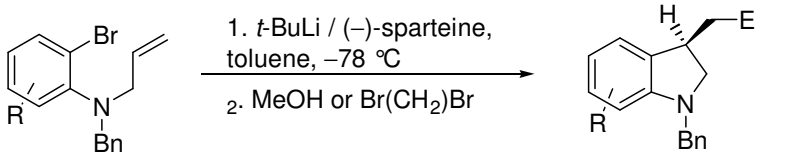


101a R = allyl
101b R = Me

102a R = allyl (69 %, *ee* 86 %)
102b R = Me (88 %, *ee* 70 %)

Scheme 29

Treatment of *N,N*-diallyl-2-bromoaniline **101a** with *t*-BuLi in *n*-pentane/diethyl ether at –78 °C generated an aryllithium which, in the presence of 2.1 equivalents of (–)-sparteine at –40 °C underwent cyclization to provide (*R*)-(–)-1-allyl-3-methylindoline **102a** in high yield and ee (Scheme 29). As could be expected, the use of THF as a solvent resulted in almost complete loss of enantioselectivity (2% *ee*). The cyclization was more enantioselective at lower temperatures (*i.e.*: 76% *ee* at 0 °C *vs*. 86% *ee* at –40 °C), although at lower temperatures the cycloisomerization was too slow to be of practical value. It is also interesting that cyclization of amine **101b** under identical conditions was less enantioselective than the analogous diallyl substrate **101a** (70% *vs*. 86%), a fact that indicated that the presence of two enantiotopic allyl groups contributed to the enantioselectivity of the process.



103

R = H, 4-OBn, 5-OBn, 4-CH_3, 4-F
E = H, Br

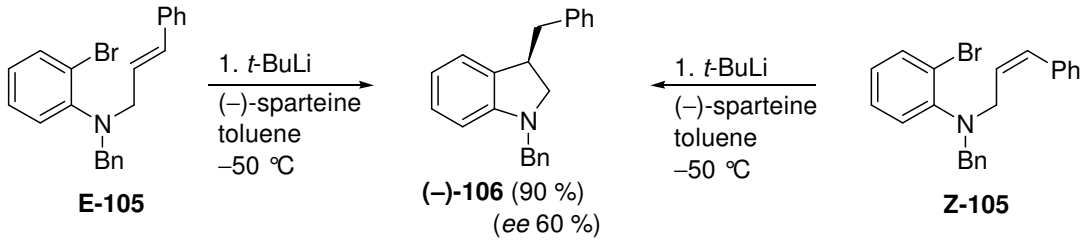
104 (65–90 %)
(*ee* 82–90 %)

Scheme 30

However, simultaneously Groth reported an enantioselective carbolithiation of *N*-benzyl-*N*-allyl-2-bromoanilines **103** with *t*-BuLi in the presence of (–)-sparteine, using toluene as solvent.[56] The resulting

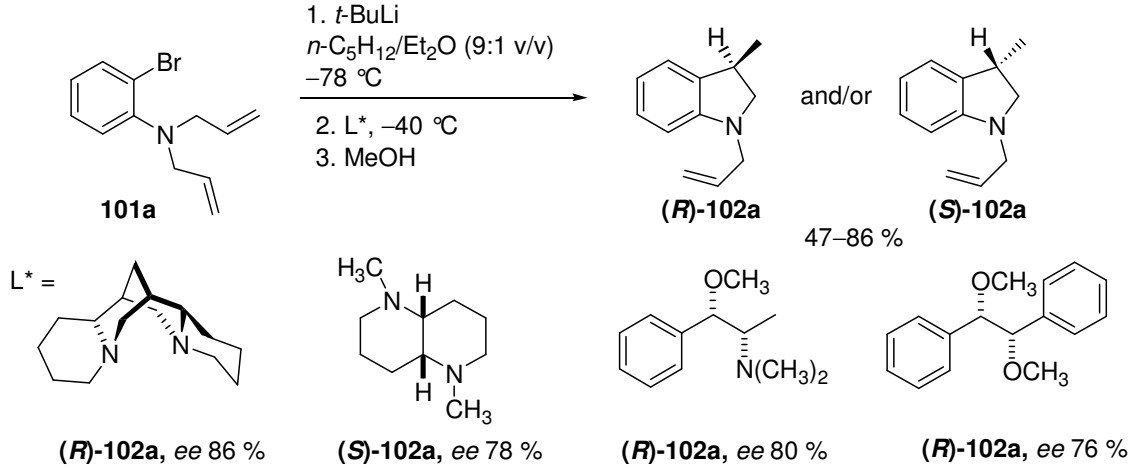
lithiomethylindolines were protonated or trapped with dibromoethane to obtain indolines **104** in high yield and *ee* (Scheme 30).

Interestingly, the stereochemistry of the olefin had no influence on the enantioselectivity of the carbolithiation. As depicted in Scheme 31, both bromoanilines ***E*-105** and ***Z*-105** produced identical indoline **106** with moderate *ee* (60%). In this case, lithium-bromine exchange was carried out at –78 °C, but carbolithiation required higher temperatures.



Scheme 31

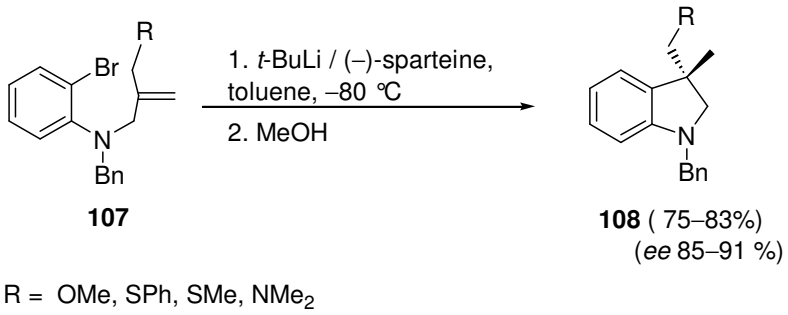
Subsequently, the ability of a large and chemically diverse set of 30 chiral ligands to effect the asymmetric intramolecular carbolithiation of *N*,*N*-diallyl-2-bromoaniline **101a** was investigated by Bailey[57] (Scheme 32) in an attempt to elucidate the structural motifs required to provide high enantiofacial selectivity in the ring closure. Although none of the ligands examined afforded 1-allyl-3-methylindoline **102a** in significantly higher *ee* than previously observed for the cyclization of **101a** in the presence of the benchmark ligand (–)-sparteine, several ligands, structurally unrelated to sparteine and available in either enantiomeric form, were found to match the utility of (–)-sparteine in this chemistry. With regard to chiral diamine ligands, *ee*'s were only maintained using *cis*-1,5-diazadecalin, though the reaction led to the indoline of opposite configuration. Unfortunately, this diamine is not commercially available and its synthesis requires resolution. Among ethers and aminoethers ligands, (1*S*,2*S*)-1,2-dimethoxy-1,2-diphenylethane and (1*S*,2*S*)-*N*,*O*-dimethylpseudoephedrine are particularly effective surrogates for sparteine, affording 3-methylindoline in good yield and high *ee*.



Scheme 32

Groth[58] has also examined this procedure in more detail by studying the assistance of a chelating donor in the side chain of the allylic moiety (Scheme 33). Thus, it has been shown that *N*-allyl-*N*-benzyl-2-bromo-

anilines **107** underwent an asymmetric intramolecular carbolithiation in the presence of *t*-BuLi and (–)-sparteine yielding 3,3-disubstituted indolines **108** in moderate to high enantiomeric excesses depending on the nature of the substituent on the alkene. The best results regarding both chemical yields and *ee*'s were obtained when R=OMe, SPh, SMe and NMe_2. In these cases, the reactions were carried out at –80 ºC in toluene as solvent, whereas the use of alkyl substituted anilines (R=Me, *i*-Pr) required higher temperature to achieve cyclization (the reaction mixture should be allowed to warm to room temperature).



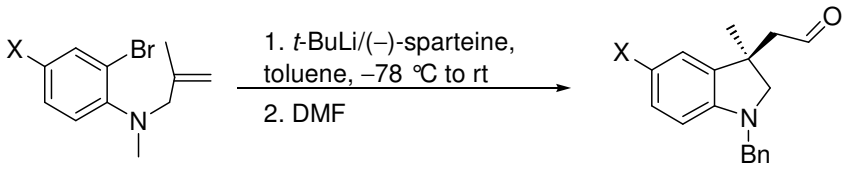
107

108 (75–83%)
(*ee* 85–91 %)

R = OMe, SPh, SMe, NMe_2

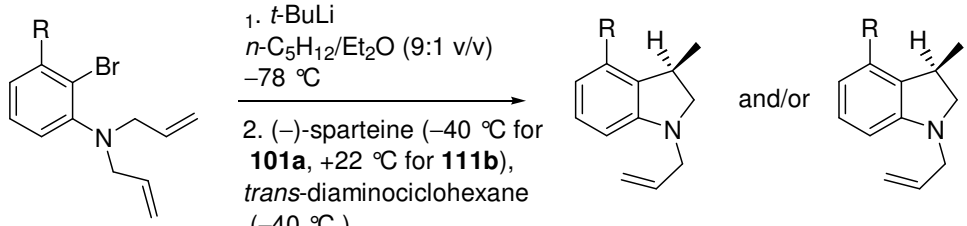
Scheme 33

Although these authors claimed that the substituents of the aromatic system did not influence the cyclization, there seems to be influenced in yields and enantioselectivity as it is shown in the cyclization of 2-bromo-4-methoxyaniline derivative **109b** they described (Scheme 34). In this context, Bailey[57] has also shown that the presence of a substituent in the *ortho* position to the lithium atom led to lower yields and lower enantiomeric excesses (Scheme 34).



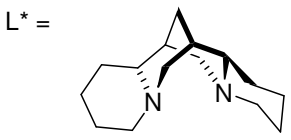
109a X = H
109b X = OMe

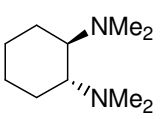
110a X = H (75%, *ee* 72%)
110b X = OMe (31%, *ee* 60%)



101a R = H
111b R = Me

(*R*)-112 **(*S*)-112**





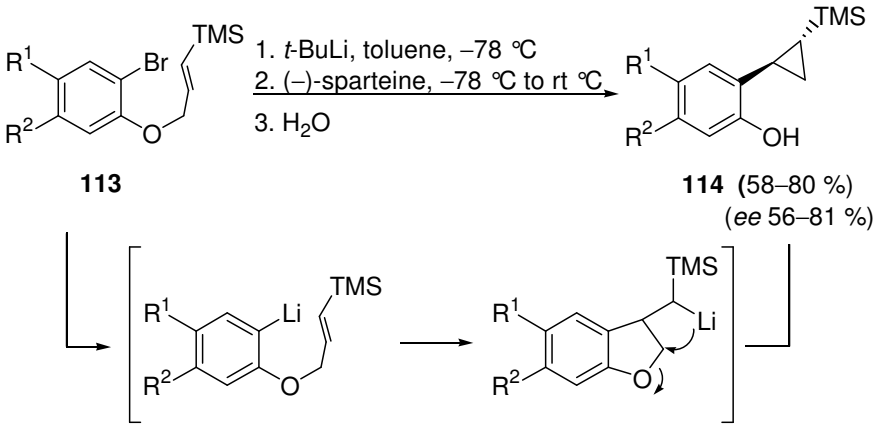
(*R*)-112a 89%, ee 80 %
(*S*)-112b 16%, ee 22 %

(*R*)-112 79%, *ee* 62 %
(*R*)-112 62%, *ee* 70%

Scheme 34

Therefore, caution should be taken in generalizing the results of this type of reactions, since seemingly minor variation in substrate structure may have a pronounced effect on the ability to give ligand to facilitate cyclization.

On the other hand, Barluenga[59] has shown that achiral allyl *o*-lithioaryl ethers also underwent the tandem carbolithiation/γ-elimination in the presence of (–)-sparteine, giving the corresponding cyclopropane derivatives in moderate to good enantioselectivities (Scheme 35). The best results were obtained when the reactions were carried out in apolar solvents, such as toluene or hexane, at –78 ºC for the halogen-lithium exchange and then allowing to reach room temperature.

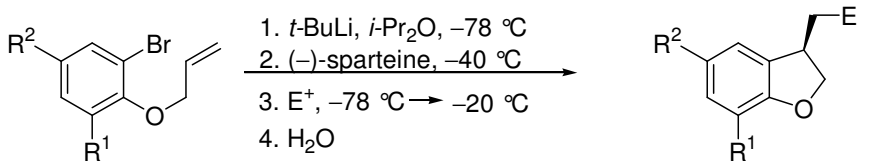


113 **114** (58–80 %) (*ee* 56–81 %)

R^1 = H, Me, Cl, F, H, OMe; R^2 = H, F

Scheme 35

As shown on Scheme 9, substitution at the 6-position of the aromatic ring also prevents the isomerization of the lithiomethyldihydrofuran and functionalized 2,3-dihydrobenzofurans could be obtained in moderate to good yields (47–76%) and high *ee*`s (77–87%) *via* (–)-sparteine-mediated intramolecular carbolithiation (Scheme 36).[20] The best results were obtained when allyl 2-bromoaryl ethers were treated with *t*-BuLi a –78 ºC in diisopropyl ether as solvent, followed by addition of (–)-sparteine and quenching with several external electrophiles.



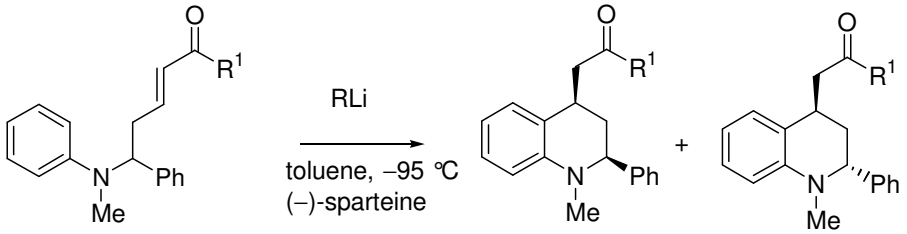
33 **35** (47–76 %) (*ee* 77–87 %)

R^1 = Me, *t*-Bu, TMS, *i*-Pr; R^2 = Me, H
E^+ = Ph_2CO, PhNCO, D_2O, Ph_2S_2, Me_2SO_4
E = Ph_2COH, PhNHCO, D, PhS, Me

Scheme 36

Our group has reported the first example of this type of enantioselective 6-*exo* cyclization process. Thus, it has been shown that the intramolecular carbolithiation of *N*-alkenyl substituted *o*-iodoanilines **83** afforded enantiomerically enriched 2,4-disubstituted tetrahydroquinolines **86** and **87** by using (–)-sparteine as

chiral ligand.[51] Thus, several experiments were carried out by adding anilines **83b,c** over a solution of the alkyllithium (*t*-BuLi or *n*-BuLi) and (–)-sparteine, using toluene as solvent to allow the coordination of the organolithium with the amine. However, the substitution of the amide was relevant, as, when the diethyl derivative **83b** was used, the mixture of tetrahydroquinolines **86b** and **87b** was obtained with poor diastereoselectivity and each of the diastereomers with low enantiomeric excess. However, when the Weinreb amide **83c** was used as substrate and *n*-BuLi as metalating agent at –95 ºC, the cyclization proceeded with reasonable diastereoselectivity (dr 33:67) and excellent *ee* for each of the isolated diastereomers (**86c**, 92% *ee* and **87c**, 90% *ee*). Thus, in the presence of (–)-sparteine, one of the enantiomers would react more rapidly leading to the major stereoisomer (Scheme 37).



83b R^1 = $CONEt_2$
83c R^1 = CONMeOMe

(2*S*,4*R*)-**86b,c** (2*R*,4*R*)-**87b,c**

R	RLi	Yield	*dr* **86:87**	*ee* **86**	*ee* **87**
NEt_2	*t*-BuLi	91%	42:58	17	5
NEt_2	*n*-BuLi	63%	27:73	17	33
NMe(OMe)	*t*-BuLi	31%	30:70	8	2
NMe(OMe)	*n*-BuLi	48%	33:67	92	94

Scheme 37

The stereochemical outcome was opposite to that obtained with TMEDA (Scheme 25), affording the *trans* quinolines **87b,c** as the major diastereomer. A similar reversal of the stereochemical outcome when (–)-sparteine is used instead of TMEDA has been observed in alkylation reactions,[60] although the change in the solvent from THF, that may bind to the lithium cation, to toluene may also play a role.[61]

3. Conclusion

The very fast lithium-halogen exchange generates functionalized aryllithiums that can react intramolecularly with double and triple carbon-carbon bonds, generating a new organolithium intermediates. Thus, the possibility of further functionalization and the stereoselectivity associated with this anionic cyclization open new strategies that can play a crucial role in natural products synthesis. As shown, carbolithiation of aryllithiums through 5-*exo*-trig and 5-*exo*-dig cyclizations has been successfully applied for the preparation of five-member carbocycles and heterocycles, even in a diastereo and enantioselective manner. However, the cyclization to six-member cycles has been less studied and generally requires the introduction of an electron withdrawing group of the alkenes or stabilization of the resulting organolithium intermediate. The potential of this anionic cyclization for the synthesis of six-member or larger rings has not been fully developed, mostly in the field of stereoselective synthesis.

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ORGANOMETALLIC CHEMISTRY OF 2-PYRIDINE- AND 2-PYRROLEIMINES, APPLICATIONS IN ORGANIC SYNTHESIS AND CATALYSIS

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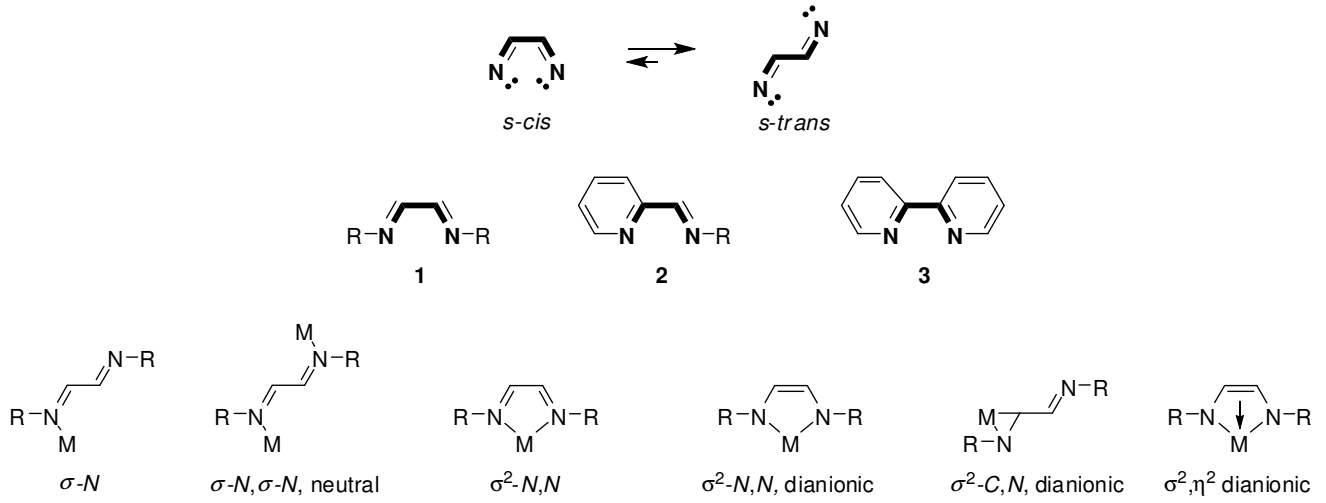
Abstract. *The peculiar ability of bidentate and tridentate pyridine- and pyrrole-imines and -diimines to coordinate metal salts and organometallic compounds allows their versatile applications as ligands or precursors of ligands in the fields of polymer chemistry and asymmetric catalysis and as building blocks for the stereoselective synthesis of more complex structures and natural compounds.*

Contents

1. Introduction

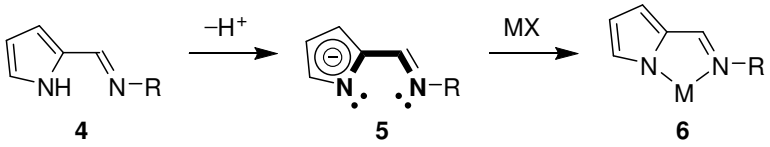
The 1,4-diazadiene moiety is an unsaturated functional group which displays interesting properties and serves as a useful precursor for the preparation of more complex, functionalized molecules. In the absence of structural rigidity, the preferred conformation is the *s-cis*, which is 20–28 kJ/mol more stable than the *s-trans* conformation (Scheme 1). Its reactivity is dictated by two structural features: a) the four electrons conjugated π system that is responsible of the electron-acceptor capability and electrophilic properties; b) the electron pairs on both nitrogen atoms, which therefore display Lewis basic and chelation properties towards metal ions, metal salts and organometallic compounds. The strength of such properties varies depending on the molecular structure, as one or both or none of the two azomethine groups may be included in a heteroaromatic ring. The most common compounds whose structures correspond to the aforementioned

possibilities are the symmetrical glyoxal diimine **1**, the unsymmetrical 2-pyridineimine **2** and 2,2'-bipyridine **3** (Scheme 1). Mono- or bidentate metal complexes, with different bonding types can be formed between these ligands and the metal species, as exemplified for the glyoxal diimine.[1]



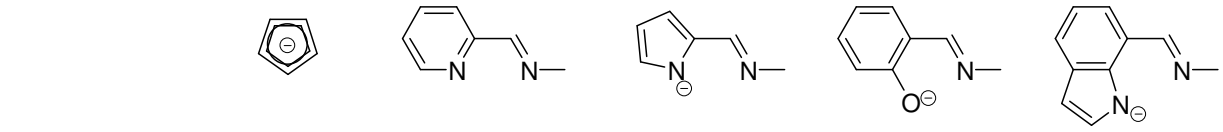
Scheme 1

2-Pyridineimines display analogous bidentate coordination properties towards metal species.[2] Also, the 2-pyrrolide-imine **5** formed by deprotonation of the 2-pyrroleimine **4** meets the structural and electronic requirements to be compared with previously described 1,4-diazadiene derivatives and can be easily converted to anionic metal complexes **6** (Scheme 2).[3]



Scheme 2

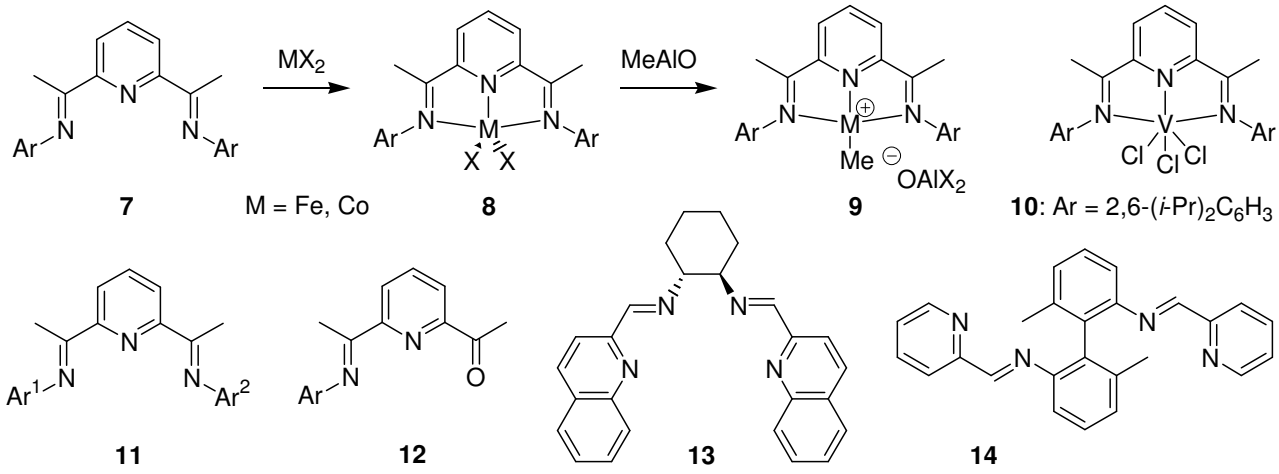
The π-acceptor capacities of typical compounds featuring the 1,4-diazadiene moiety were determined by NDDO calculations and found to decrease in the order: glyoxal diimine (**1**)>2-pyridineimine (**3**)>2,2'-bi-pyridine (**2**).[4] Bi- and tridentate ligands containing the 2-pyridineimine or 2-pyrroleimine moiety have found useful application for complexation of metal salts active as pre-catalysts in polymerization and oligomerization of alkenes. For this application, "fundamentally active ligands" reported in Scheme 3 possess small energy gap between HOMO and LUMO, hence well balanced electron-donating and -withdrawing properties and presumably display more flexible properties than the cyclopentadienyl ligand.[5]



Scheme 3

Particularly, the neutral nickel and palladium complexes of aliphatic 1,2-diimines have been developed as catalysts of olefin polymerization, as an alternative to metallocenes (Scheme 4).[6]

The 2,6-diiminopyridine ligand has gained a relevant interest for organic chemists because it shows a unique tendency to become involved in chemical reactions, hence it plays an active, "non innocent" role in several transition metal-catalyzed reactions,[7] particularly as polymerization catalysts.[8] The π-acceptor capability of diiminopyridine (DIP) is due to single electron transfer (SET) from the metal to the ligand resulting in charge transfer complexes with low singlet-triplet gaps.[9] Calculations at the DFT level showed that DIP ligands bearing aryl substituents at the imine nitrogens are only fair σ-donors but exceptionally good π-acceptor.[10] 2,6-Diiminopyridines **7** can act as bi- or tridentate ligands towards metal species, *e.g.* the tridentate complexes **8**, and are capable to stabilize the metal in a wide range of oxidation states. Iron(II) and cobalt(II) complexes **8**, where the tridentate ligands bear bulky aryl substituents at the imine nitrogens, were found to be extremely active catalysts for the preparation of linear, high molecular weight polymers from ethylene. Really, both complexes **7** and **8** act as pre-catalysts, as the true catalytic species are cationic complexes, *e.g.* **9**, which are formed *in situ* in the presence of Lewis acids such as methylalumoxane (MeAlO, "MAO") or the system $B(C_6F_5)_3/Al(i\text{-}Bu)_3$. By a similar mechanism, the complex formed by MePtCl and a glyoxal diimine bearing 2,6-disubstituted phenyl substituents at the nitrogens, upon treatment with $AgBF_4$, afforded a Pt^+ catalyst for the polymerization of electron-rich alkenes.[11] It has been recently reported that the bis(imino)pyridine-VCl_3 complex **10**, mediates the controlled radical polymerization of vinyl acetate at 120 °C using AIBN as initiator, wherein the linear increase of the molar mass with monomer conversion was observed.[12]



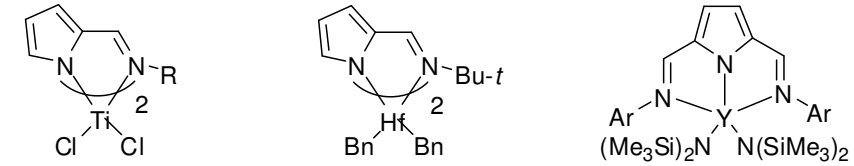
7 **8** **9** **10**: Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$

11 **12** **13** **14**

Scheme 4

A number of analogous ligands bearing the pyridine or quinoline nucleus were prepared and their metal complexes tested as catalysts for polymerization reactions in the presence of Lewis acids. For example the $FeCl_2$ complexes of symmetrical and unsymmetrically *N*-substituted diiminopyridine ligands afforded tunable polymers of ethane and propene with molecular weights of 10^{-2}–10^{-6}, depending on the steric bulk of the *ortho*-aryl substituents.[13] Among many other ligands, bis(quinolineimine) **13** and bis(pyridineimine) **14**, where the two imine nitrogens are linked by an aliphatic and aromatic tether, respectively, were converted to $MnCl_2$ complexes which catalyzed the polymerization of ethane; the highest activity [67 Kg PE/(mol of Mn) h)] was obtained with **13**-$MnCl_2$-MAO at 80 °C.[14]

Similarly, bidentate iminopyrrolide ligands were found useful ligands of transition metal salts, *e.g.* the titanium and hafnium complexes **15**[15] and **16**,[16] respectively, for the catalytic polymerization of ethylene in presence of Lewis acid activators, whereas the tridentate yttrium complex **17** proved to be useful for the polymerization of ε-caprolactone (Scheme 5).[17]



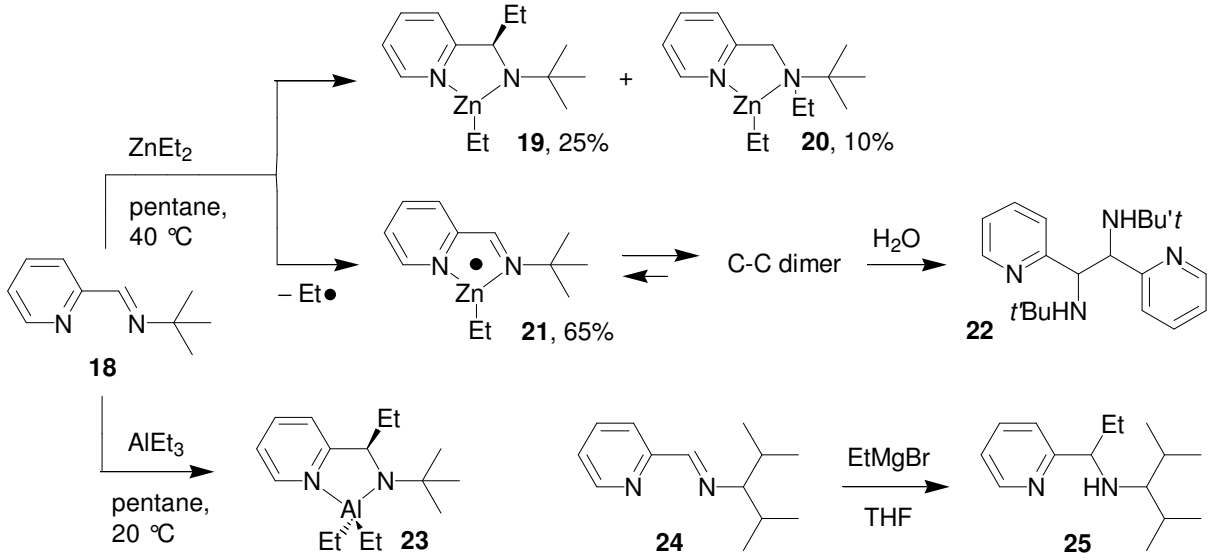
15: R = Ph, *c*-Hex **16** **17**: Ar = 2,6-$Me_2C_6H_3$

Scheme 5

2. Organometallic reactions of 2-pyridineimines

2.1. Mechanism

The chelation and π-acceptor capacities of the 1,4-diazadiene moiety especially affect the mechanism of the reactions with organometallic reagents. The reactions of glyoxal diimines and 2-pyridineimines with dialkylzinc and trialkylaluminum reagents in hydrocarbon solvents were extensively studied by van Koten in his pioneering work and successively by other authors, and led to *C*- and *N*-alkylated adducts and C–C–dimers through formation of charge transfer complexes and SET processes.[18] The homolytic cleavage of the carbon-platinum bond in the complex formed by tetramethylplatinum and a glyoxal diimine occurred upon irradiation, resulting in electron transfer from the HOMO of C–Pt σ-bond to the LUMO π* of the diazabutadiene, and ultimately leading to *C*- and *N*-methylated products.[19] More recently, reactions of *N*,*N*'-di(*t*-butyl)glyoxal diimine with Grignard, lithium and aluminium reagents were investigated in ethereal solvents and *C*- and/or *N*-alkylation products were obtained depending on the nature of the organometallic reagent.[20] The addition of the tetrabenzylhafnium and -zircomium to aliphatic 1,2-diimines has been recently exploited to prepare mono- and bis(amido)metal complexes as catalysts precursors for the isospecific polymerization of α-olefins.[21]

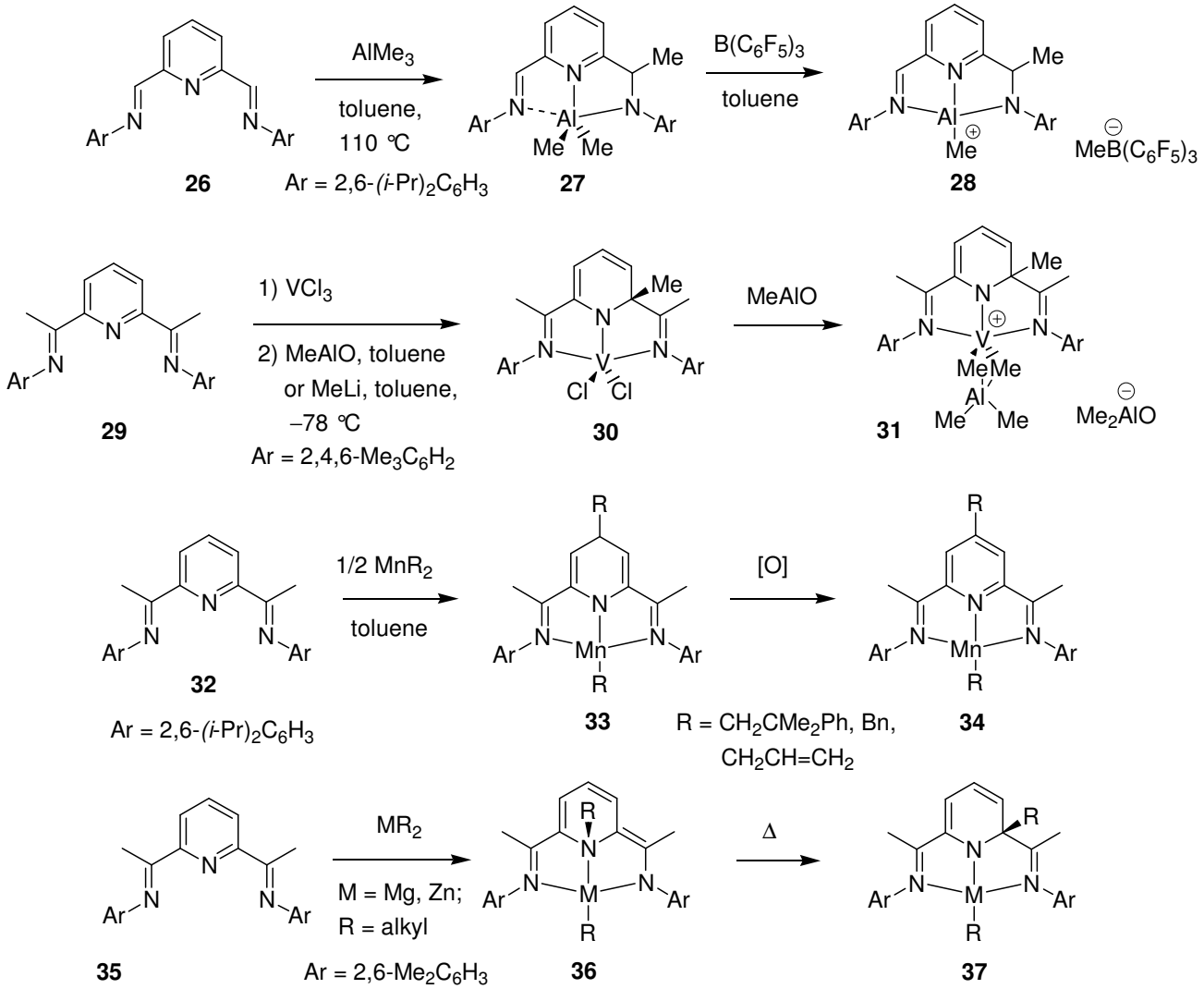


Scheme 6

The organometallic reactions of 2-pyridineimines followed the same mechanism and pathways as observed with the glyoxal diimine. For example, the *N*-*t*-butylimine **18** in pentane gave minor amounts of *C*- and *N*-alkylation adducts **19** and **20**, respectively, the prevalent product being the dimer **22**, coming from the intermediate radical **21**. On the other hand, the *C*-alkylation adduct **23** was formed by reaction with triethylaluminum (Scheme 6).[22] Similarly, the Grignard reaction of the analogous imine **24** afforded the *C*-alkylation product **25**.[23]

2.2. Organometallic reactions of 2-pyridine- and 2-pyrroleimines, particularly applied to the preparation of olefin polymerization catalysts

Organometallic addition to 2,6-pyridinediimines bearing bulky aryl substituents at the imine nitrogen atoms, and their metal complexes has been a topic of particular interest in the contest of developing new active catalysts for organic reactions, particularly oligomerization and polymerization of olefins. It was found that transfer of alkyl groups to the lateral azomethine function or to the pyridine rings can occur in the different cases. The addition of Me_3Al to the dialdimine **26** produced the imine methylation product **27**, which was then converted to the active catalyst, salt **28**, by treatment with tris(pentafluorophenyl)borane (Scheme 7).[24]

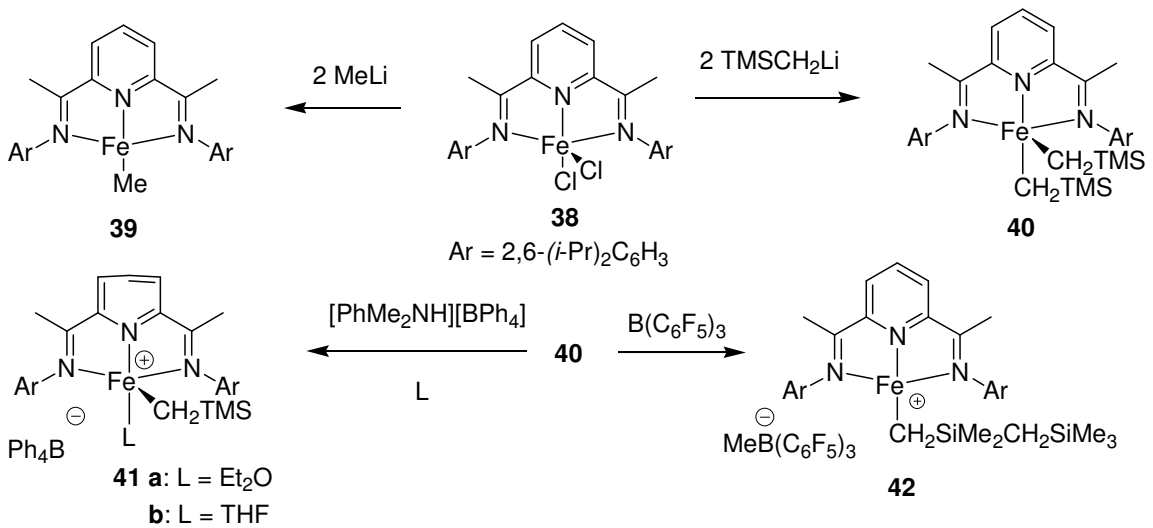


Scheme 7

A different pathway was observed when the diimine **29**-VCl_3 complex was treated with methylaluminoxane (MAO) or MeLi, as the transfer of the methyl group to the C2 of the pyridine ring occurred.[25] The adduct **30** was then converted to the salt **31** by reaction with excess MAO. Similarly, alkyation of the **32**-VCl_3 complex, *i.e.* **10** in Scheme 4, with $AlEt_2Cl$ resulted in an active catalyst for polymerization of ethylene at 50 °C.[26]

On the other hand, addition of a dialkylmanganese compound to the diimine **32** gave the C4-ring alkylated adduct **33**, which underwent aerobic dehydrogenation in the presence of CrO_3/K_2CO_3 to give the organomanganese compound **34**.[27] Most surprisingly, 2,6-pyridinediimines such as **35** underwent addition of MeLi and especially dialkylmagnesium and -zinc compounds to afford the products coming from pyridine *N*-alkylation, *e.g.* **36**, which slowly isomerized to the C2-alkylation adduct **37**.[28] In all these examples, the azomethine addition was disfavoured owing to the steric effect of the aryl substituents. Moreover, lack of aromaticity following ring addition was compensated by extensive delocalization of the negative charge. Recently, nickel complexes of 2-pyridinemethanamines with large substituent R=2,4,6-trimethylphenyl in 2-PyCH(R)NH[2,6-(*i*-$Pr)_2C_6H_3$], obtained by reduction of the corresponding ketimines, were used as catalysts for longstanding living ethylene polymerization promoted by MAO to give branched polymers.[29]

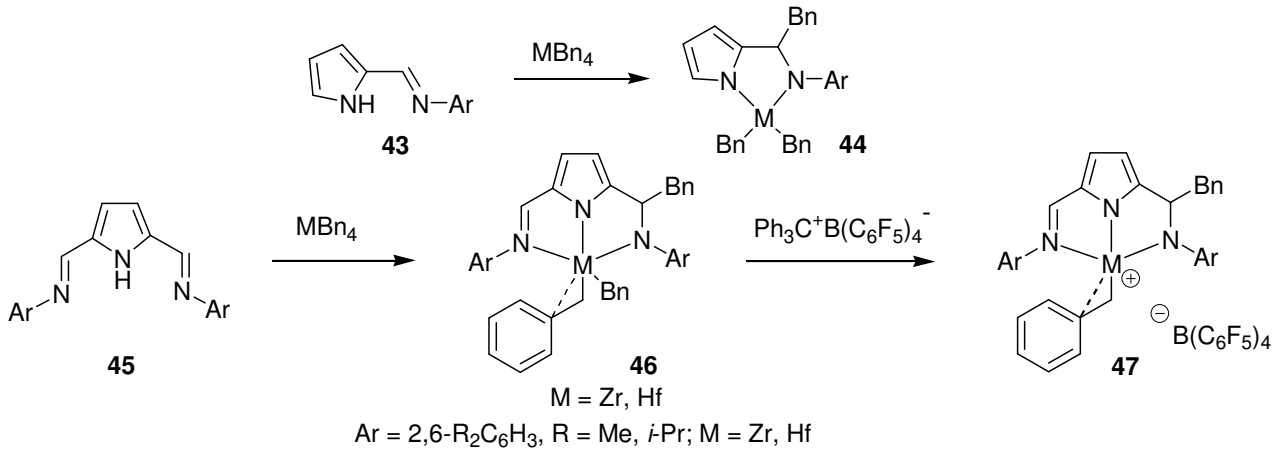
The reaction of the pentacoordinate Fe(II) complex **38** with 2 equivalents of MeLi gave the product of reductive alkylation **39**, whereas the reaction with bulky trimethylsilylmethyllithium furnished the corresponding ferrous dialkyl complex **40** (Scheme 8).[30] Treatment of the latter with dimethylanilinium tetraphenylborate in Et_2O and THF resulted in the protonation of one of the alkyl ligands to give the complexes **41a,b**. Moreover, treatment of **40** with tris(pentafluorophenyl)boron resulted in silicon methide abstraction, followed by rearrangement to provide the cationic complex **42**. All these complexes were characterized by X-ray diffraction and were tested as catalyst for ethylene polymerization. While the THF complex **41b** was inactive and the Et_2O complex **41a** was moderately active, the base-free complex **42** was the most efficient giving linear polyethylene with slightly higher molecular weight and narrower polydispersities compared to those of the polymer produced by the **38**-$FeCl_2$/MAO system.



Scheme 8

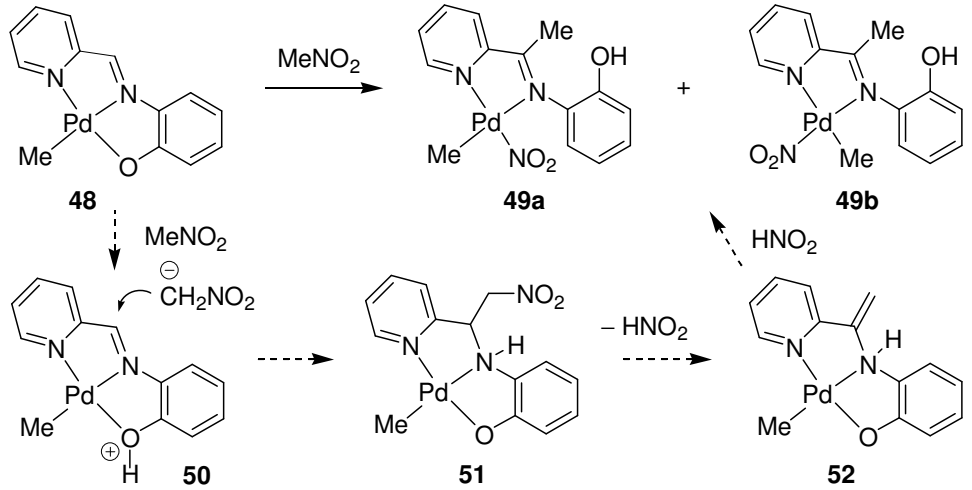
Similarly, the reactions of tetrabenzylhafnium and -zirconium with one equivalent of mono- and diiminopyrroles **43** and **45** bearing bulky *o*-substituted phenyl substituents at the imine nitrogens afforded

the bidentate and tridentate complexes **44** and **46**, respectively, resulting from the deprotonation of the pyrrole NH group and alkylation of one imino group (Scheme 9). The zirconium complexes of the tridentate ligand exhibited high catalytic activities in ethylene polymerization upon combining with Lewis acid (MMAO). Cationic complexes are involved in the catalytic process, as it was demonstrated by the preparation of the salts **47**, which were found to catalyze ethylene polymerization in the absence of Al-cocatalyst.[31] Recently, reaction of the potassium salt of ligand **45** with $Nd(BH_4)_3$ resulted in the reduction of one imine group and formation of a complex of the anionic ligand with the $Nd(BH_4)(BH_3)$ fragment which proved very active in the polymerization of 1,3-butadiene with good *cis*-selectivity.[32]



Scheme 9

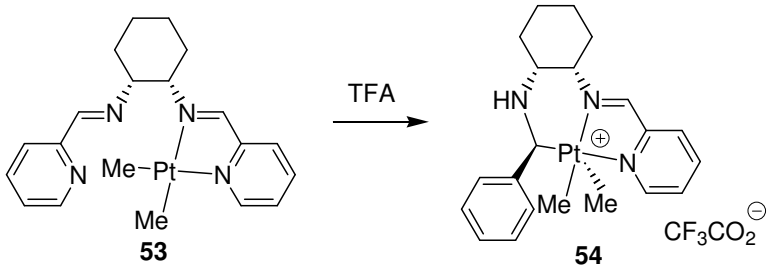
The reaction of nitromethane with the methylpalladium complex **48** with the tridentate *N*,*N*,*O*-anionic ligand featuring the 2-pyridineimine moiety gave the stereoisomeric complexes **49a,b** with a *C*-methylated imine ligand.[33] The mechanism involves the protonation of the ligand by nitromethane and subsequent attack of nitronate anion to the imine group of the intermediate **50** to give the neutral adduct **51**. Elimination of HNO_2 followed by tautomerization leads to the products **49a,b** (Scheme 10).



Scheme 10

Activation of the free imine function of bis(iminopyridine)$PtMe_2$ complexes occurred by treatment with trifluoroacetic acid affording diastereoselectively aminoalkylplatinum(IV) complexes (Scheme 11).[34]

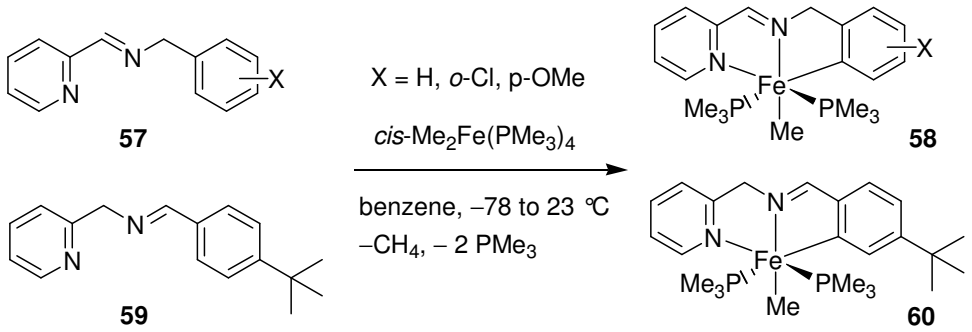
The reaction appears general for bis(2-pyridineimines) and 2-bis(quinoline)imines tethered by a two- or three-carbon alkyl chain, but analogous intermolecular reactions of a Me_2Pt-bipyridyl complex with aromatic imines were not successful, as protonolysis of the Pt-Me bond only occurred. For example, treatment of the complex **53** with trifluoroacetic acid gives the aminobenzylplatinum complex **54** through protonation of the free imine nitrogen followed by oxidative addition of the intermediate iminium ion.



Scheme 11

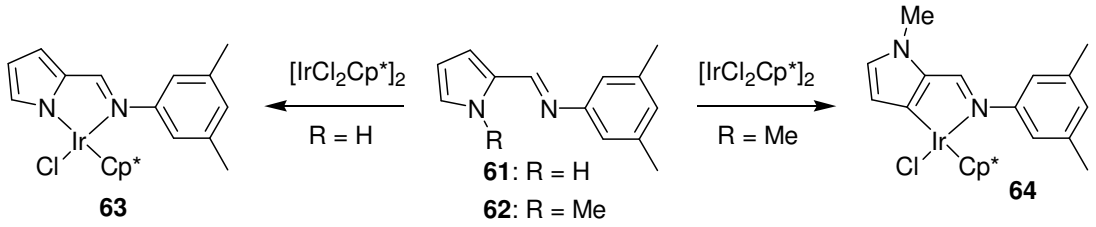
2.3. C–H Activation of 2-pyridine- and 2-pyrroleimines by organo-transition metal complexes

Following literature reports of aryl C–H bond activation of arylimines by the *cis*-$Me_2Fe(PMe_3)_4$ complex, the related reaction of several 2-pyridineimines **57** was investigated. Successful metalation was achieved *via* the loss of methane and two phosphine ligands affording the iron complexes **58** as dark green microcrystals. The analogous dark blue iron complex **60** was isolated from the benzaldimine **59** (Scheme 12).[35] For another example of C–H activation of a pyridinediimine-Fe ligand, see Scheme 47.



Scheme 12

Activation of the N–H bond is favoured over C–H activation upon treatment of pyrrole with transition metal complexes, although the Rh(III)-catalyzed C–H arylation of NH-free pyrrole and indoles has been reported.[36] In the case of pyrroleimines, it has been reported that the NH-free pyrroleimine **61** reacts with $[IrCl_2Cp^*]_2$to give the *N*-metalated complex **62**. Conversely, the reaction of the *N*-methyl imine **63** gave the C–H activation product **64** in good yield (Scheme 13).[37]

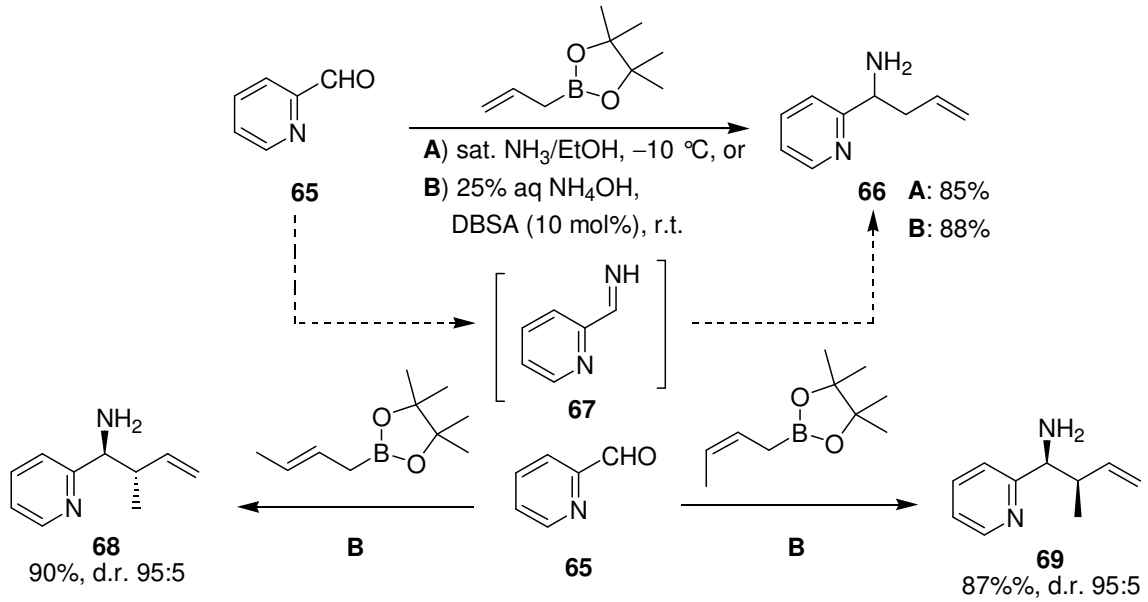


Scheme 13

3. Stereoselective organometallic reactions of 2-pyridine- and 2-pyrroleimines

3.1. Chemoselective and stereoselective α-aminoallylation of 2-pyridinecarboxaldehyde

Although *N*-substituted 2-pyridineimines are easily prepared and display high reactivity towards allylmetal reagents for the synthesis of homoallylic secondary amines,[38] two protocols have been developed to synthesize homoallylic primary amines from aldehydes, including 2-pyridinecarboxaldehyde **65**, using an allylboronate and avoiding the preliminary preparation of the imine (Scheme 14).



Scheme 14

By the first procedure, the aldehyde was dissolved in a saturated ethanolic solution of ammonia at −10 °C, then allylboronate was added and the mixture stirred for 2 hours.[39] Such α-aminoallylation was totally chemoselective, whereas with most other aromatic and aliphatic aldehydes minor amounts of the homoallylic alcohol were produced by allylation of the aldehydes. The *N*-unsubstituted imine, *e.g.* **67**, may be an intermediate in the reaction. Indeed, the formation of the *N*-unsubstituted imine from benzaldehyde was demonstrated by ^{1}H NMR study. However, it could not be excluded that a modified allylboron reagent was formed from allylboronate and ammonia. Noteworthy, when *iso*-propylamine and benzylamine were used instead of ammonia, only the corresponding benzaldimines were obtained.

In order to perform the reaction in aqueous medium, the presence of an additive with either acidic and anionic surfactant properties was necessary, and dodecylbenzenesulfonic acid (DBSA) gave the best performance.[40] The corresponding crotylation reactions were highly stereospecific, as (*E*)- and (*Z*)-crotylboronates gave the *anti*- and *syn*-adducts **68** and **69**, respectively, with high diastereomeric ratios. An enantioselective methodology can be developed using a chiral boronate, but only one example of enantioselective *a*-aminoallylation of benzaldehyde was reported (34% e.e.).

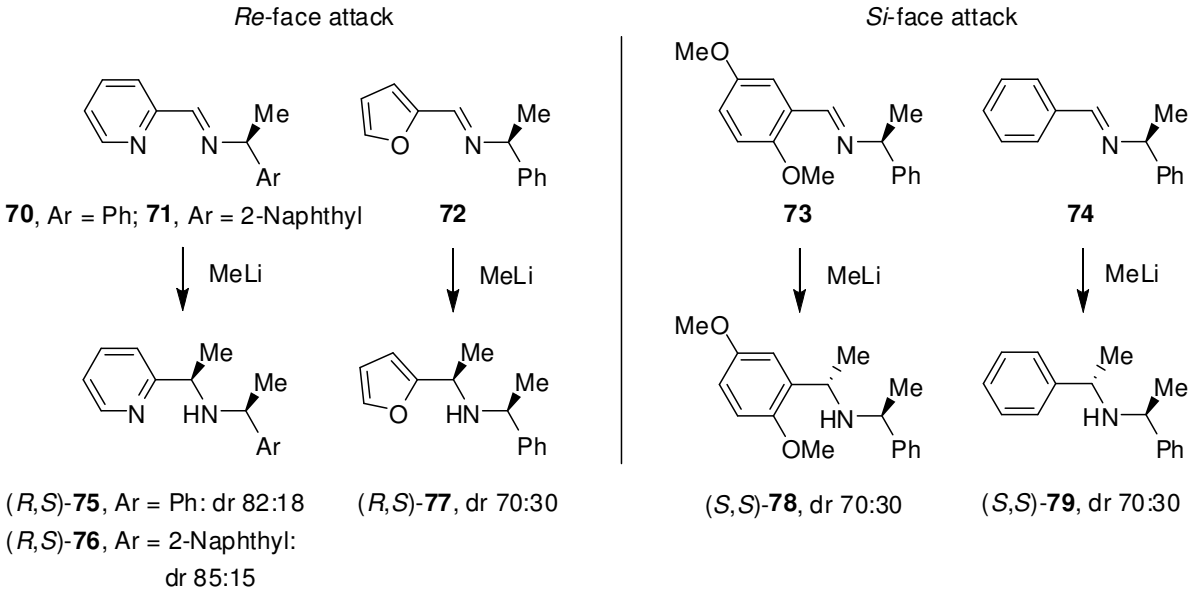
3.2. Organometallic reactions of chiral 2-pyridineimines bearing chiral *N*-substituents

3.2.1. The role of the *N*-substituent (chiral auxiliary). Factors affecting the diastereoselectivity

1,2-Diamines[41] and 1-(2-pyridyl)alkylamines[42] are useful ligands of metals species involved in catalytic asymmetric processes. A convenient strategy for the stereoselective synthesis of these compounds

is the addition of organometallic reagents to chiral 1,2-diimines and 2-pyridylimines obtained by the simple condensation of the carbonyl compounds with an optically pure primary amine, R*NH_2.[43] This strategy is complementary to the alternative route based on the diastereoselective reduction of the corresponding chiral 2-pyridine ketimines.[44] After removal of the chiral auxiliary R*, a new substituent can be introduced on nitrogen. Alternatively, the nitrogen substituent R* can be transformed retaining the inherent stereocentre.

Clearly, the main requisite for the efficient asymmetric synthesis is to achieve the highest degree of diastereoselectivity in the organometallic step. With this regard, the bidentate binding property of the 1,4-diazadiene moiety towards the Lewis acid-organometallic involved compound plays a determinant role. A dramatic evidence of that was provided by the stereochemical outcomes of the addition of methyllithium to a series of imines derived from different aromatic aldehydes and (*S*)-1-phenylethylamine (THF, −78 °C).[45] As a matter of fact, it was observed that the 2-pyridineimines **70** and **71**,[46] and 2-furylimine **72**, which are capable to form five-membered chelation complexes with the metal, underwent attack prevalently at their *Re* faces to give the secondary amines (*R*,*S*)-**75–77** with moderate diastereoselectivities. Conversely, the reactions of the 2,5-dimethoxybenzaldimine **73** and benzaldimine **74** gave mainly the (*S*,*S*)-diastereomers of the amines **78** and **79** (Scheme 15).

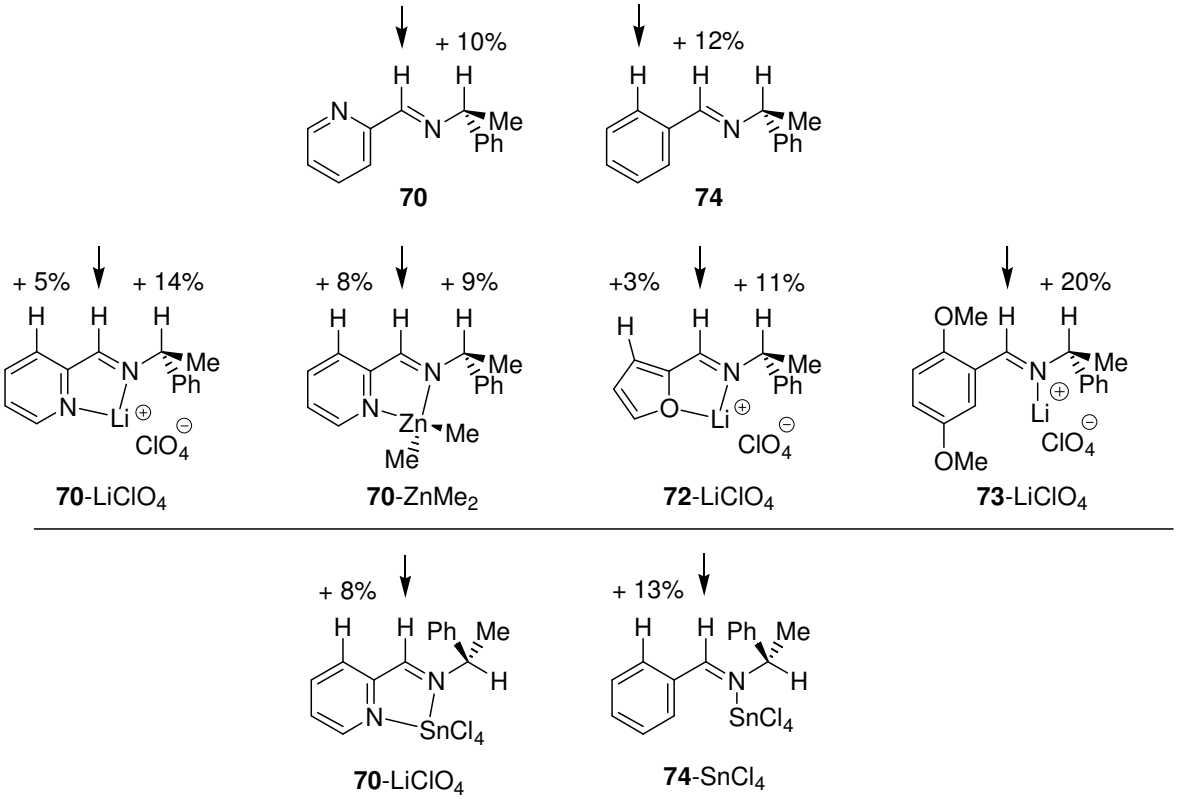


Scheme 15

An explanation of these results was envisioned after ^{1}H NMR and n.O.e. studies on the conformation of the aromatic imines and a few of their complexes with different metal species, *i.e.* $LiClO_4$, $SnCl_4$ and Me_2Zn, which were chosen owing to their different properties (Scheme 16).

First of all, it was established that the prevalent conformation of both the 2-pyridineimine **70** and benzaldimine **74** was the one with eclipsed imine (H–C=N) and auxiliary (H–C*) hydrogens. In fact, in both cases, irradiation of the imine hydrogen resulted in a clear response of H–C*; moreover, *anti* conformation of the pyridine and imine nitrogen was deduced by lack of response of the pyridine C6–H. On the other hand, irradiation at H–C=N of the 2-pyridineimine complexes **70**-$LiClO_4$ and **70**-$ZnMe_2$, as well as the 2-furylimine complex **72**-$LiClO_4$, resulted in response of both H–C* and H–aryl, demonstrating that bidentate complexation largely occurred without affecting the preferred orientation of the imine

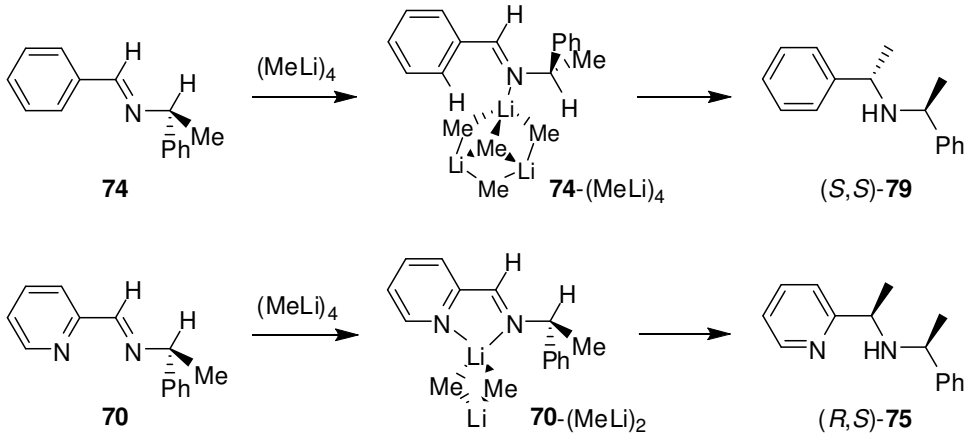
N-substituent. The same experiment carried out on the 2,5-dimethoxybenzaldimine complex **73**-$LiClO_4$ showed that a six-membered chelation complex was not formed, as the aryl C6–H gave no response. On the other hand, upon complexation of $SnCl_4$, both the 2-pyridineimine and benzaldimine changed orientation of chiral *N*-substituent, as an almost exclusive response of the aryl hydrogens was observed in **70**-$SnCl_4$ and **74**-$SnCl_4$. It is likely that H–C* assumes the orientation eclipsed with the metal in order to minimize the steric interactions of the auxiliary and tin substituents.



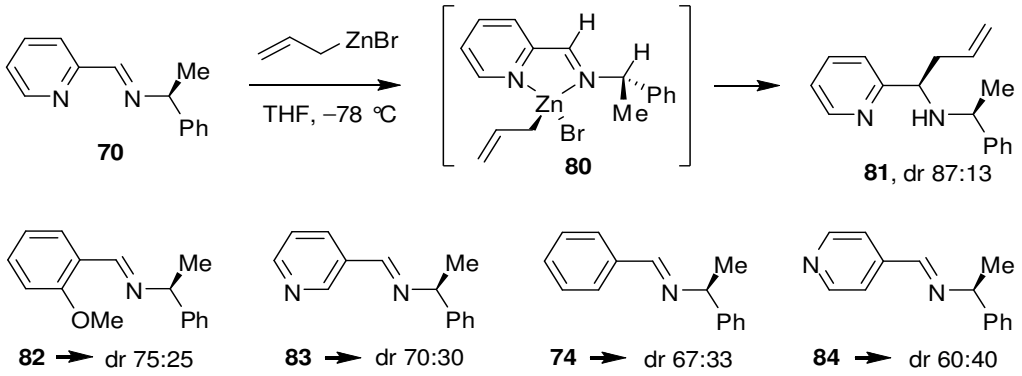
Scheme 16

The opposite diastereoselectivity displayed by the different aromatic imines can be explained by the different orientation taken by the *N*-substituent following complexation of the aromatic imine moiety with methyllithium. It should be considered that methyllithium has a tetrameric associate structure even in the Lewis basic solvent THF and it is likely that it is largely tetrameric even after complexation with the benzaldimine **74** to give **74**-$(MeLi)_4$, which assumes the more stable Li–H–C* eclipsed conformation. C–C bond formation would then occur to the more accessible *Si* face of the imine moiety, owing to the different steric properties of Me and Ph groups of the auxiliary, leading to the amine(*S*,*S*)-**79**. On the contrary, the bidentate 2-pyridylimine **70** cleaves the $(MeLi)_4$ to a complex **70**$(MeLi)_2$ in which the orientation of the *N*-substituent is retained. The amine (*R*,*S*)-**75** is then formed by preferential *Re* face attack (Scheme 17).

A similar, although less pronounced effect of the imine structure was observed in the additions of allylzinc bromide (Scheme 18).[47] The diastereomeric ratio of the homoallylic amines decreased following this order of the starting imines: 2-pyridineimine **70**>2-methoxybenzaldimine **82**>3-pyridineimine **83**>benzaldimine **74**>4-pyridineimine **84**. Hence, the diastereoselectivity was not affected by stereo-electronic effects of the aryl substituents, but was favoured by the bidentate nature of the imines that allows complexes such as **80** to be formed as intermediates.

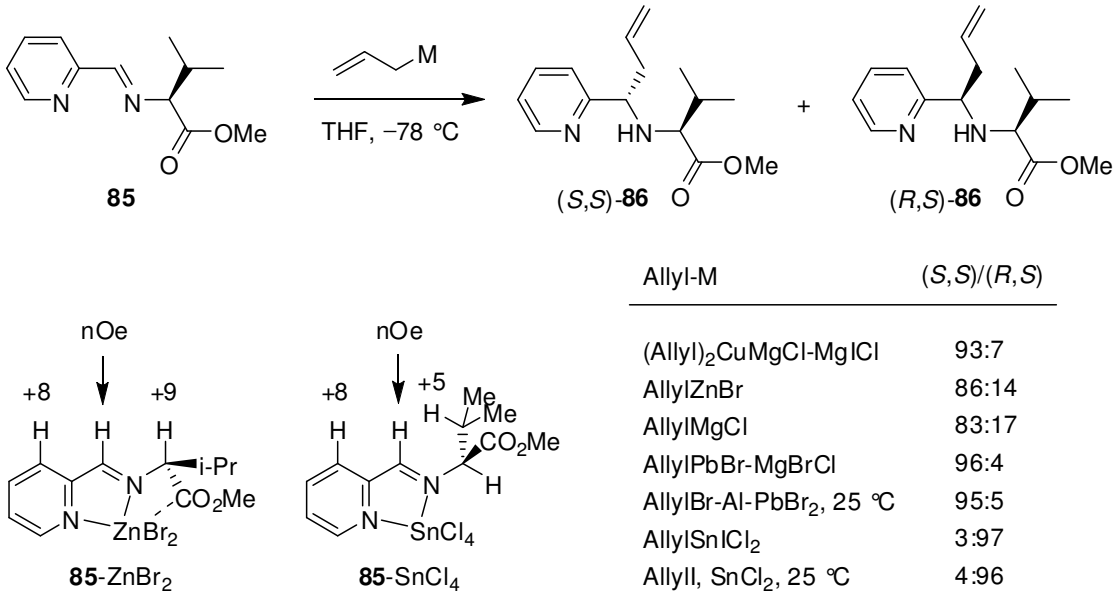


Scheme 17



Scheme 18

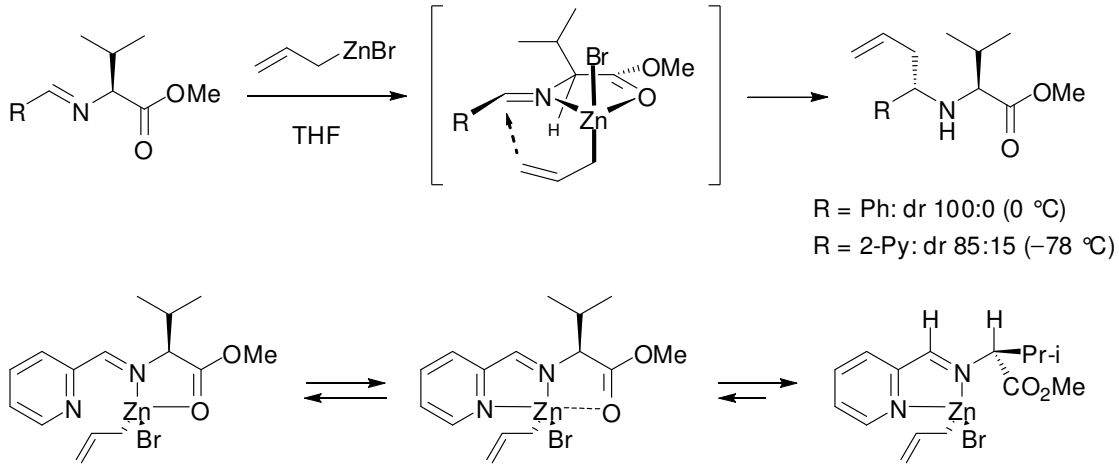
Using methyl (*S*)-valinate as the chiral auxiliary, excellent yields and diastereomeric ratios were obtained for both enantiomers of the homoallylic amine, as the sense of asymmetric induction was dependent on the nature of the allylmetal reagent used (Scheme 19).[48] Even in this case, the size of the allylmetal species was the key factor affecting the diastereoselectivity. The addition of copper, zinc and lead reagents at −78 °C afforded the product with *S* configuration of the newly formed stereocentre. The highest dr (96:4) was obtained with allyllead bromide formed *in situ* by transmetalation of the Grignard reagent, however, a Barbier procedure using the redox couple Al/$PbBr_2$ at room temperature gave excellent results, too (dr 95:5). On the contrary, the use of bulky allyltin(IV) reagents, either pre-formed or formed *in situ* in a Barbier protocol from allyl iodide and $SnCl_2$, allowed to obtain the (*R*,*S*)-diastereomer with even better stereocontrol (dr up to 97:3). The divergent diastereoselectivity is again consistent with the different orientation taken by the chiral auxiliary upon binding the metal reagents. In fact ^{1}H NMR n.O.e. studies performed on the model complexes of the imine with $ZnBr_2$ and $SnCl_4$ by irradiation of H–C=N gave different responses of H–C*. Apparently, the zinc complex retained the conformation of the auxiliary with eclipsed hydrogens (H–C=N and H–C*), whereas the tin complex gave no response of the H–C*, presumably owing to rotation along the N–C* bond. Moreover, two absorptions for the ester C=O group were observed in the IR spectrum, indicating that a link between zinc and the ester group was only partially formed, although the δ_C NMR absorption of the carbonyl carbon was shifted in the $ZnCl_2$ complex with respect to the free imine. On the other hand, lack of coordination between the ester group and Sn was evidenced by IR and ^{13}C NMR studies.



Allyl-M	(*S*,*S*)/(*R*,*S*)
$(Allyl)_2CuMgCl$-MgICl	93:7
AllylZnBr	86:14
AllylMgCl	83:17
AllylPbBr-MgBrCl	96:4
AllylBr-Al-$PbBr_2$, 25 °C	95:5
Allyl$SnICl_2$	3:97
AllylI, $SnCl_2$, 25 °C	4:96

Scheme 19

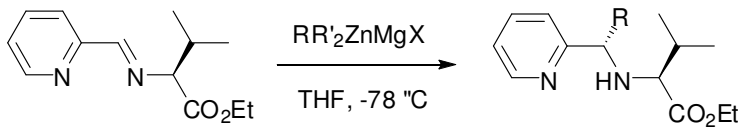
It is noteworthy that the allylzincation of the 2-pyridineimine **85** derived from methyl (*S*)-valinate was less diastereoselective than the corresponding reactions of analogous aromatic and aliphatic imines, *e.g.* the benzaldimine **87**, which afforded the homoallylic amine **89** with complete stereocontrol (Scheme 20).[49] This can be easily explained considering that, in the cases of imines prepared from non-hetero-substituted aldehydes, the reaction proceeds through the formation of a rigid complex, *e.g.* **88**, where the auxiliary is involved in the metal coordination, so impeding the rotation along the N–C* bond. On the other hand, the basic properties of the pyridine nitrogen successfully compete with the ester oxygen, so that an equilibrium can be established among different bidentate and tridentate complexes **90–92**. Clearly, rotation of the *N*-substituent is possible in the *N*,*N*-bidentate complex **92**, so affecting the level of stereocontrol.



Scheme 20

The preferred reagents to achieve the efficient and diastereoselective additions to the 2-pyridineimine **93** derived from ethyl (*S*)-valinate were found to be triorganozincate R_3ZnMgX or, preferably, mixed zincates RMe_2ZnMgX derived from Grignard reagents and dimethylzinc, considering that only one group R could be transferred to the imine and methyl is less prone to react. High selectivity for the transfer of the

group R and high level of diastereoselectivity were obtained in the formation of the amines **94**, apart for the addition of allyl, *t*-butyl and benzyl groups (Scheme 21).[50]



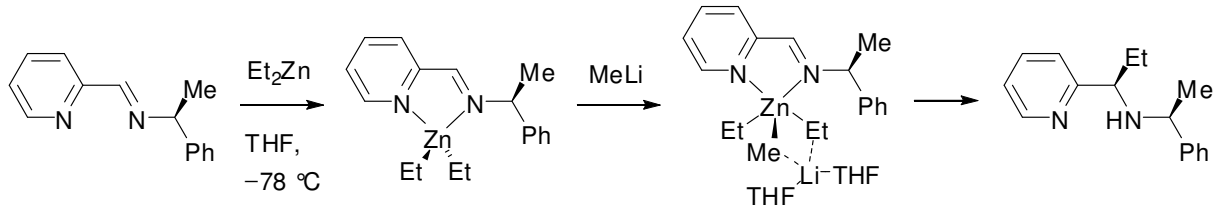
93

94: 73:27 < dr < 99:1
R = Alkyl, Allyl, Vinyl

Zincate	R	Dr
$Me_3ZnMgCl$	Me	92:8
$EtMe_2ZnMgCl$	Et	96:4
n-$BuMe_2ZnMgCl$	*n*-Bu	94:6
t-$BuMe_2ZnMgCl$	*t*-Bu	82:18
i-$PrMe_2ZnMgCl$	*i*-Pr	95:5
$BnMe_2ZnMgCl$	Bn	88:12
$AllylMe_2ZnMgBr$	Allyl	73:27
$VinylMe_2ZnMgBr$	Vinyl	99:1

Scheme 21

1-Phenylethylamine was a less effective chiral auxiliary for the addition of zincates to the 2-pyridine-imine **70**, as only moderate levels of stereoselection were observed. An interesting result was observed when methyllithium was added to the preformed complex **70**-Et_2Zn: in this case, the selective addition of the ethyl group, rather than methyl, was obtained. This result demonstrated that MeLi did not attack the imine function, instead the formation of an intermediate complex **70**-$Et_2MeZnLi$ occurred prior to the ethyl group transfer step (Scheme 22).



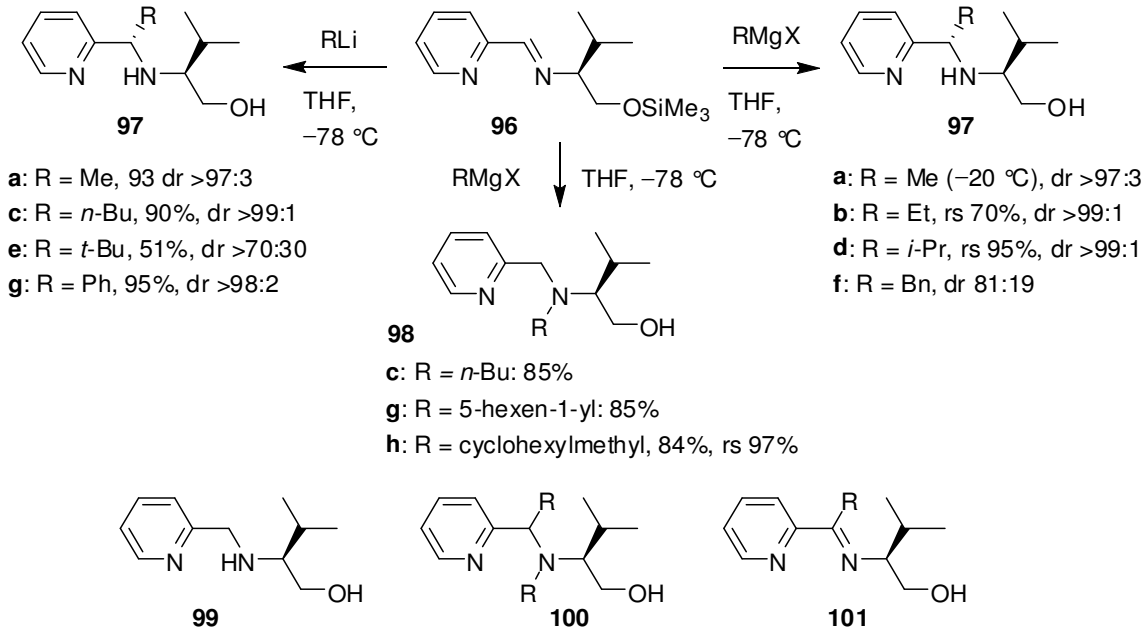
70 **70**-Et_2Zn **70**-$Et_2MeZnLi$ **95**, 95%, dr 62:38

Scheme 22

Ultimately, *O*-trimethylsilyl (*S*)-valinol proved to be the best chiral auxiliary for either aromatic and aliphatic imines (Scheme 23).[51] Organolithium reagents, either alkyl and aryl reagents, were the reagent of choice, as they reacted at −78 °C to afford exclusively, after removal of the silyl protection, the *C*-alkylation products with excellent yields and diastereoselectivities, *e.g.* **97a,c,g**. The only exception was the addition of *t*-BuLi, which gave **97e** in 70:30 diastereomeric ratio.

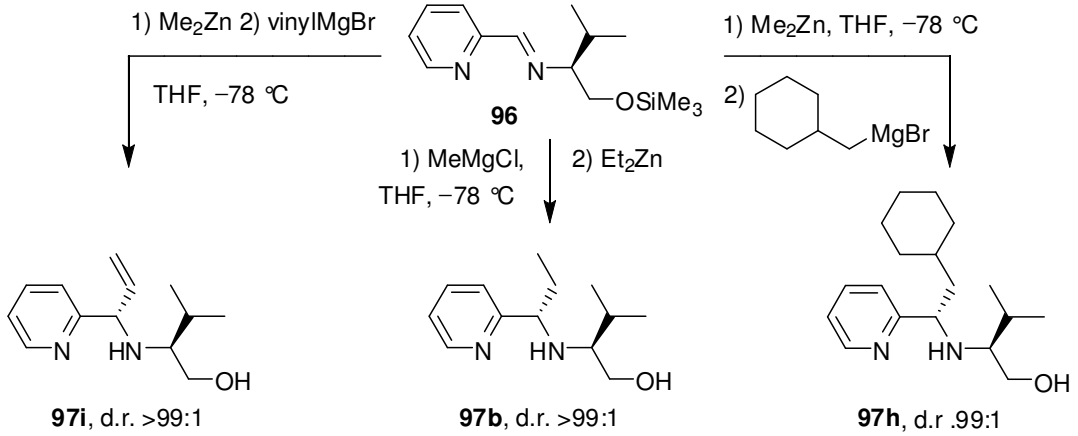
On the other hand, problems of regioselectivity (*C- vs N*-alkylation) were encountered using Grignard reagents. The additions of methyl- and benzylmagnesium halides occurred exclusively at carbon to give **97a** and **97f**, but primary alkyl reagents such as *n*-butyl-, 5-hexen-1-yl- and cyclohexylmethyl, afforded the *N*-alkylation products **98c,g,h**. On the other hand, EtMgBr and *i*-PrMgCl produced mixtures of regioisomers where the *C*-alkylation **97b,d** products were prevalent at different degrees. Excellent stereocontrol was often observed for the *C*-alkylation products, apart for **97d**. Although the yields were often very high in these organometallic reactions, the presence of one or more by-products, *e.g.* **99–101**, in the crude reaction mixtures could be assessed by GC-MS analyses, and their structures were determined by the mass spectral

fragmentation or by comparison with authentic specimen. The occurrence, at least in part, of a SET mechanism accounts for the formation of these by-products.



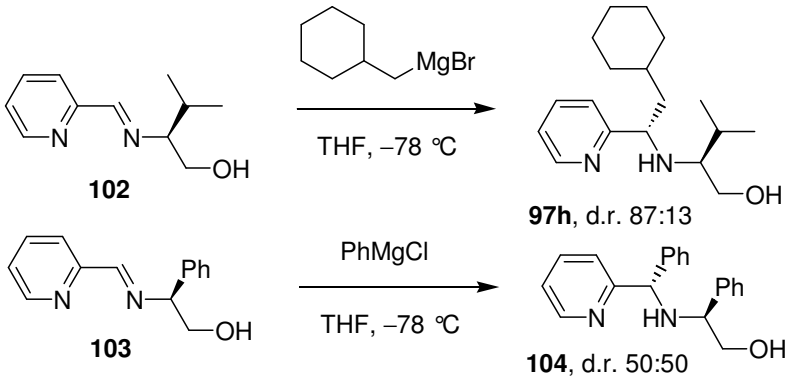
Scheme 23

Considering that primary alkylmagnesium reagents can be more conveniently prepared than the corresponding lithium reagents, a protocol was devised in order to exploit such Grignard compounds for the completely regio- and diastereoselective alkylation of the 2-pyridineimine. The strategy consists in the preparation *in situ* of dimethyl- or diethyl(alkyl)zincates by treatment of primary alkylmagnesium halides with dimethylzinc. For example, while cyclohexylmethylmagnesium chloride gave the *N*-alkylation product **98h**, the mixed cyclohexyl(dimethyl)zincate selectively transferred the larger alkyl group to the imine carbon to give **97h** as a single diastereomer (Scheme 24). Similarly, the reactions with $MeEt_2ZnMgCl$ and vinyl $Et_2ZnMgBr$ gave the **97b** and **97i**, respectively, more efficiently than those with the simple Grignard reagents.



Scheme 24

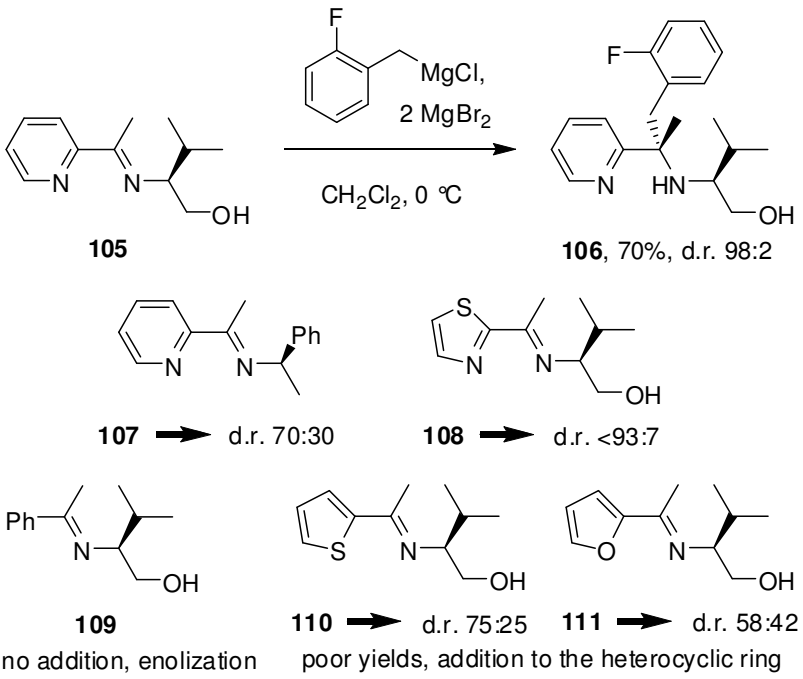
Besides the excellent diastereoselectivity and the wide applicability of different organometallic reagents, the use of the *O*-silyl-protected valinol as chiral auxiliary is convenient because the silyl protection is easily introduced as well as removed after the organometallic step. The unprotected auxiliaries (*S*)-valinol and (*S*)- and (*R*)-phenylglycinol had been previously used in organometallic reactions of aldimines, with excellent results in terms of diastereoselectivity;[43a] in this case, the imines are in equilibrium with tautomeric oxazolidines. However, the use of the unprotected auxiliary requires the use of an excess of the organometallic reagent and the *O*-metallated auxiliary displays modified coordination properties, thereby affecting the stereocontrol of the organometallic addition. As a matter of fact, the addition of cyclohexylmethylmagnesium bromide to the unprotected imine **102** resulted in lower yield and especially lower diastereoselectivity of the *C*-alkylation product **97h** (Scheme 25).[44a]



Scheme 25

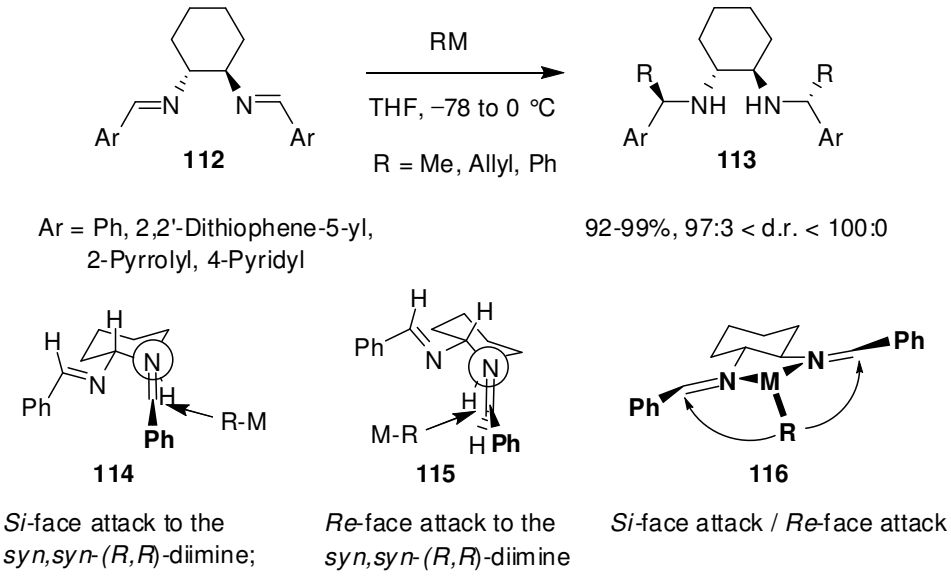
Similarly, the addition of phenylmagnesium chloride to the oxazolidine derived from 2-pyridine-carboxaldehyde and (*S*)-phenylglycinol gave a 1:1 mixture of diastereomeric amines **104**, whereas the alternative addition of the 2-pyridylmagnesium reagent to the benzaldehyde imine/oxazolidine occurred with 81% diastereomeric excess.[52] In the latter case, the high stereocontrol was attained because of the rigid structure of the metal chelated chiral auxiliary. Such *N*,*O*-bidentate metal chelation, which determines the rigidity of the chiral auxiliary, is adversed with the pyridine imine, where *N*,*N*-chelation is competitive.

Ketimines are less reactive than the corresponding aldimines for steric and stereoelectronic effects. Moreover, a side reaction is the α-metalation of the alkyl substituent, nevertheless, optimal reaction conditions were determined for the C-alkylation of the ketimine **105** by 2-fluorobenzylmagnesium chloride. Indeed, the use of 2 equivalents of $MgBr_2$ as an additive in dichloromethane at 0 °C allowed to obtain the desired product **106** in good yield and with excellent diastereoselectivity.[53] The presence of the hydroxyl group in the chiral auxiliary was a requisite for obtaining high diastereoselectivity. In fact, when the same reagent conditions were applied to the imine **107** derived from 1-phenylethylamine, the product **108** was obtained as a diastereomeric mixture, similarly to the stereochemical outcomes of the reactions of the same imine with allyl- and benzylmagnesium chloride (d.r. 68:32 and 91:9, respectively).[54] Further experiments also demonstrated that the *N*,*N*-bidentate structure was necessary for ketimines to undergo successful alkylation. As a matter of fact, the analogous 2-thiazoleimine **108** reacted successfully, but no reaction apart metalation occurred with the imine **109** derived from acetophenone, whereas the 2-thiopheneimine **110** and 2-furanimine **111** gave mixtures of products coming from alkylation of both the imine and the heterocyclic ring (Scheme 26).



Scheme 26

Hence, it appears that chiral auxiliaries with bidentate chelation ability are useful to achieve high diastereoselectivity in the organometallic additions to 2-pyridine ketimines. This is contrary to what observed with the 2-pyridinealdimines, as the use of such chiral auxiliaries gave lower diastereoselectivity with respect to other aromatic aldimines. This trend has been recently confirmed studying the addition of organometallic reagents to aromatic diimines derived from (*R*,*R*)-1,2-diaminocyclohexane (Scheme 27).[55]

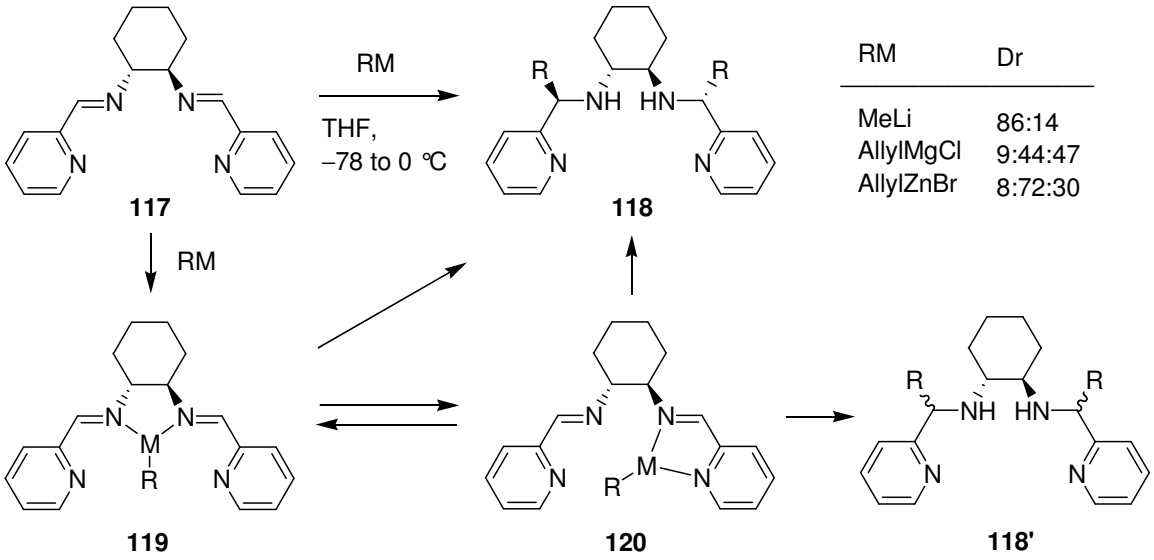


Scheme 27

In fact, the additions of organometallic reagents (RLi, allylMgCl) to the diimines **112** derived from benzaldehyde, and 2-thiophene, 2-pyrrole- and 4-pyridinecarboxaldehydes proceeded with high efficiency and stereocontrol, through two consecutive additions to the imines *Re* faces, lately giving the products **113**,

with *R* configuration of the newly formed stereocentres. It should be observed that external attack to the *Si* face of the imine in the most stable *syn*,*syn*-conformation (model **114**) should be favoured, because it is consistent with the Felkin-Anh model. Instead the stereochemical outcome is rationalized by the attack on the nucleophile to the internal *Re* face of the imine, as in model **115**. It was assumed that the reaction proceeded through the preliminary formation of the bidentate chelation complex **116** involving both nitrogen atoms of the diaminocyclohexane moiety. In this case, attack of the nucleophile R to the one or the other imine function would lead to the opposite configuration of the newly formed stereocentre, however, attack to the *Re* face should be favoured by the reduced steric interactions.

This explanation of the diastereoselectivity was supported by the observation that the analogous reactions of the diimine **117** prepared from 2-pyridine carboxaldehyde gave the corresponding diamines **118** with reduced stereocontrol, presumably because the complex **119**, which is the precursor of the all-(*R*)-diastereomer, is in equilibrium with the complex **120** involving the pyridine-imine moiety, where the free rotation along the N–C* bond leads to a number of alternative conformations and consequently to a reduced stereocontrol resulting in the formation of a diastereomeric mixture **118'** (Scheme 28).



Scheme 28

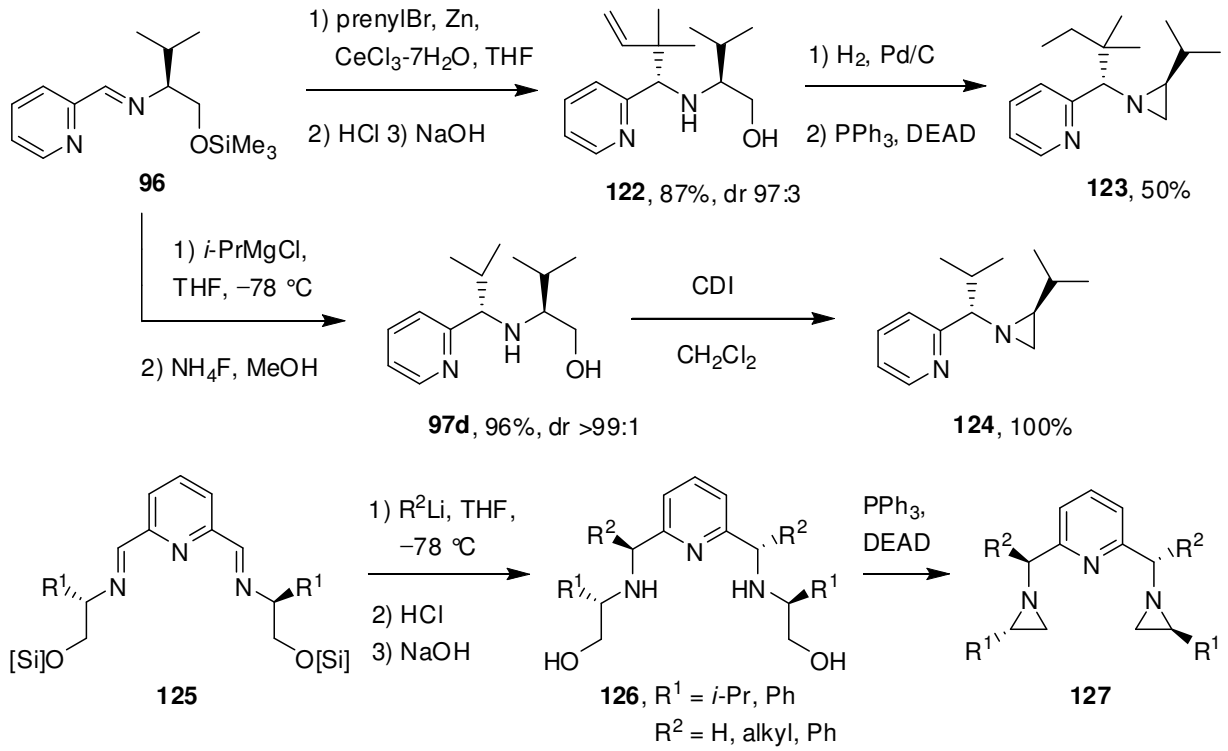
The recently described reduction of the ketimines derived from 1,2-diaminocyclohexane and aryl alkyl ketones by $NaBH_4$-Ti(*i*-PrO)$_4$ is an alternative method to prepare the same compounds.[56] Although moderate to high levels of diastereoselectivity were often observed, a 2:1 diastereomeric ratio was obtained in the case of 2-acetylpyridine.

3.2.2. Synthesis of pyridine-aziridine compounds

3.2.2.1. Synthesis of 2-[1-(2-pyridyl)alkyl]aziridines

The diastereoselective addition of organometallic reagents to *O*-silylated 2-pyridine **96** and analogous 2-quinolineimines derived from (*S*)-valinol and (*S*)-phenylglycinol was used to prepare chiral pyridine-aziridine *N*,*N*-bidentate ligands which proved active in Pd-catalyzed asymmetric allylic alkylation (AAA) reactions, typically the addition of malonate carbanions to 1,3-diphenyl-2-propenyl acetate and carbonate. Examples of the synthetic strategy are shown in Scheme 29. After the organometallic step, proceeding with

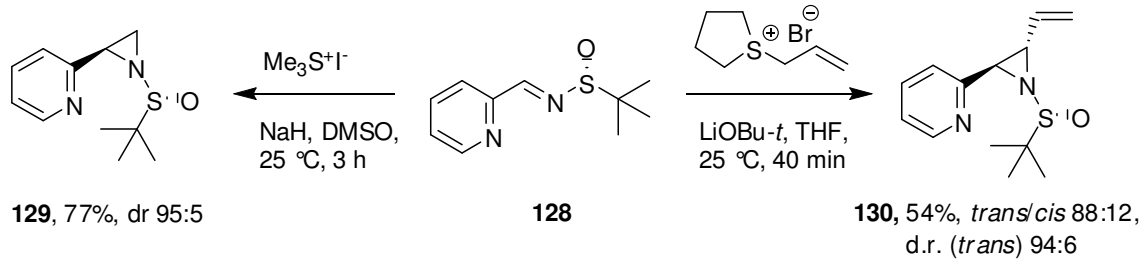
high diastereoselectivity, for example to give the β-aminoalcohols **122** and **97d**, the nitrogen substituent was not removed, instead, the β-aminoalcohols moieties were transformed into a substituted aziridine ring, *e.g.* **123** and **124**. The influence of the substituents placed in the different positions of the skeleton, *i.e.* the aziridine C2, the pyridine C6 and the benzylic carbon, on the enantioselectivity of the AAA reaction was thoroughly investigated in order to optimize the ligand structure.[57] Finally, among several C2-symmetric pyridine-bis(aziridines) **127**, derived from 2,6-diiminepyridine **125** through the β-aminoalcohols **126**, the one with R^1=Ph and R^2=Me was found to be the ligand of choice, as it was obtained with the best diastereoselectivity (d.r. 99:1) and displayed the best e.e. (up to 99% e.e.) in the AAA reactions.[58]



Scheme 29

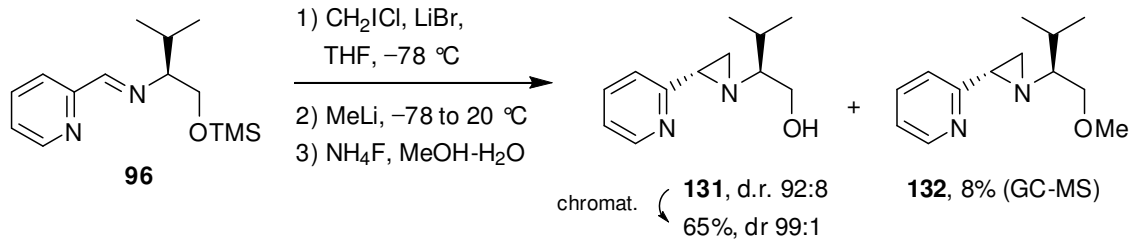
3.2.2.2. Synthesis of 2-(2-pyridyl)aziridines

Formation of the aziridine ring by addition of sulfonium ylides to chiral aromatic imines, derived from (*R*)-*t*-butylsulfinamide, occurred with high diastereoselectivity. In the case of the 2-pyridineimine **128**, either the 2-substituted aziridine **129**[59] and the *trans*-2,3-disubstituted aziridine **130**[60] were obtained with moderate to good yields and high diastereoselectivities (Scheme 30).



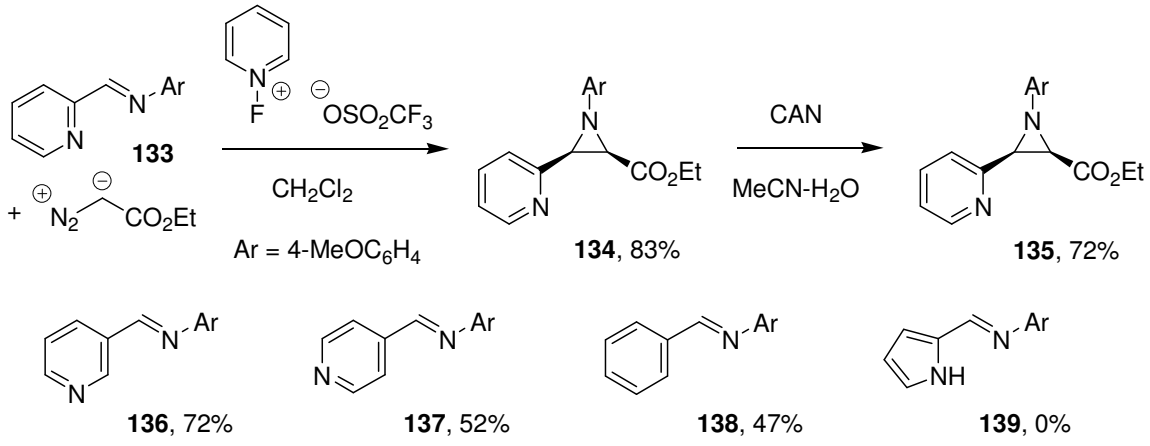
Scheme 30

Removal of the chiral auxiliary from these aziridines has not been reported. Usually, such a step for analogous secondary amines is accomplished by acidic hydrolysis. However, it has been claimed that 2-aryl-1-(*t*-butylsulfinyl)aziridines, when treated with aq hydrochloric acid, undergo ring opening to give 2-chloro-alkylamines.[61] The reagent prepared *in situ* at low temperature by adding methyllithium to iodochloro-methane in the presence of lithium chloride allowed the chemoselective aziridination of chiral 2-pyridine and 2-quinolineimines, whereas other aromatic imines including 3- and 4-pyridineimines were recovered. The bidentate nature of the imine, *e.g.* **96**, is necessary to enforce the nucleophilic power of the reagent, presumably $ClCH_2Li$-LiCl, whose carbenoidic character is indicated by the formation of the methyl ether **132** as byproduct.[62] After desilylation, the 2-(2-pyridyl)aziridine **131** was obtained with good yield and high diastereoselectivity (Scheme 31). The main diastereomer was obtained pure by column chromatography on a silica gel column. Successively, it was converted to a variety of more functionalized compounds by opening of the aziridine ring with heteronucleophiles.[63] More recently, it has been reported that the reagent prepared *in situ* by adding MeLi to diiodomethane is capable to form aziridines by reaction with activated, aliphatic and aromatic, *N*-tosylimines.[64]



Scheme 31

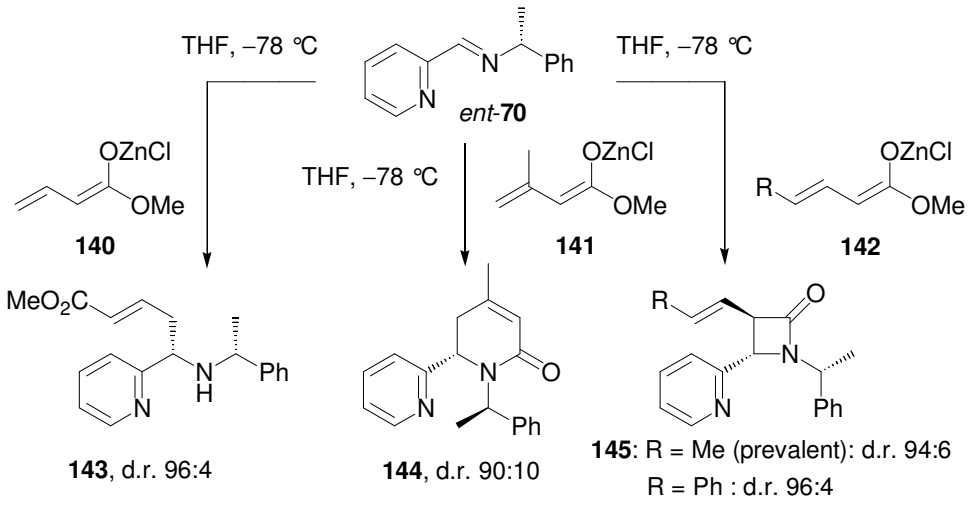
To complete the picture of available aziridination protocols of 2-pyridineimines, it should be mentioned that *N*-fluoropyridinium triflate activated the nucleophilic attack of ethyl diazoacetate to *N*-anisyl aromatic imines affording exclusively *cis*-2,3-disubstituted aziridines. The *N*-aryl-2-pyridineimine **133** showed higher reactivity than other imines including 3- and 4-pyridineimines, **136** and **137**, respectively, and benzaldimine **138**. The aziridine **134** was obtained in high yield, then the *N*-substituent could be removed by oxidative cleavage with cerium ammonium nitrate (CAN) leaving the NH–aziridine **135**. Conversely, electron-rich imines such as the 2-pyrroleimine **139** were unreactive (Scheme 32).[65]



Scheme 32

3.2.3. Synthesis of ω-(2-pyridyl)-ω-lactams

The asymmetric synthesis of ω-(2-pyridyl)-β- and -δ-lactams was achieved by the addition of zinc dienolates to the 2-pyridylimine *ent*-**70** derived from (*R*)-1-phenylethylamine.[66] The regioselectivity of the attack, at the α- or γ-position of the dienolate, was dependent on the substitution pattern of the reagent, which was prepared by metalation of the unsaturated ester with LDA (THF, −78 °C), followed by transmetalation with $ZnCl_2$. The unsubstituted zinc dienolate **140** gave the product of γ-attack, **143**, which polymerized even at low temperature. The β-methyl substitution in the dienolate **141** prevented polymerization and the 5,6-dihydropyridin-2-one **144** was exclusively obtained through the intermediate (*Z*)-δ-amido-α,β-unsaturated ester which then underwent cyclization. On the other hand, γ-substituted dienolates **142** gave *trans*-3,4-disubstituted azetidin-2-ones **145** as the prevalent or exclusive products, coming from the preferential α-coupling of the (*Z*)-dienolate to the imine through a six-membered chair transition state. In all cases, high diastereoselectivities were obtained (Scheme 33).

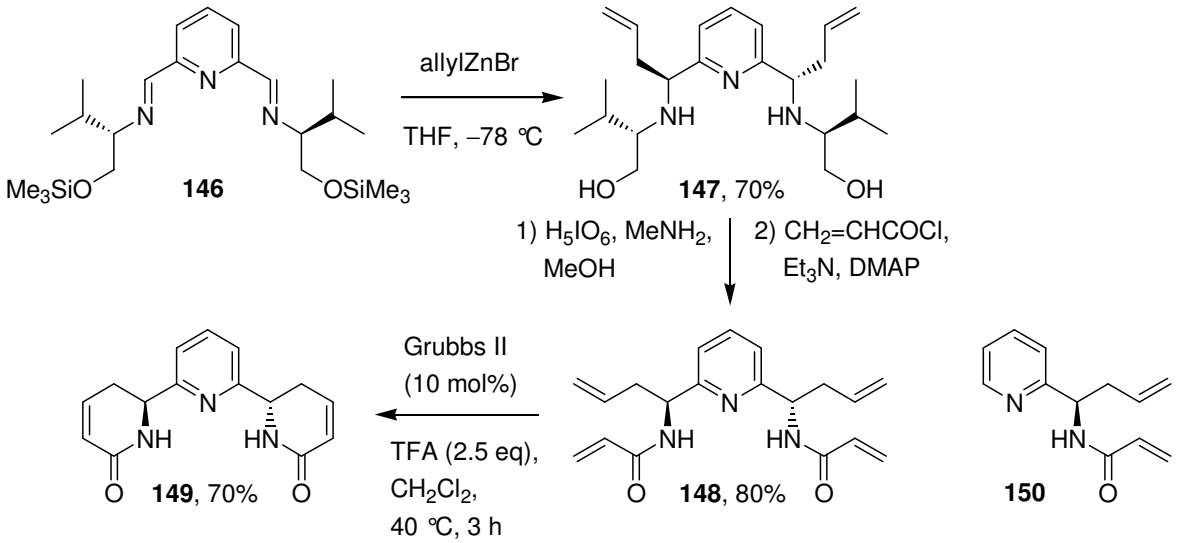


Scheme 33

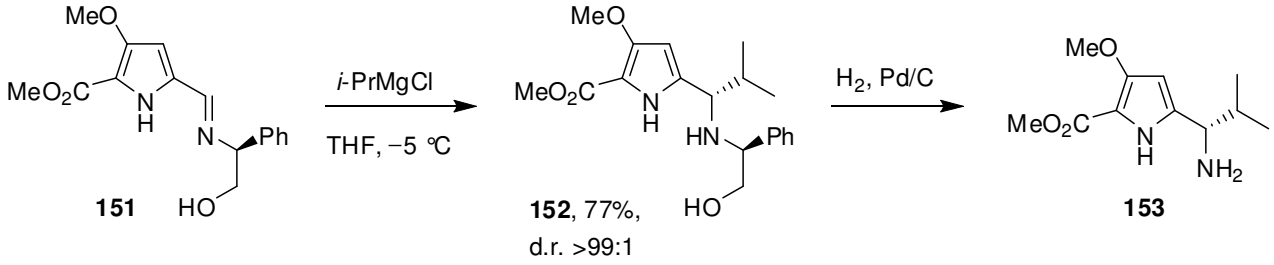
The pyridine **149** with two α,β-unsaturated-δ-lactam rings attached at C2 and C6 was prepared with complete diastereoselectivity exploiting the previously described protocol for the synthesis of homoallylic amines from 2-pyridineimine. After the allylzincation step performed on the bisimine **146** to give **147**, the chiral auxiliary was oxidatively removed and the crude secondary amine was converted to the acryloyl amide **148**. Finally, a ring closing metathesis (RCM) with the 2nd generation Grubbs catalyst afforded with good overall yield the pyridine-bislactam **149**, which is potentially useful as an intermediate to prepare more functionalized compounds, *e.g.* ligands, exploiting the reactivity of the unsaturated lactam rings (Scheme 34).[67] Surprisingly, the RCM reaction was not successful on the more simple unsaturated pyridine derivative **150**, available from the monoimine **96**.

3.2.4. Stereoselective organometallic reactions of chiral 2-pyrroleimines

(*S*)-Phenylglycinol and (*S*)-valinol have been used as chiral auxiliaries for the stereoselective synthesis of 1-(2-pyrrole)alkylamines. In a first example, the secondary amine **152** was obtained with good yield and complete diastereoselectivity by the addition of *i*-PrMgCl to the imine **151** prepared from a substituted 2-pyrrolecarboxaldehyde and (*S*)-phenylglycinol. Removal of the chiral auxiliary by routine hydrogenolysis gave the primary amine **153** which was used to prepare a dipeptide mimic (Scheme 35).[68]

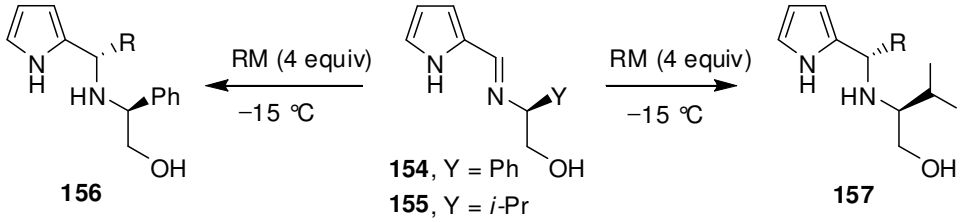


Scheme 34



Scheme 35

The scope of the method has been more thoroughly investigated on the unsubstituted 2-pyrroleimines derived from (*S*)-phenylglycinol and (*S*)-valinol, so ascertaining that either organolitium, Grignard reagents and mixed zincates are useful reagents, apart methyl-, vinyl- and phenylmagnesium bromides which did not react. Noteworthy, the conversion of Grignard reagents to mixed zincates can be used to improve the diastereoselectivity. The vinyl- and phenyl-substituted compounds could not be purified by chromatography (SiO_2) owing to extensive decomposition. In all cases, very high diastereoselectivities were obtained for the products, but *t*-BuLi gave a mixture of diastereomers (d.r. 55:45 from **156**) (Scheme 36).[69]

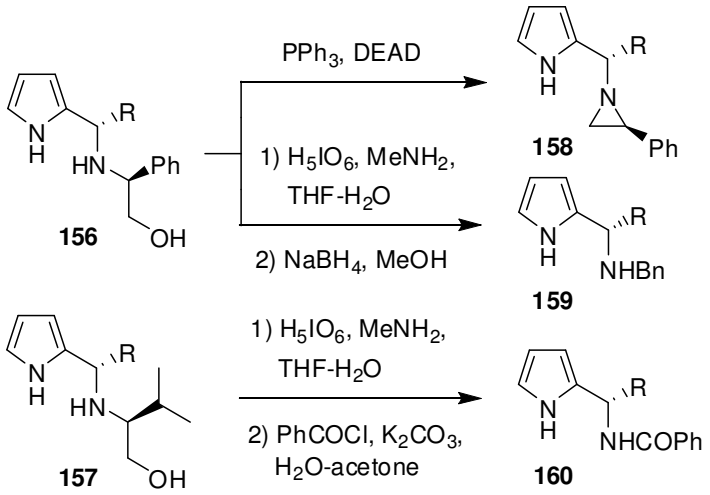


a (MeLi): R = Me, 96%, d.r. >95:5
b (*n*-BuLi): R = *n*-Bu, 91%, d.r. >99:1
c (*i*-PrMgCl): R = *i*-Pr, 92%, d.r. >95:5
d: AllylMgCl): R = Allyl, 87%, d.r. >95:5
d (2 Et_2Zn, 2 AllylMgCl): R = Allyl, 86%, d.r. >99:1
e (BnMgCl): R = Bn, 91%, d.r. >95:5
f (PhLi): R = Me, 95%, d.r. >95:5

a (MeLi): R = Me, 91%, d.r. >99:1
b (*n*-BuLi): R = *n*-Bu, 87%, d.r. >99:1
d (AllylMgCl): R = Allyl, 78%, d.r. >99:1
d (2 Et_2Zn, 2 AllylMgCl): R = Allyl, 89%, d.r. >99:1
e (BnMgCl): R = Bn, 90%, d.r. >99:1
f (PhLi): R = Me, 91%, d.r. >95:5
g (2 MeLi, 2 VinylLi): R = Vinyl, 92%, d.r. >99:1

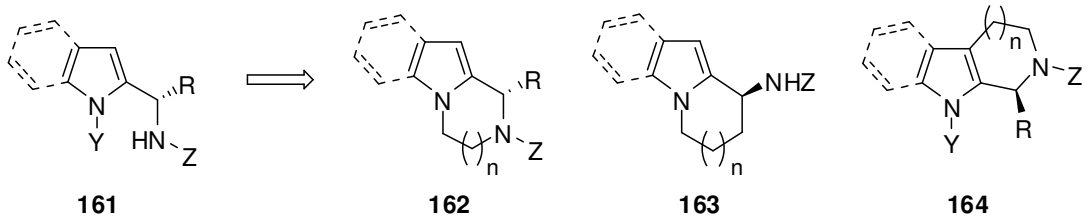
Scheme 36

The secondary amines could be easily converted to aziridines by Mitsunobu cyclization of the β-aminoalcohol moiety, *e.g.* the preparation of **158** from **156**, or converted to the *N*-benzyl derivative **159** by reduction of the intermediated benzylidene imine which was formed *in situ* by the oxidative cleavage with periodic acid. Similarly, oxidative cleavage of the (*S*)-valinol auxiliary of **157** gave the primary amine which was protected as the benzoyl derivative **160** (Scheme 37). The organometallic route to 1-(2-pyrrolyl)-alkylamines is complementary to the hydrogenation/reduction of the corresponding chiral 2-pyrrole ketimines.[70]



Scheme 37

The products obtained by the organometallic additions to chiral 2-pyrroleimines and analogous 2-indoleimines **161** can be useful intermediates for the synthesis of fused bicyclic and tricyclic molecules by properly exploiting the reactivity of the pyrrole and amino NH groups, *e.g.* **162** (Y=H), of functionalities present in the substituents Y and R, *e.g.* **163**, or the reactivity of *N*-substituted pyrrole (indole) nucleus at C3, *e.g.* **164** (Scheme 38).

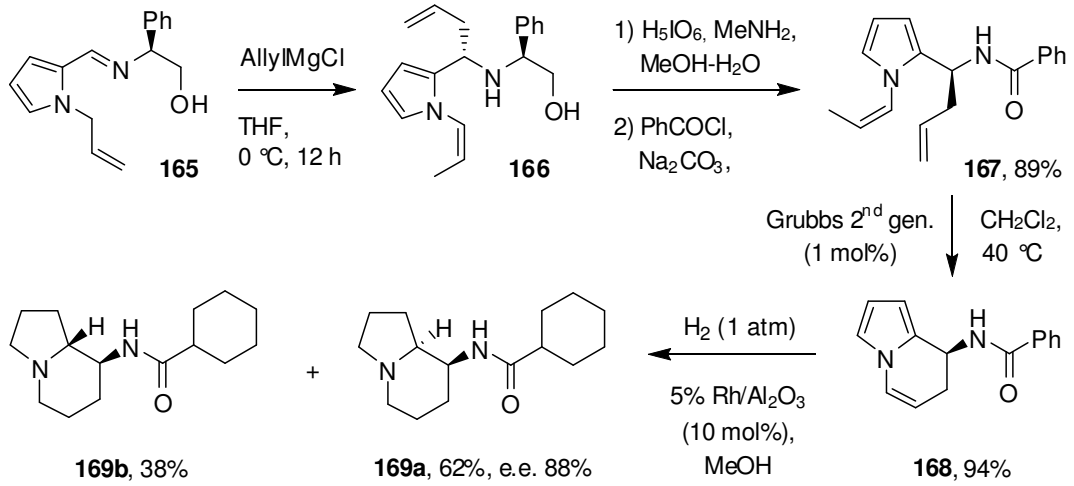


161 **162** **163** **164**

Scheme 38

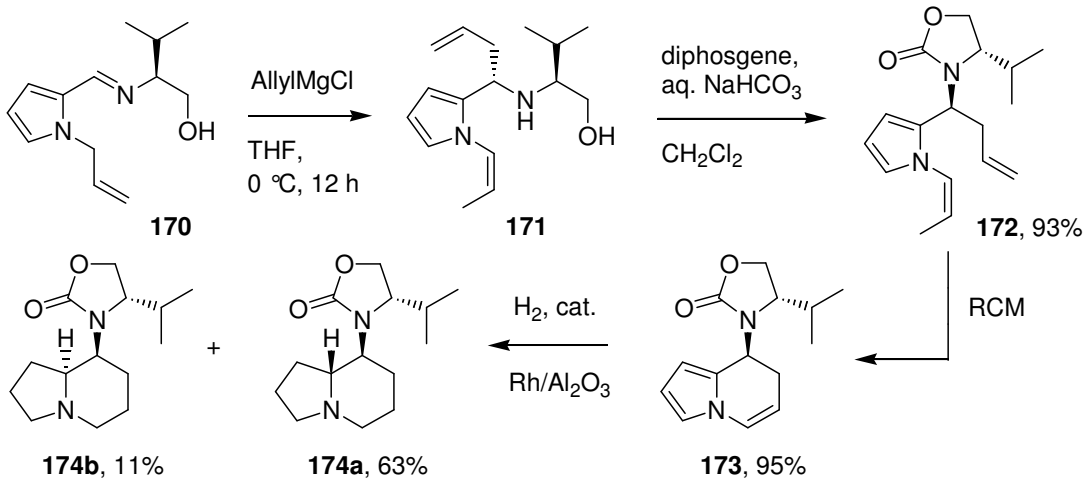
Optically pure *N*-protected 8-aminoindolizidine have been synthesized (Scheme 39).[71] For this purpose, the imine **165**, obtained from 1-allyl-2-pyrrolecarboxaldehyde, was reacted with an excess of allylmagnesium chloride and the reaction mixture was stirred at 0 °C overnight, so allowing the preparation of the amine **166** with complete isomerization of the pyrrole allyl substituent to (*Z*)-1-propenyl. Removal of the chiral auxiliary and protection of the primary amine gave the diene derivative **167** with high overall yield and this was submitted to RCM reaction with the 2nd generation Grubbs ruthenium catalyst to construct the unsaturated bicyclic skeleton of **168**. Finally, complete hydrogenation of the alkene and both the aromatic

rings gave the 8-aminoindolizidine derivatives as a mixture of diastereomers **169a,b**. The prevalent one, **169a**, was not obtained enantiomerically pure because partial epimerization of the C8 stereocentre occurred during hydrogenation.



Scheme 39

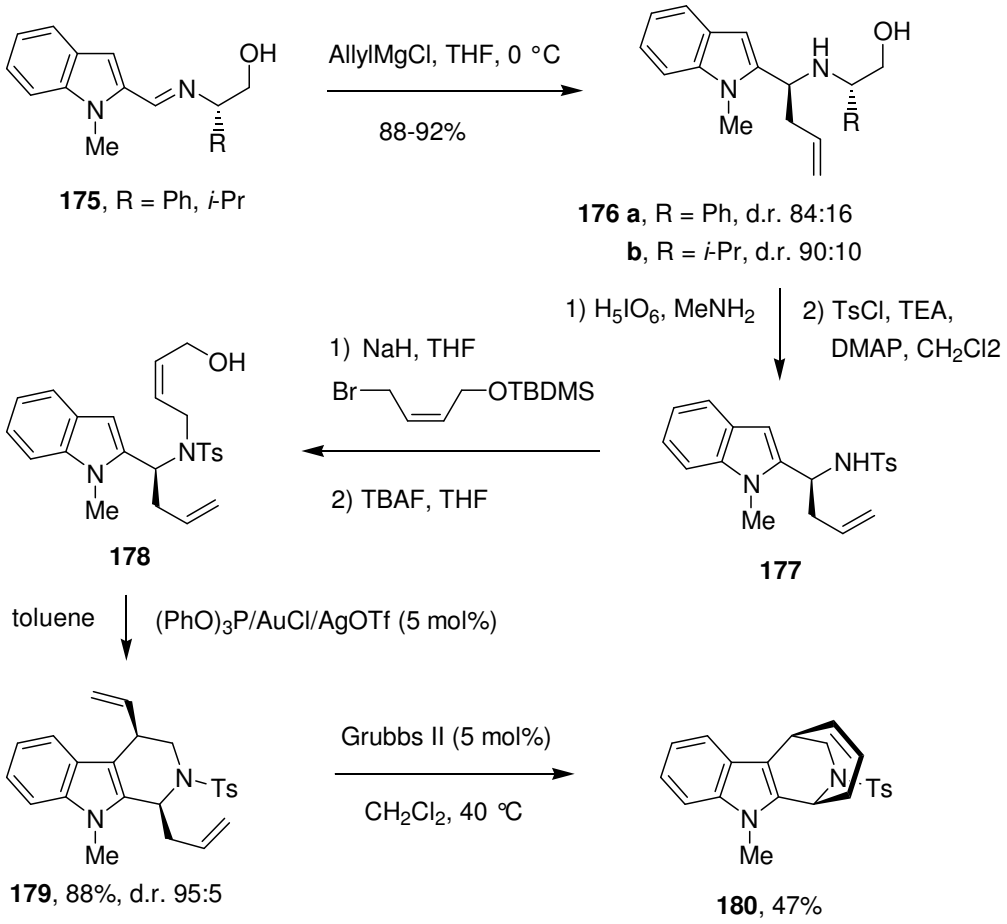
Moreover, the configuration of the stereocentre formed at position 8a was affected by the nature of the nitrogen substituent (Scheme 40). The same reaction sequence was carried out starting from the (*S*)-valinol-derived imine **170** which gave the allylated product **171**. Reaction with diphosgene afforded the pyrrole derivative **172** where the amino function was protected as oxazolidinone. After routine RCM reaction, the bicylic compound **173** was hydrogenated in the same previously used conditions to give the *N*-substituted 8-aminoindolizidine as a diastereomeric mixture **174a,b**. In this case, however, the main diastereomer **174a** had the *S* configuration of the 8a stereocentre. Since the chiral auxiliaries are available with either *S* and *R* configuration, the 8-aminoindolizidine can be prepared as diastereomeric mixtures enriched of one of the four possible diastereomers.



Scheme 40

The addition of benzyl- and allylmagnesium halides to the 2-indoleimines **175** occurred with high diastereoselectivities and in good yields. The products, *e.g.* **176**, were used to construct the tetrahydro-β-carboline skeleton applying a dual-metal (Ag-Au) catalytic approach for the allylic alkylation of the indole

nucleus at C3 (Scheme 41). The formation of **179** occurred with high *cis*-stereoselectivity, so allowing a successive RCM by catalysis of the Grubbs II Ru-carbene complex to give **180** in moderate yield.

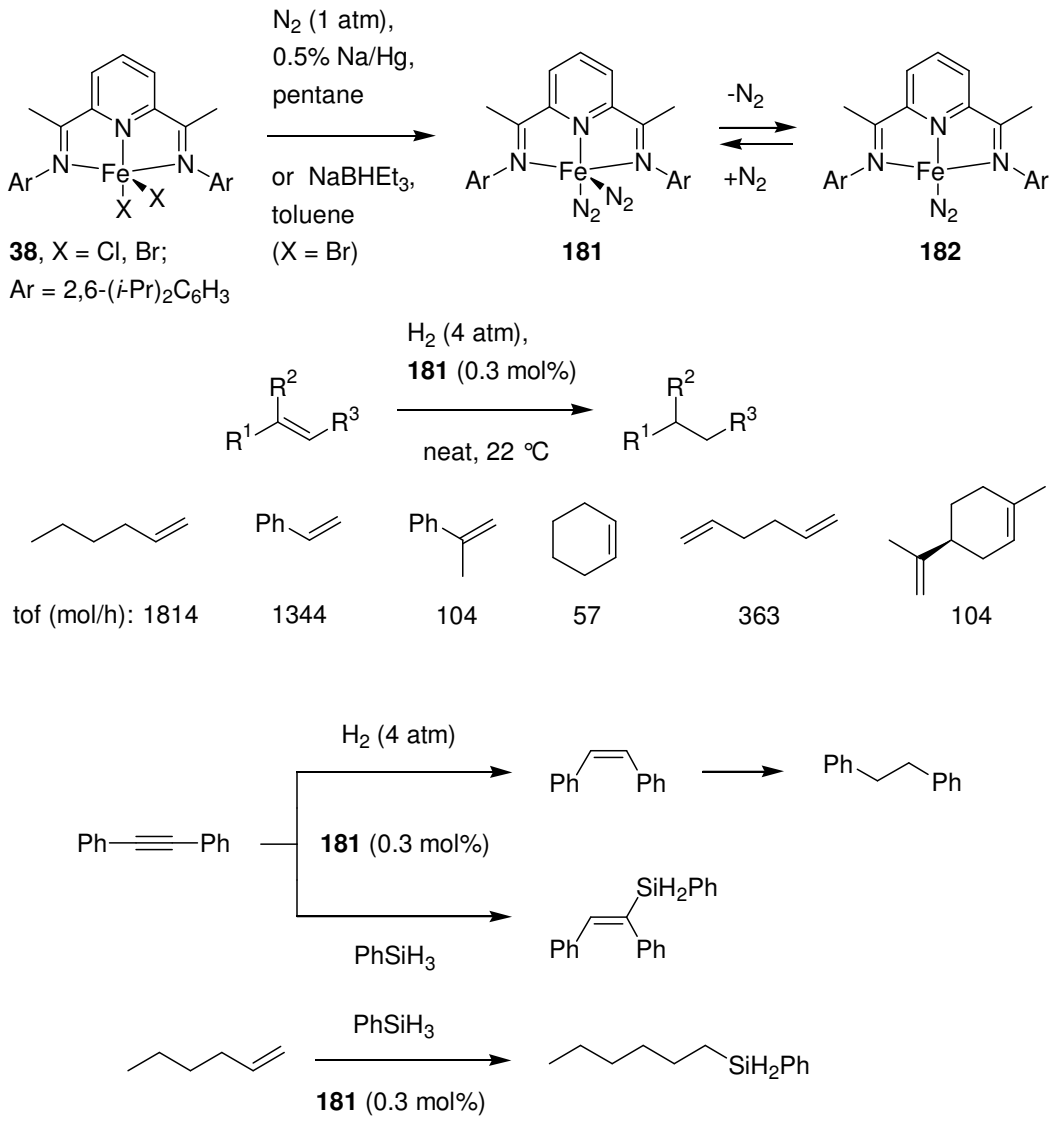


Scheme 41

4. 2-Pyridineimines as ligands in metal-catalyzed organic syntheses

Owing to their ability to coordinate Lewis acidic metal centres, 2-pyridineimines have found use in a number of organic transformation catalyzed by transition metal salts. The iron-diiminopyridine complex **8** was easily reduced by sodium amalgam or sodium triethylborohydride to the Fe(0)-bis(dinitrogen) complex **181**, which in solution is in equilibrium with the mono(dinitrogen) complex **182**. Both complexes serve as precatalysts for the hydrogenation and hydrosilylation of alkenes and alkynes (Scheme 42).[72] Both the reactions are chemo-, regio- and stereoselective; for example, (*R*)-limonene was hydrogenated to (+)-*p*-menthene. Attempts to hydrogenate trisubstituted olefins were unsuccessful. Turnover frequency (tof) for the hydrogenation of 1-hexene was quite higher than tofs determined in the same conditions for other common catalyst, such as Pd/C and $(Ph_3P)_3RhCl$. Full hydrogenation of diphenylacetylene proceeds through formation of the intermediate (*Z*)-stilbene.

In order to get light on the reaction mechanisms, isotopic labelling studies on norbornene and reactions of excess 1-hexene with **181** in the absence of dihydrogen or silane were performed (Scheme 43). In the latter case, isomerization to mixtures of hexenes was observed. Moreover, several stoicheiometric reactions of the complex **181** were conducted leading to the isolation of the stilbene complex **183**, disilane complex **184** and dihydrogen complex **185**.



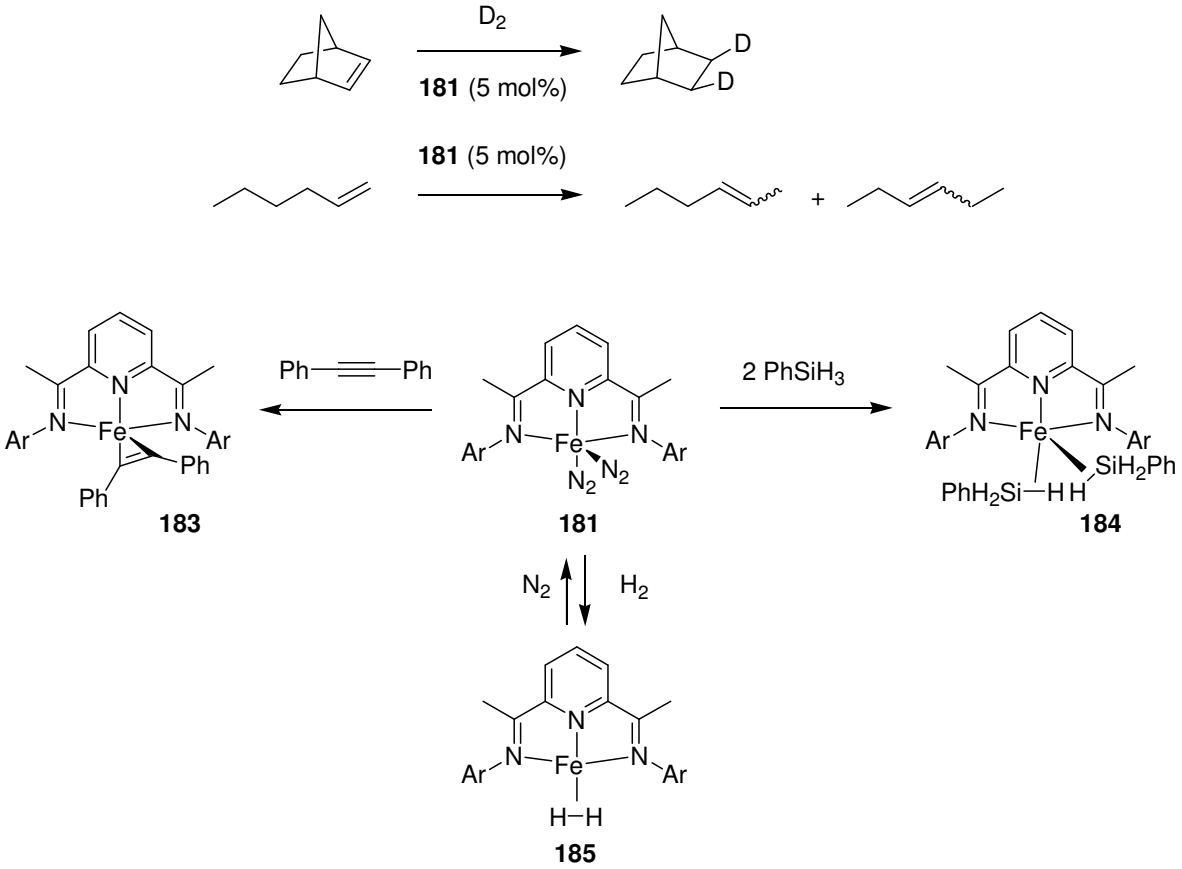
Scheme 42

A complex analogous to **181** was prepared from dibenzoylpyridine, following the same protocol. The substitution of phenyl for methyl *C*-substituents of the imino groups only slightly modified the structural and electronic properties of the complex as compared to **181**, apart for an increased electrophilicity of the iron centre. The use of the new complex in hydrogenation and hydrosilylation of 1-hexene demonstrated a superior activity of the catalyst, but for more hindered alkenes the opposite trend was observed. In these cases, deactivation of the catalyst was due to the irreversible formation of η^6-phenyl- and η^6-aryliron complexes which were unreactive toward dihydrogen, silanes and alkenes.[73]

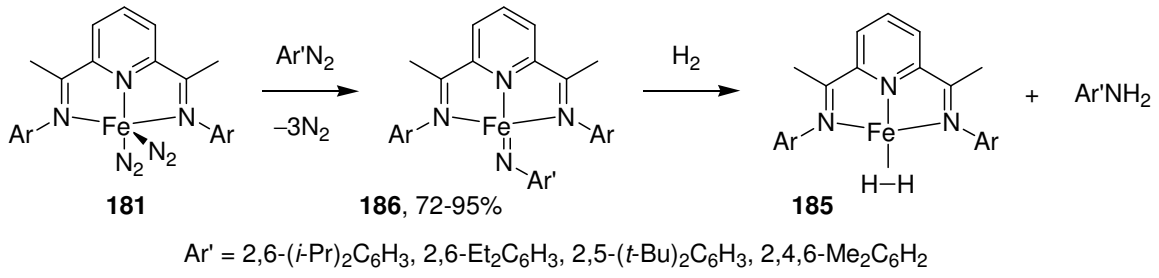
Iron imides **186** were formed in high yields by treatment of the complex **181** with aryl azides with concomitant loss of 3 equivalents of N_2 (Scheme 44).[74] X-Ray structure, magnetic and Mossbauer data were indicative of a ferric ion antiferromagnetically coupled with the pyridinediimine ligand centred radical. Exposure of the iron imide to 1 atm of H_2 afforded the dihydrogen complex **185** and the arylamine.

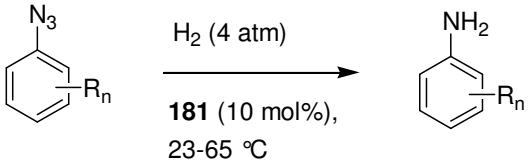
Since the complex **185** rapidly converts to the bis(dinitrogen) complex **181**, the latter complex seemed an ideal candidate for the catalytic hydrogenation of aryl azides to the corresponding anilines. As a matter of fact, the hydrogenation of aryl azide with 10 mol% of complex **181** occurred successfully only for those

azide bearing bulky substituents in the ortho position(s). No hydrogenation occurred for the 2,4,6-trimethylphenyl azide.



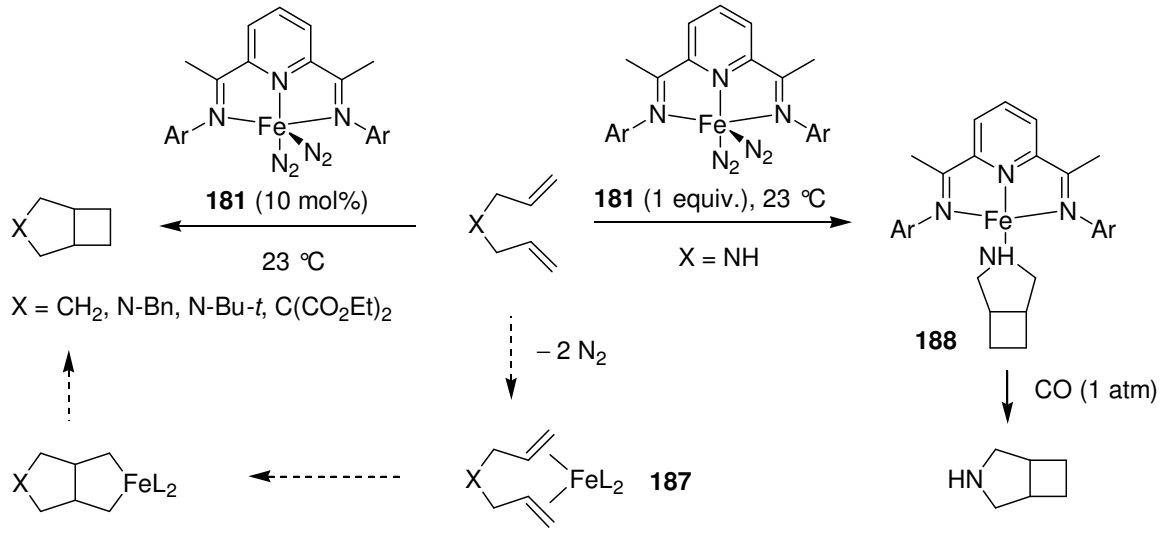
Scheme 43





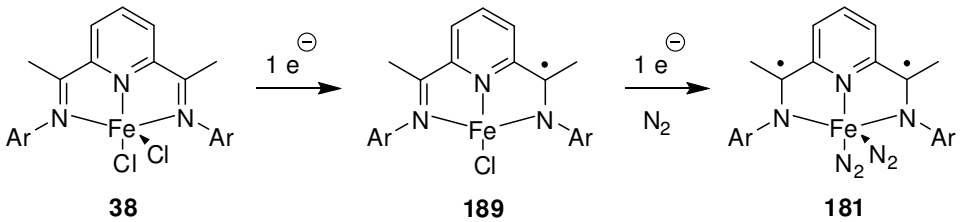
Scheme 44

The [2+2] cycloaddition of 1,6-heptadienes was catalyzed by the bis(dinitrogen)iron complex **181**, which was preferably formed *in situ* by reduction of air stable complex $FeBr_2$, complex analogous to **38** with $NaBEt_3H$ (Scheme 45).



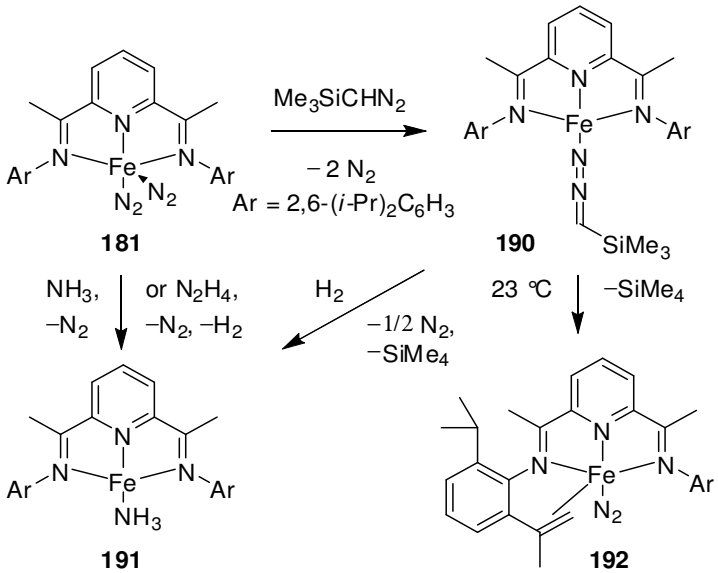
Scheme 45

The observed lack of reactivity of diallylamine was attributed to the increased nucleophilicity of the less substituted azabicycle which coordinates more strongly with the metal, so inhibiting conversion. In this case, a stoicheiometric amount of the iron complex was required, cleanly affording the complex **188**. Exposure of this complex to 1 atm of CO afforded the free azabicyclo[0.2.3]heptane.[75] The mechanism involves substitution of the N_2 ligands by the diene to form a (diene)Fe^{2+}(diiminopyridine)$^{2-}$ complex **187**, rather than an iron(0) complex, on the basis of computational, spectroscopic and structural data of this and other related iron complexes. Overall, these studies demonstrated that the reduction of the complex **38** by alkali metal or borohydride reagents occurs by sequential electron transfers to the conjugated π system of the ligand L, rather than to the metal, so giving first the radical anion-Fe(II) complex **189** and ultimately the dianion-Fe(II) complex **181** (Scheme 46).[76,7] The related cobalt complex exhibited similar behaviour.[77]



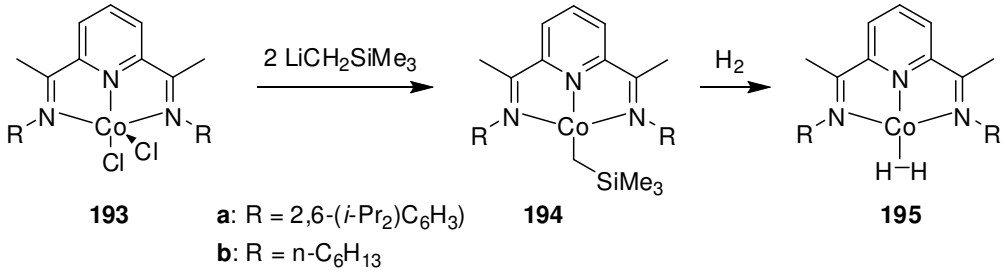
Scheme 46

Further studies on the reactivity of the bis(dinitrogen) complex **181** led to the discovery of novel C–N and N–N hydrogenolysis and C–H activation processes (Scheme 47).[78] The reaction of **181** with trimethylsilyl diazomethane in pentane furnished the diazoalkane complex **190**, which was then submitted to a 1 atm of hydrogen pressure, so giving the ammonia complex **191**. The latter compound was also produced directly from **181** by treatment with ammonia or hydrazine. The diazoalkane complex **190** slowly decomposed in benzene solution at room temperature to give the olefin-iron-dinitrogen complex **192**. Alkane dehydrogenation, previously unknown for iron complexes, in this case presumably occurred by a complex pathway involving 1,2-addition of an isopropyl C–H bond to an iron alkylidene followed by β-hydride and reductive eliminations.



Scheme 47

The square planar Co(I)CH_2SiMe_3 complexes **194**, obtained by addition of $LiCH_2SiMe_3$ (2 equivalents) to the Co(II) complexes **193** and previously used as intermediates for the polymerization of ethylene, were also active catalysts for the hydrogenation of alkenes (Scheme 48). The nature of the substituent R at the imine nitrogens did not affect much the catalyst activity, in contrast to the effect the ligand had in polymerization. The reaction of **194** with dihydrogen presumably afforded the cobalt hydride complex **195**, which was considered to be the active catalyst in the hydrogenation process.[79]

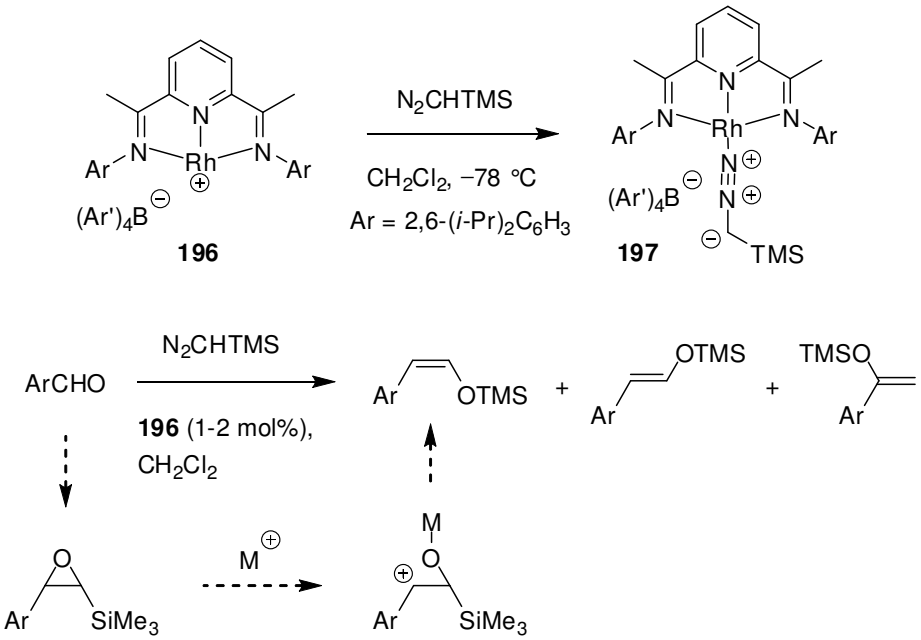


Scheme 48

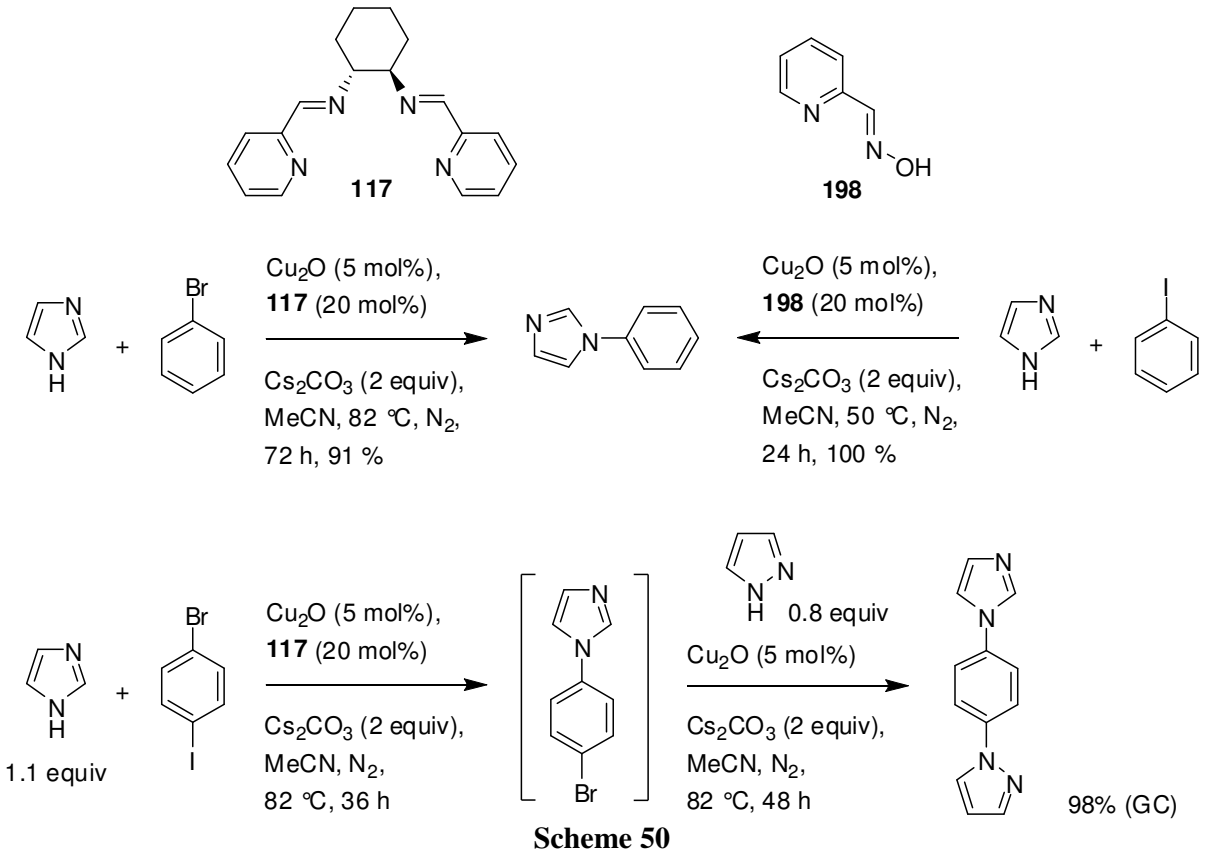
The rhodium complex **196** catalyzed the one-carbon homologation of aromatic aldehydes in the reaction with trimethylsilyldiazomethane in dichloromethane. Mixtures of (*Z*)- (prevalent) and (*E*)-silyl enol ethers were produced in 50–80% yields, together with trace amounts of 1-aryl-1-trimethylsilyoxyethylene (Scheme 49). The (*Z*)-silyl enol ethers were separated from the isomers by flash chromatography on silica gel; then hydrolysis gave the corresponding aldehydes. The reaction proceeds through the formation *in situ* of the Rh(I)-trimethylsilyldiazometane complex **197**, which was isolated and characterized by X-ray and spectroscopic studies. The reaction mechanism includes formation of an epoxide which undergo ring-opening, favoured by electron-donating substituents on the aromatic ring.[80]

Iron, cobalt and nickel complexes with the bis(imino)pyridine ligands bearing *N*-alkyl and *N*-aryl substituents were electrochemically characterized and their electrocatalytic acitivities towards reduction of carbon dioxide in non aqueous solvent was investigated. The electrocatalytic activity was dependent on the nature of both the metal and the ligand, and was rationalized in terms of electronic effects and on whether

the redox process was localized on the ligand or the metal.[81] The complex **38** and the analogous complex of $FeCl_2$ with the ligand **29** dissolved in acetonitrile were electrochemically reduced at a glassy carbon cathode and the electrocatalytic activity of the deposited material to the reduction of dioxygen was studied by hydrodynamic voltammetry. The material obtained from **38** appeared a promising candidate for power sources, oxygen sensors and some chemical processes.[82]



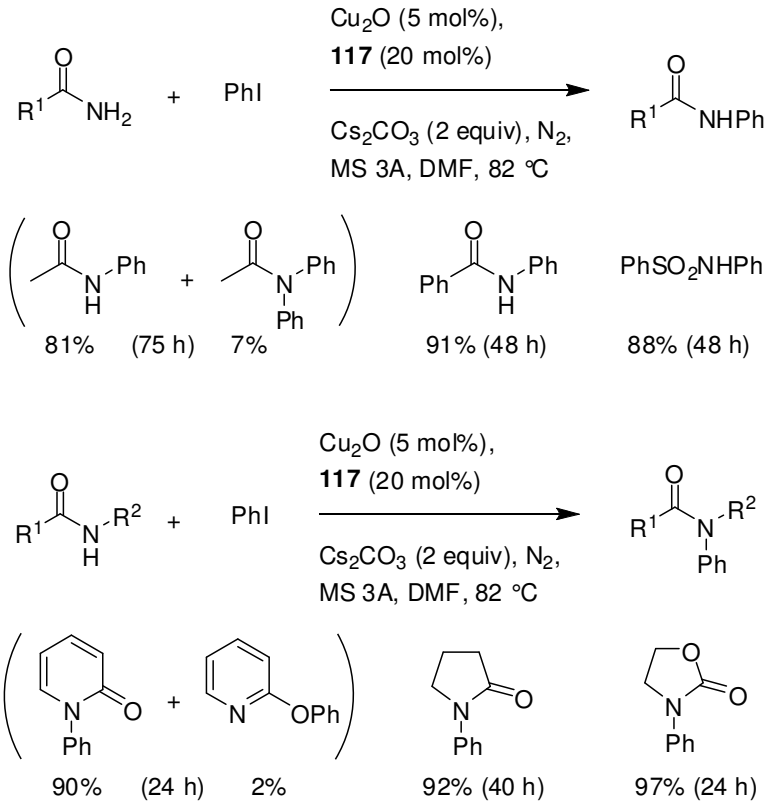
Scheme 49



Scheme 50

Among many bidentate and tetradentate ligands featuring imine, oxime, hydrazone, 1,2-diamino and 1,4-diazadiene moieties, the bis(pyridineimine) *rac*-**117** and the 2-pyridineoxime **198** were useful in copper-catalyzed *N*-and *C*-arylations with aryl bromides and iodides (Scheme 50).[83] The tetradentate Schiff base **117** generated a remarkably general copper catalyst for *N*-arylation of five-membered aromatic nitrogen heterocycles, amides and carbamates and *C*-arylation of malonates and analogous enolizable compounds in relatively mild conditions (50–82 °C) as compared to previously described catalytic systems. The use of inexpensive Cu_2O and 2 equivalents of $CsCO_3$ in acetonitrile or DMF was identified as the most efficient system. The loading of either Cu_2O and the ligand could be reduced at the expense of increased reaction times or slightly reduced yields and a high ligand/copper ratio, *e.g.* 10:1, was beneficial. The reactions were totally or almost totally selective with respect the substrate and the aryl halide. Biaryl byproducts were never observed and less of 1% of the hydrodehalogenated arene was formed. Moreover, bromobenzene proved to be unreactive toward NH and OH groups present in the ligand. For example the *N*-arylation of imidazole was accomplished with bromobenzene using the ligand **117** at 82 °C, whereas the same product was obtained at 50 °C with the more reactive iodobenzene with the ligand **198**. The different reactivities of bromo- and iodobenzene was exploited for the efficient and selective preparation of a benzene derivative substituted with two different azaheterocycles. On the other hand, the order of reactivity in the azole series was determined as follows: pyrazole>imidazole>indole>1,2,4-triazole>>1,2,3,4-tetrazole. The arylation of pyrazole and substituted derivatives with aryl bromides was thoroughly studied by varying all the experimental conditions, including ligand, copper source, base, solvent and temperature.[84]

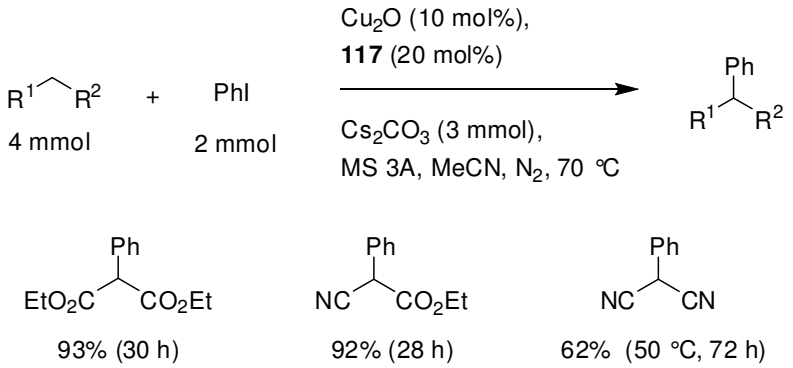
The copper-catalyzed *N*-arylation of carboxamides, sulfonamides and carbamates was achieved with aryl iodides under mild conditions (Scheme 51).[83]



Scheme 51

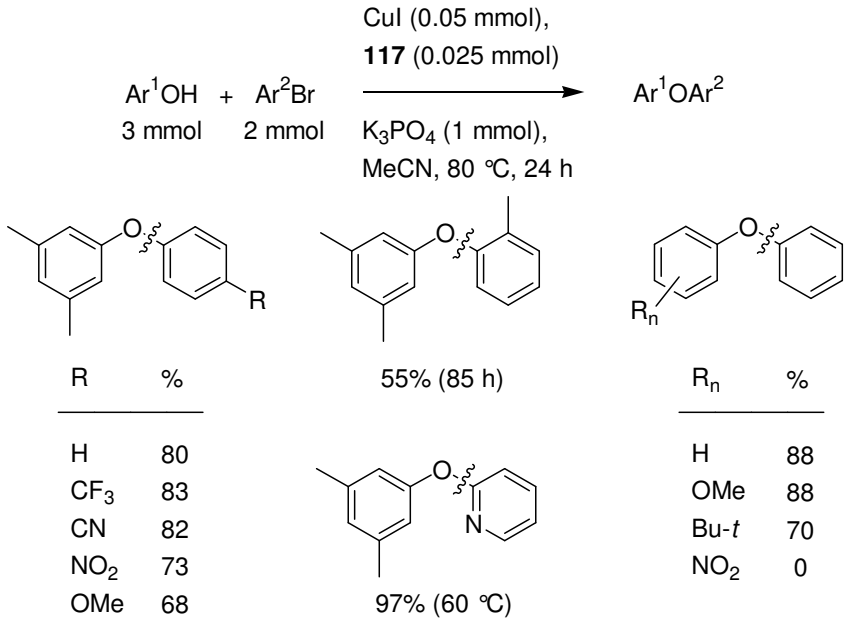
In the case of *N*-unsubstituted amides, the selective mono-phenylation was achieved with benzamide and benzenesulfonamide, whereas from acetamide a minor amount of the diphenylated product was obtained in addition to the prevalent *N*-phenylacetamide. Excellent yields were also obtained from cyclic amides and carbamates, although from pyridin-2-one a trace amount of the *O*-phenyl derivative (lactim) was formed.

The Cu-catalyzed arylation of malonic acid derivatives was similarly accomplished (Scheme 52). However, diethyl methylmalonate was unreactive owing to steric hindrance and/or decreased acidity.



Scheme 52

Another protocol for the efficient and selective coupling of phenols and aryl bromides makes use of the system **117**-CuI in an optimized 0.5 ratio in the presence of the less expensive base K_3PO_4 in acetonitrile at 80 °C (Scheme 53).[85] The robustness of the catalyst consisting of equimolar amounts of ligand and copper iodide was highlighted by the possibility to conduct the coupling reaction of 3,5-dimethylphenol and iodobenzene at a loading less than 0.1 mol%.



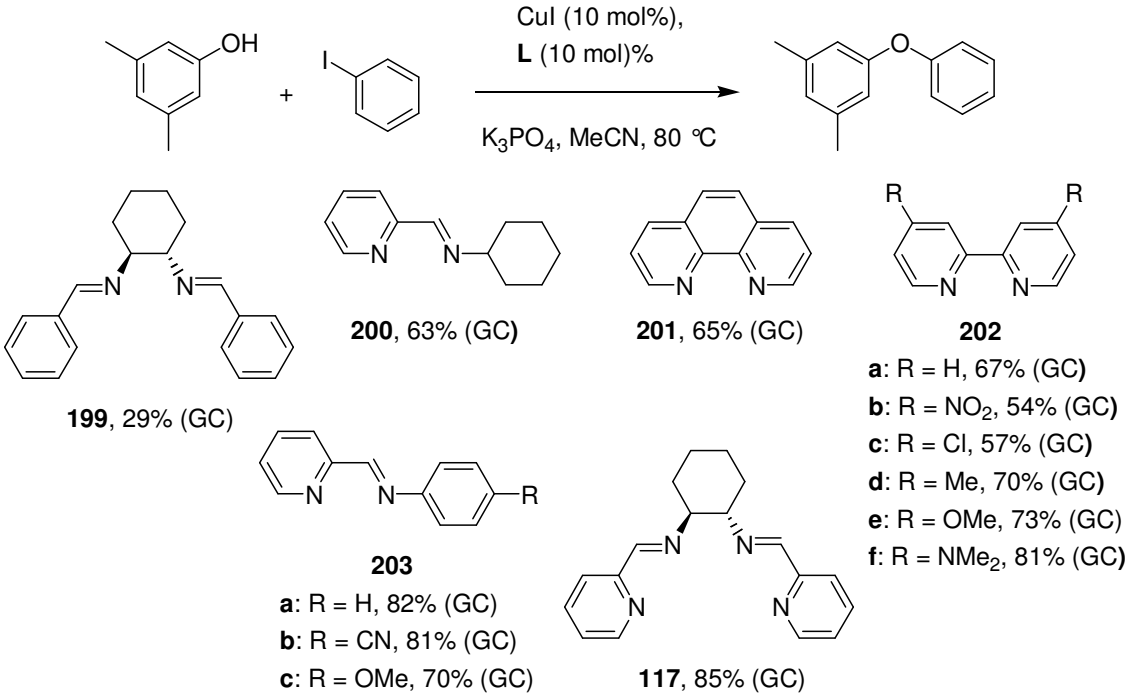
R	%
H	80
CF_3	83
CN	82
NO_2	73
OMe	68

R_n	%
H	88
OMe	88
Bu-*t*	70
NO_2	0

Scheme 53

The coupling of 3,5-dimethylphenol and iodobenzene was taken as a model reaction to study the structural and electronic features that make a ligand efficient. With this aim, the tetradentate ligand **117** was compared to other bidentate ligands **199–203** (Scheme 54).[86] The obtained results demonstrated that two

isolated imino groups present in ligand **199** do not enable acceleration of the reaction, as the same yield of the diaryl ether was obtained in the absence of ligand. On the other hand, it was observed that bidentate ligands featuring conjugated bispyridine and pyridineimine moieties are effective ligands. Particularly, the *N*-phenyl-2-pyridineimine **203** (R=H) was almost as active as the tetradentate ligand **117**.



Scheme 54

Choosing **202a** and **203a** as model ligands, the electron density on the pyridine and imine nitrogens, respectively, was modified by the introduction of *para*-substituents R on the pyridine and benzene rings and the corresponding effects on the reaction outcomes were evaluated. These studies established that higher yields were obtained when the electron density was increased on the pyridine nitrogen of **202** and reduced on the imine nitrogen of **203**. Thus, the iminopyridine pincer present in the ligand **203** (R=H) displays a good balance between electron-donating and electron-withdrawing properties. The more electron rich pyridine nitrogen would facilitate the oxidative addition step of ArX on Cu(I), whereas the more electron-poor the imine nitrogen would promote the reductive elimination step. The synergy of the two binding sites within the same molecule can explain the high efficiency of the ligand (Figure 1).

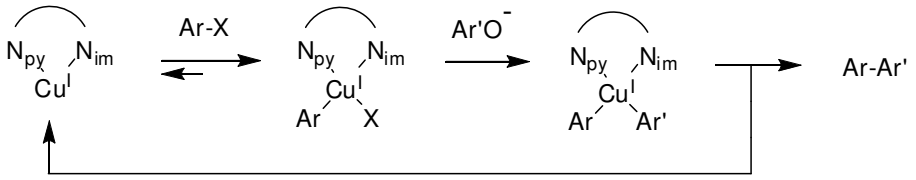
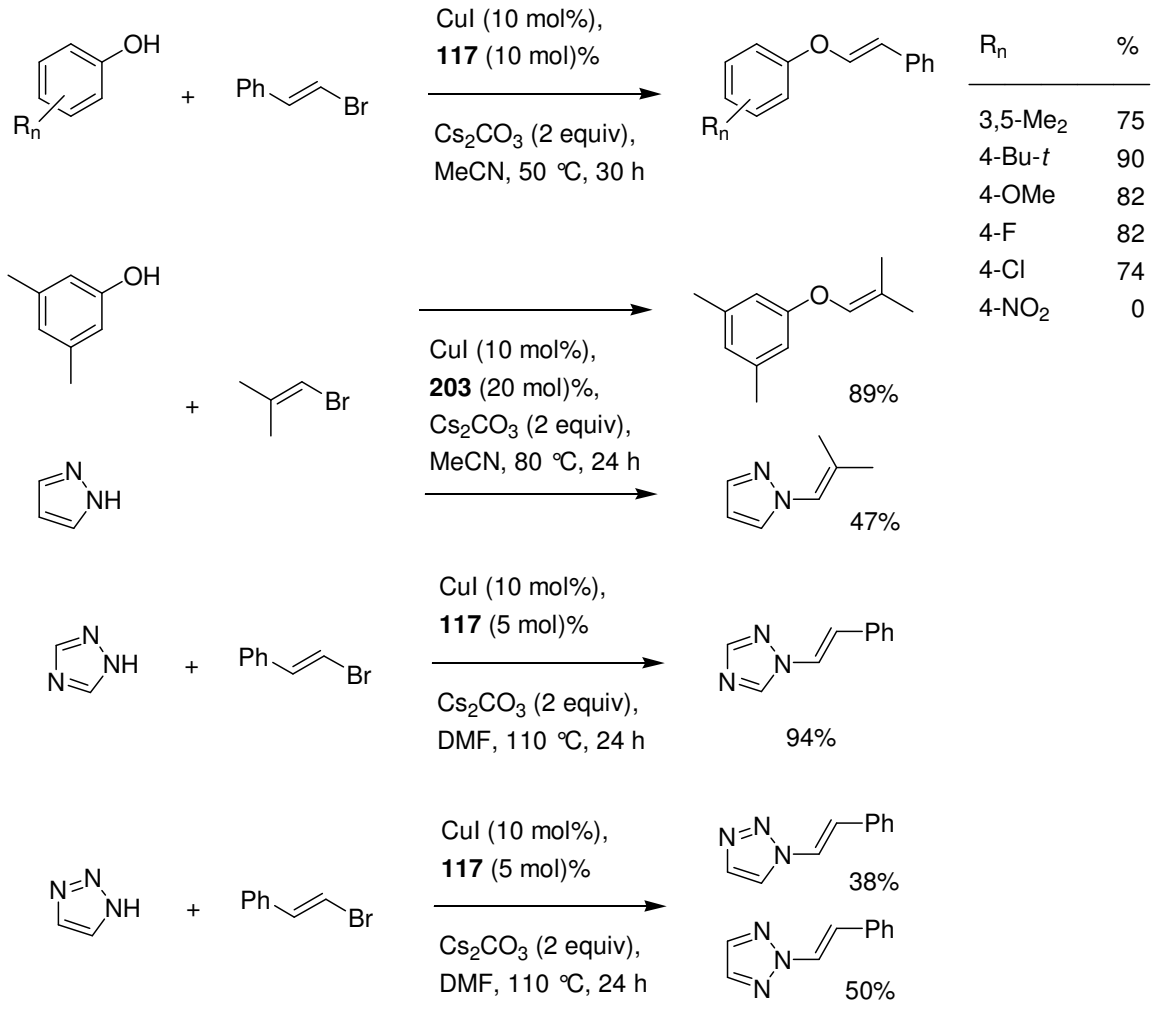


Figure 1

The copper-catalyzed coupling of phenols and five-membered nitrogen heterocycles with vinylic bromides was also accomplished by the same protocol using the tetradentate ligand **117** (Scheme 55).[87] The reaction with β-bromostyrene (*E*/Z 90:10) with a variety of phenols occurred yet at 50 °C in acetonitrile, but

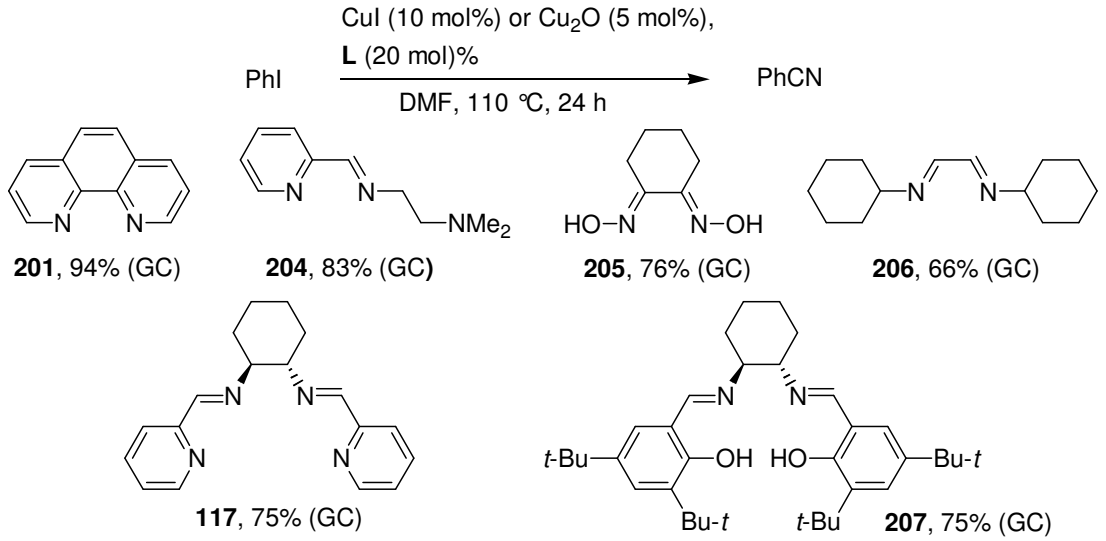
4-nitrophenol did not react at all. Only the (*Z*)-isomer underwent coupling, whereas the (*Z*)-isomer was converted to 1-phenylacetylene and a mixture of other by-products. On the other hand, the coupling of 3,5-dimethylphenol, pyrazole and 1,2,4-triazole with more hindered 1-bromo-2-methyl-1-propene required the use of DMF as the solvent at 110 °C to obtain the desired products. 5-Phenyl-1,2,3,4-tetrazole was unreactive.



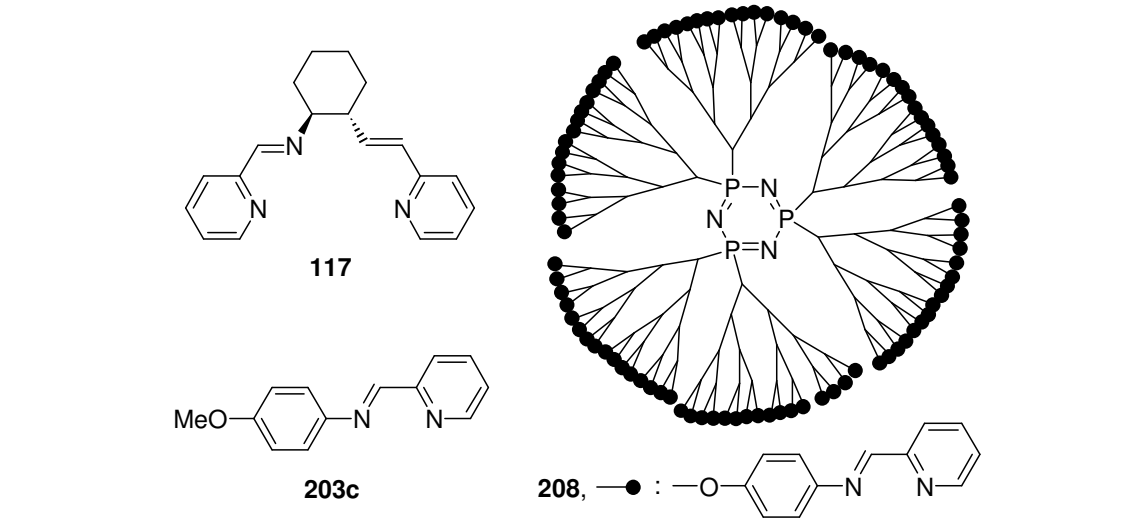
Scheme 55

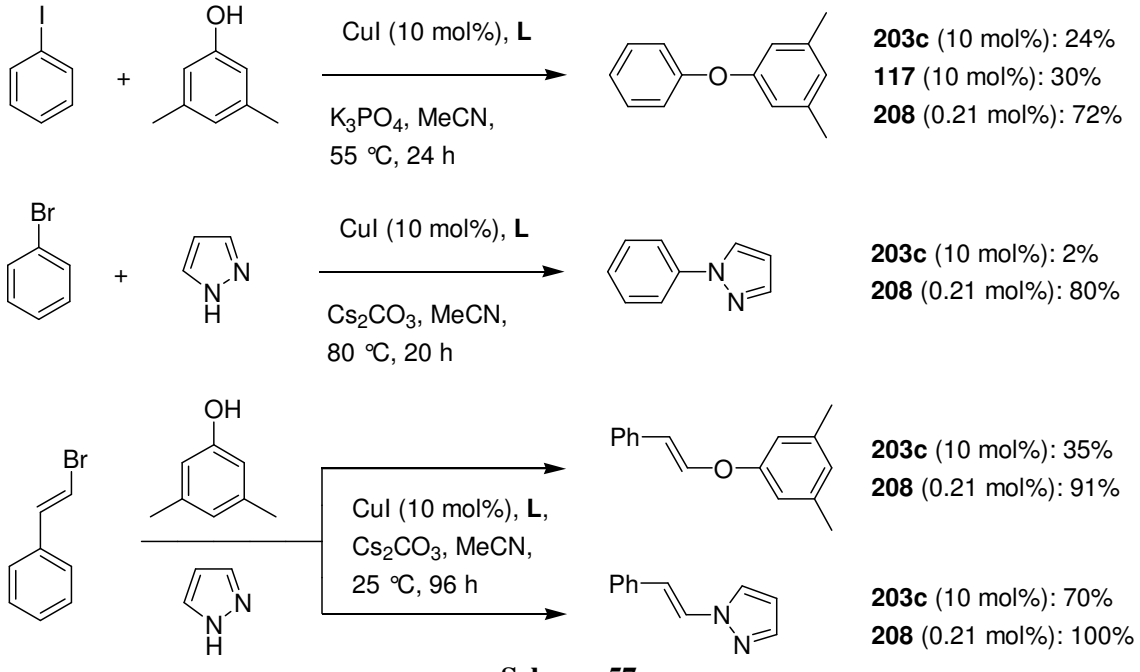
The copper-catalyzed cyanation of iodobenzene was reported to occur in relatively mild conditions (DMF, 110 °C) making use of the tetradentate ligand **117** and the tridentate pyridineimine **204**, although phenantroline **201** was the ligand of choice for this reaction. The 1,2-dioxime **205**, the 1,2-diimine **206** and salen ligand **207** were effective too (Scheme 56).[88] Using the phenantroline ligand, aryl nitriles were also conveniently obtained in good yields and with excellent selectivities from aryl bromides using acetone cyanohydrin as the source of cyanide ion, in the presence of KI (50%) and triethylamine. The conditions were tolerant of several functionalities, including amino, nitro and carbonyl groups.

The simple bidentate pyridineimine ligands **203** proved to be less versatile than the tetradentate ligand **117**. However, using dendrimer-bound iminopyridine ligand **208** the highest yields under the mildest conditions were obtained for *N*- and *O*-arylation and vinylation reactions of pyrazole and phenols (Scheme 57).[89]



Scheme 56

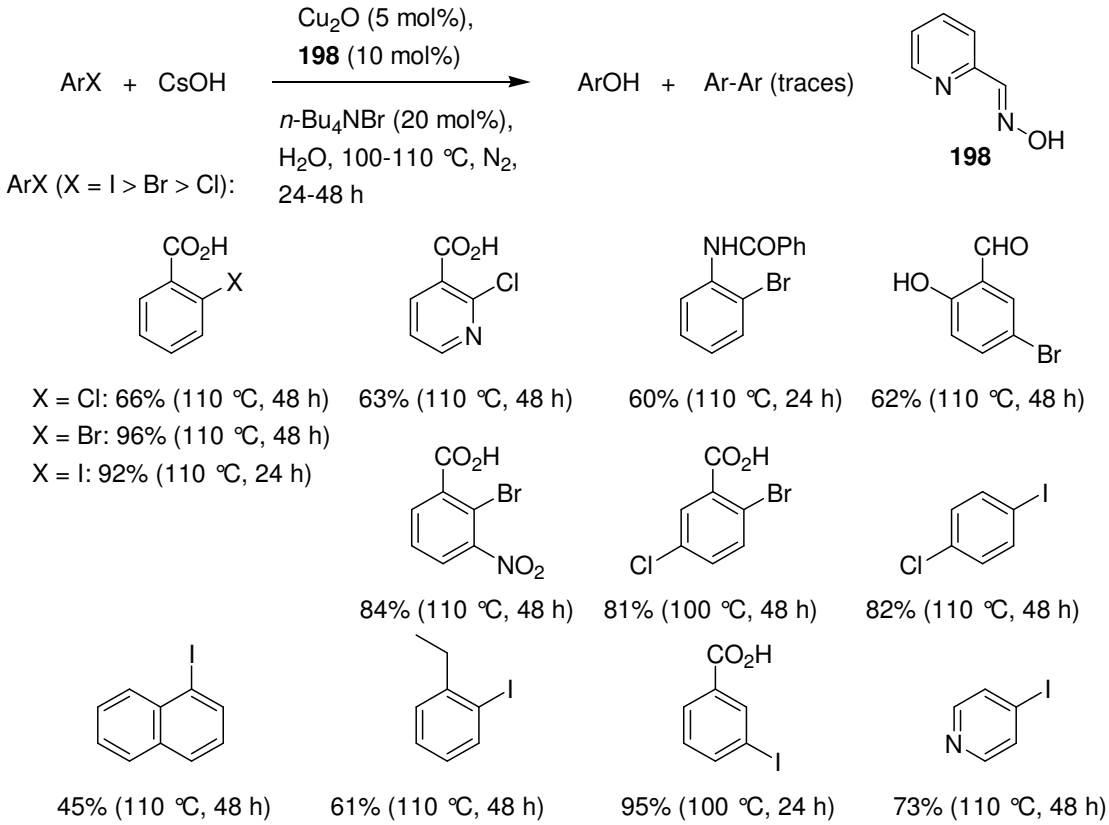




Scheme 57

As a matter of fact, the reactions carried out with the ligands **117** and **203c** in the same conditions and with the same ratio *N*,*N*-chelate/Cu were always less efficient, in some case dramatically, *e.g.* in the couplings of bromobenzene and β-bromostyrene. Especially, it is noteworthy that using the dendrimer-bound ligand, it is possible to obtain in some cases the desired products in quantitative yield and with complete selectivity in a reasonable time at room temperature.

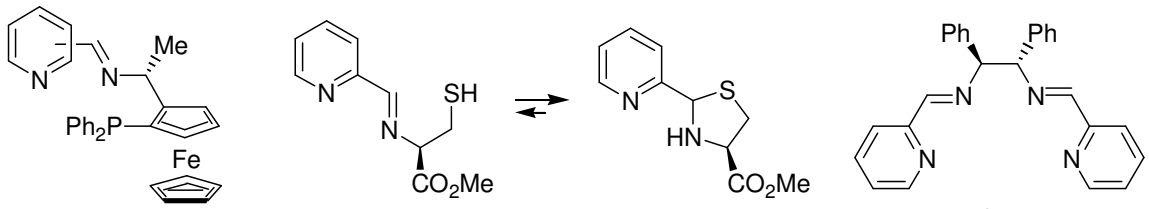
The synthesis of substituted phenols by the Cu_2O-catalyzed reactions of aryl halides with cesium hydroxide has been achieved in water as the solvent in the presence of the 2-pyridinealdoxime **198** and tetra(*n*-butyl)ammonium bromide under relatively mild conditions (100–110 °C) (Scheme 58).[90] Copper(I) halides were less effective and the ligand **198** proved superior to a number of other ligands, including glyoxal dioxime, terpyridine, *N*,*N*'-dimethylethylenediamine, proline, 2-pyridinecarboxylic acid and 1,3-pentanedione. Only trace amounts of the symmetric diaryl ethers were formed. The usual order of reactivity of the halides was observed, that is: iodides>bromides>chlorides. The method proved to be tolerant of various functional groups, but the acetamide group was hydrolyzed to carboxylic acid. Electron-withdrawing substituents accelerate the hydroxylation reaction and allowed to reduce the reaction time and/or the temperature. In order to evaluate the effect of the oxime function of the ligand, *i.e.* the nitrogen substituent, a comparison would have been useful with the corresponding *N*-arylimine and hydrazone.



Scheme 58

The use of chiral pyridine-containing ligands, including 2-pyridineimines, in asymmetric catalysis has been reviewed a few years ago and the reader should find the relevant information therein.[91] Here, it can be only underlined that in most cases the chiral 2-pyridineimines did not work satisfactorily, as low to moderate yields and enantioselectivities were achieved in a variety of metal-catalyzed reactions. So, 2-pyridineimines

are mostly useful for the preparation of the corresponding pyridine-substituted alkylamines by alkylation or reduction of the azomethine group, *e.g.* the bis(aziridine) **127** described in Scheme 29. A ferrocene-based phosphine/2-pyridineimine **209a** was even unreactive in Pd-catalyzed asymmetric allylic alkylation where the corresponding 3-pyridine- and 4-pyridineimines **209b,c** demonstrated high efficiency and enantioselectivity (Scheme 59).[92] Noteworthy, an exception to the negative trend observed for 2-pyridineimines is the cysteine derivative which exists in equilibrium between the open-chain imine **210a** and the prevalent ring-closed oxazolidine **210b** forms. The latter is presumably the actual ligand in the rhodium(I)-catalyzed hydrosilylation of acetophenone with diphenylsilane, where up to 97.6 % of e.e was achieved at –20 °C. The analogous pyrrole ligand proved unsatisfactory in the same reaction.[93] Moreover, the highly diastereoselective and enantioselective (up to 91 % of e.e.) pinacol coupling of aromatic aldehyde was efficiently catalyzed by a titanium complex of the bis(pyridineimine) **211** (Mn powder, TMSCl, $TiCl_4(THF)_2$, **211**, MeCN, 0 °C).[94]



209

a: 2-Py; **b**: 3-Py; **c**: 4-Py

210a **210b** **211**

Scheme 59

5. Conclusion

This review has surveyed the rich chemistry of 2-pyridineimines and 2-pyrroleimines that is based on the ability to strongly coordinate metal ions as well as metal centres of covalent organometallic compounds. The binding mode of the 2-pyridineimine is the result of its σ-donor and π-acceptor properties, whereas the 2-pyrroleimine forms bidentate metal complexes by deprotonation of the pyrrole N–H function. Particularly, the 2,6-pyridinediimine ligand bearing aryl *N*-substituents can act as an electron reservoir, being able to accept up to 3 electrons and consequently is capable to stabilize metals in different oxidation states. The reactions of metal complexes of 2-pyridineimines, 2,6-pyridinediimines and 2-pyrroleimines with organometallic reagents have been studied because the intermediate complexes were useful catalysts or pre-catalysts in the polymerization of α-olefins, especially ethylene. Moreover, a number of transition-metal-catalyzed organic reactions, including hydrogenation of multiple bonds, hydrogenolysis, cycloaddition and coupling reactions were performed exploiting 2-pyridineimines and 2,6-pyridinediimines as ligands. In a limited number of cases, enantioselective catalytic reactions were carried out efficiently using optically active ligands containing the 2-pyridineimine moiety.

On the other hand, the addition of organometallic reagents to chiral 2-pyridineimines, 2,6-pyridinediimines bearing stereocentre in the *N*-substituent was used to synthesize bi- and polydentate ligands which were valuable precursors of more complex molecular structures or effective ligands in asymmetric metal-catalyzed processes. In a few cases, the organometallic route was applied to 2-pyrroleimines for the stereoselective synthesis of biologically active and naturally occurring compounds.

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CONVERSION OF *N*-ARYLIMINO-1,2,3-DITHIAZOLES INTO BIOLOGICALLY ACTIVE HETEROCYCLES

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Dedicated to the memory of Professor Charles W. Rees (Imperial College, London)

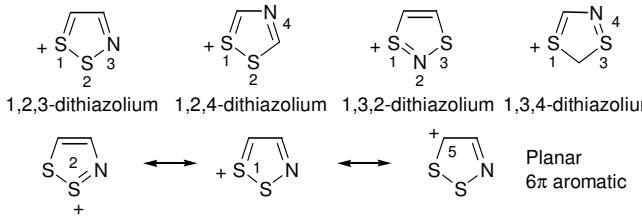
Abstract. *The reactions of 4,5-dichloro-1,2,3-dithiazolium chloride* ***1*** *(Appel salt) with primary aromatic amines allow access to N-arylimino-1,2,3-dithiazoles* ***5*** *usually in high yields. These imines have proved to be very versatile synthetic intermediates in heterocyclic chemistry, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring. Exploring the chemistry of Appel salt, we demonstrate in this paper that the starting imines* ***5*** *can be easily converted into 2-cyano derivatives of benzothiazoles, thiazolopyridines, indoles, benzimidazoles, benzoxazoles, quinazolines, benzoxazines, benzothiazines, indolines and iminoquinolines. The heterocyclic compounds described in this review possess various biological activities or are precursors of molecules of therapeutic interest.*

Contents

1. Introduction

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Indeed, so many different heterocyclic ring systems have now been explored that it is no longer easy to find totally new structural types. Among them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers and their unique structures led to several applications in different areas.[1] These organic heterocycles with a high proportion of heteroatoms are relatively rare; they are formally derived from aromatic carbon cycles with a heteroatom taking the place of a ring carbon atom or a complete CH=CH group. Although the presence of many nitrogen and sulfur atoms in a ring was normally associated with instability and difficulties in the synthesis, stable sulfur and nitrogen heterocycles with unusual properties can be frequently obtained. The presence of heteroatoms results in significant changes in the cyclic molecular structure, due to the availability of unshared pairs of electrons and in the reactivity, compared with the parent aromatic hydrocarbons. In contrast with the number and variety of such heterocycles, the number of synthetic methods to afford sulfur and nitrogen-containing molecules is, in practice, restricted to the availability of the appropriate sulfur or nitrogen reagents.

Among the five membered heterocycles containing nitrogen and sulfur atoms, dithiazoles are particularly studied due to their unusual physical properties and chemical transformations of their derivatives. There are four possible planar dithiazolium ring systems: 1,2,3-dithiazolium, 1,2,4-dithiazolium, 1,3,2-dithiazolium and 1,3,4-dithiazolium (Scheme 1). In the absence of substitution on the rings, they are all positively charged and have 6π electrons. Three canonical forms can represent the planar 1,2,3-dithiazolium salt.[2–5] The carbon in position 5 and the two sulfur atoms in position 1 and 2 of the ring are the three most electrophilic sites (Scheme 1).

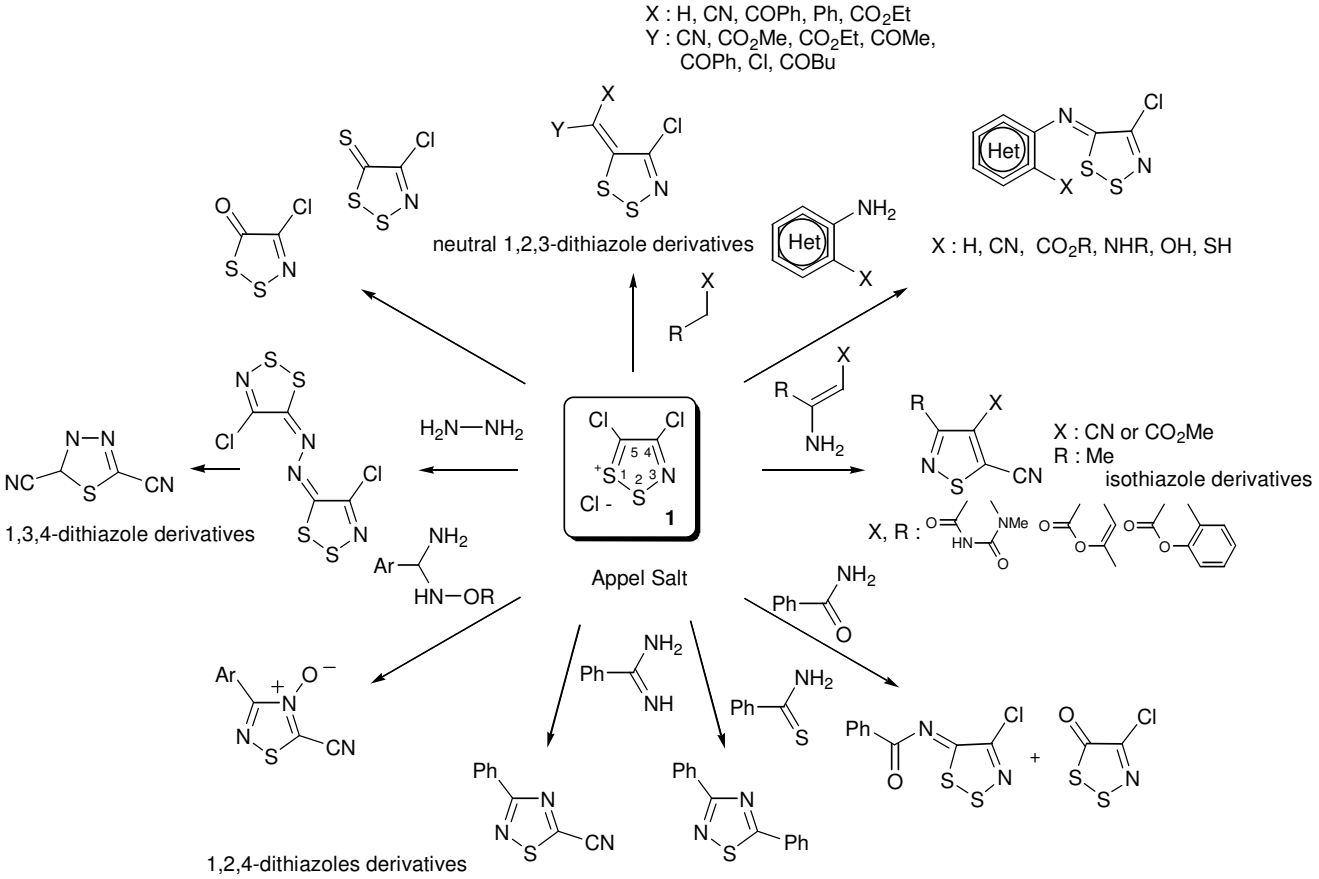


Scheme 1

Since 1985, an abundant new chemistry has revealed for 4,5-dichloro-1,2,3-dithiazolium chloride **1** when Appel and his co-workers[5] solved the chemical structure of a moisture sensitive green salt obtained from the reaction of acetonitrile, chloroacetonitrile or dichloroacetonitrile and an excess of disulfur dichloride (S_2Cl_2) in dichloromethane at room temperature (Scheme 2). Interestingly, 30 years earlier Wannagat and Schindler in 1957 incorrectly proposed the product of this reaction as the unstable 2,3,4-trichloro-1,2,3-dithiazole.[6]

The chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride is mainly characterized by nucleophilic displacement of the chloride at position 5 (Scheme 2). Displacement of the chloride at C-4 has been

described only one time when the product resulting from the reaction of **1** with 2-hydroxyaniline was converted into its phenoxide ion which cyclized to give a stable dithiazolobenzoxazine as yellow crystals[7] (see compound **27** in Scheme 19).



Scheme 2

Then, reaction of this salt with water,[5] hydrogen sulfide,[5] aromatic primary amines[5] and active methylenes[8,9] may afford stable neutral 5*H*-dithiazoles (Scheme 2). Reaction of salt **1** with primary enamine derivatives gave presumed intermediate adducts which could spontaneously afford isothiazoles.[10] Benzamide reacted with **1** to give the expected *N*-(4-chloro-1,2,3-dithiazol-5-ylidene)benzamide in low yield, whilst the major product was the 1,2,3-dithiazol-5-one presumably formed by nucleophilic attack through oxygen followed by elimination.[11–13] Thiobenzamide and benzamidine derivatives can react with **1** to form 1,2,4-dithiazole derivatives.[11–14] Benzamidoximes, or their derivatives, were also condensed with salt **1** to afford 1,2,4-dithiazole oxides.[15,16] Koutentis and his group also recently published the preparation of bis-dithiazolimines obtained by reacting Appel salt and anhydrous hydrazine in 1,2-dichloroethane.[17] The work-up originally published by Oakley[18] was modified to allow a significant increase of the yield (58% instead of 33%). The intermediate bis-imine was reacted with tetraalkylammonium halides to give 1,3,4-thiadiazoles in various yields (Scheme 2).[9,17]

In the last 20 years, a small number of research teams have actively described the access of non-fused 4-chloro-imino-1,2,3-dithiazoles and have investigated and developed their possible transformations to various heterocycles. It should be noted that nearly all the active groups working on Appel salt chemistry began their investigations under the guidance of the late Charles W. Rees at Imperial College in London, as

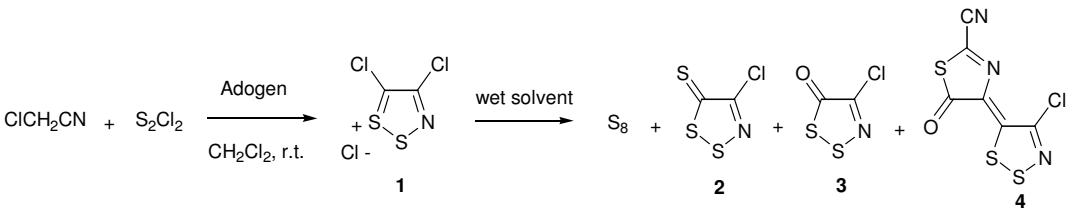
either Ph.D., post-Doc or visiting professor researchers (Kim & Rakitin). Today, over one hundred publications have appeared that describe the behaviour of 4,5-dichloro-1,2,3-dithiazolium chloride **1** and the chemistry of its derivatives for the synthesis of heterocyclic systems; a special chapter of the monograph *Comprehensive Heterocyclic Chemistry III* published in 2008[3] is dedicated to 1,2,3-dithiazoles and some recent reviews were published. A large review published by Rakitin in 2008 presents data on the most recent works,[12] whilst the publication written by Kim in 1998 was mainly focused on the Appel salt chemistry.[11] In 2006, Koutentis described the work of his group on the application of 1,2,3-dithiazole chemistry in heterocyclic synthesis.[9] Finally, Besson and his co-workers wrote in 2009 an article for *e-EROS* (*Encyclopedia of Reagents in Organic Synthesis*)[13] in which the chemistry of the reagent called "Appel salt" is presented.

This chapter aims to review recent developments in the synthesis, the chemical transformations and the pharmaceutical evaluation of various sulfur- and nitrogen-containing heterocycles mostly prepared by utilizing Appel salt and its derivatives. We focused our attention on the construction of novel neutral *N*-arylimino-1,2,3-dithiazoles that can be converted into new heterocyclic or polyheterocyclic systems *via* ring transformation. This family of compounds has generated considerable interest even for the versatility of the intermediate imines than for the potent biological activity of its various derivatives. We are also presenting synthesis of heterocyclic systems in which 1,2,3-dithiazole chemistry was explored at one step or more of the processes.

2. Synthesis of 4,5-dichloro-1,2,3-dithiazole chloride and its *N*-arylimino-1,2,3-dithiazoles

2.1. 4,5-Dichloro-1,2,3-dithiazolium chloride (Appel salt)

The first synthesis of 4,5-dichloro-1,2,3-dithiazolium chloride **1** was described in 1985 by Appel.[5] It was improved by Rees and his co-workers and described in various papers.[19,20] The salt **1** is obtained by addition of acetonitrile or chloroacetonitrile (1 equiv.) to a solution of disulfur dichloride (5 equiv.) in dichloromethane. Adogen® (3–4 drops) is then added and the reaction is placed in a bowl of cold water (Adogen® is a phase transfer catalyst used here as a source of chloride, its addition improves the quality, but not the yield of the salt). The mixture is left for 18 hours without stirring protected from atmospheric moisture by a $CaCl_2$ drying tube. The dark olive green solid is removed from the wall of the flask, filtered off under a blanket of argon and washed abundantly with dichloromethane. The dark olive prisms obtained are dried under vacuum for 2–3 hours. The salt **1** (Scheme 3) should be stored in a dry atmosphere since it slowly reacts with moisture to give acidic and sulfur-containing vapours, it should be used only in a well ventilated fume hood.



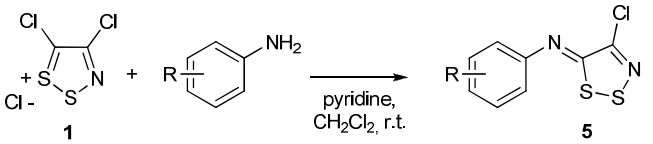
Scheme 3

It was recently demonstrated by Koutentis and his co-workers that Appel salt **1** degrades in wet solvents (THF, dichloromethane or MeCN) to give elemental sulfur, dithiazole-5-thione **2**, dithiazol-5-one **3**

and the thiazol-5-one **4** (Scheme 3).[21] Compound **3** can also be obtained in quantitative yields after transformation of the salt **1** by the treatment with catalytic amounts of DMSO (1 mol%) in MeCN in the presence of water.[22]

2.2. 5-*N*-Arylimino-4-chloro-1,2,3-dithiazole derivatives

Aromatic amines reacts with Appel salt **1** to form 5-*N*-arylimino-4-chloro-1,2,3-dithiazoles **5**. These compounds should be more formally called *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes. Nevertheless, this alternative nomenclature is more recent and, until now, it was less used than the former (Scheme 4).[5] The reaction occurs generally in high yields with almost all the primary aromatic amines. In general, excess of amine or addition of a second base (*e.g.*, pyridine or 2,6-lutidine) allows trapping of the released hydrogen chloride. The rates of the reactions and yields of the imino-1,2,3-dithiazoles **5** are reduced in the presence of electron withdrawing substituents that can reduce the nucleophilicity of the arylamine.



R in substituted aniline

N-aryl-imino-1,2,3-(5*H*)-dithiazoles or
N-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes

H,
4-Me, 2,3-diMe, 2,4,6-triMe,
4-Et, 2,4,6-triEt,
2-Br, 4-Br,
2-Cl, 4-Cl, 2,4-diCl, 2,4,6-triCl,
2-F, 3-F, 4-F, 2,4-diF, 3,4-diF,
4-I
3-CF_3,
2-OH, 4-OPh, 2-CH_2OH-5-Cl,
2-OMe, 3-OMe, 4-OMe, 2,5-diOMe, 3,4-diOMe,
3,4,5-triOMe, 3,4-O$(CH_2)_2$,
2-OMe-4-NO_2,
2-CN, 2-CN-6-Me, 2-CN-4-Cl, 2-CN-4-OMe, 2-CN-4,5-diOMe
2-CO_2H, 2-CO_2H-5-Cl, 2-CO_2H-4,5-diOMe
2-CO_2Me, 2-CO_2Et,
3-CHO, 4-OAc, 4-Ac,
2-NO_2, 3-NO_2, 4-NO_2,
2-NH_2, 2-NHMe, 2-NHPh, 2-NH-pyridyl, 2-NH-(4-CN)Ph, 2-NEt_2

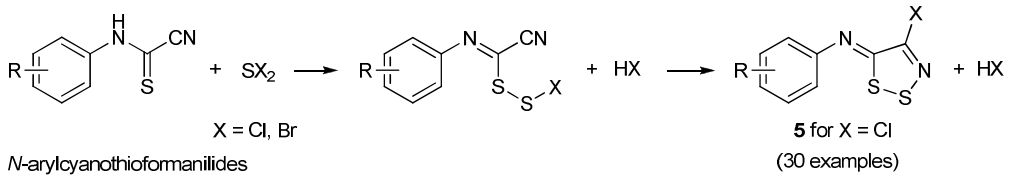
Scheme 4

Making a complete list of the amines condensed with Apple salt is not of real interest; the non-exhaustive list given in Scheme 4 allows to appreciate their diversity (experimental details and physicochemical data can be viewed in refs 5, 19–26 and 40). A large number of other aromatic amines that were reacted with **1** is presented in the next paragraphs.

The *N*-arylimines **5** usually form yellow or orange crystalline needles or powder (except for the parent system, R=Ph, or anisidines which can give oils) and are stable on storage in the atmosphere, showing no apparent hydrolysis after even extended periods. If Appel described mainly the synthesis of substituted *N*-anilino-4-chloro-1,2,3-dithiazoles from the corresponding anilines,[5] Besson and his co-workers extended this list[19,23–25] and performed the preparation of a large family of non-fused imino-1,2,3-dithiazoles with heterocylic fused anilines such as quinolines,[26–28] carbazoles,[29–32] coumarins,[33] benzodioxines,[34] quinazolines[35,36] and benzotriazoles.[37,38] Reactions of salt **1** with aromatic amines derived from naphthalenes, fluorenone and anthraquinones[39] were also described by the same group. Amino-derivatives of pyridines,[9] pyrimidines, pyrazoles, triazoles and imidazoles were published in various works.

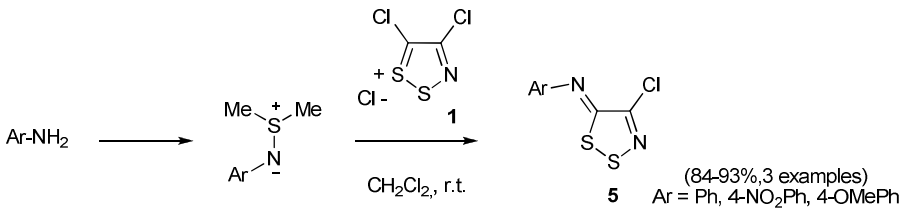
The compounds obtained in these studies were used as precursors of more complex molecules for which biological (antitumor, antifungic, antibacterial and anticancer) activities were expected.[23–39]

An alternative route to the synthesis of imines *via* Appel salt chemistry was also reported by Moore in a patent describing 4-halo-5-aryl-1,2,3-dithiazoles as useful fungicides, ovicides, insecticides and herbicides.[40] The attempted imines were prepared by the reaction of equimolar amount of cyanothioformanilides and a sulfur dihalide in the presence of formamide or quaternary ammonium salt in various solvents, at 30–100 °C (Scheme 5).



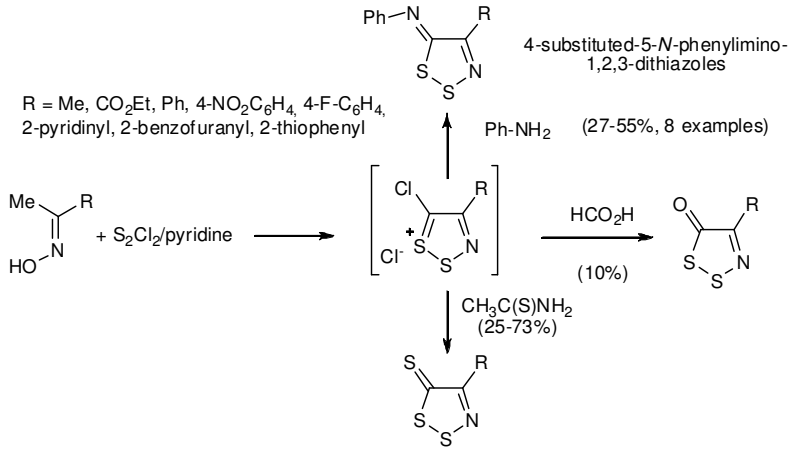
Scheme 5

Recently, Koutentis and his group described the reaction of sulfimides with Appel salt.[41] This method is limited owing to the poor availability and stability of the sulfimide reagents but it constitutes an alternative route to 1,2,3-dithiazolimines **5**, in good yields (Scheme 6).



Scheme 6

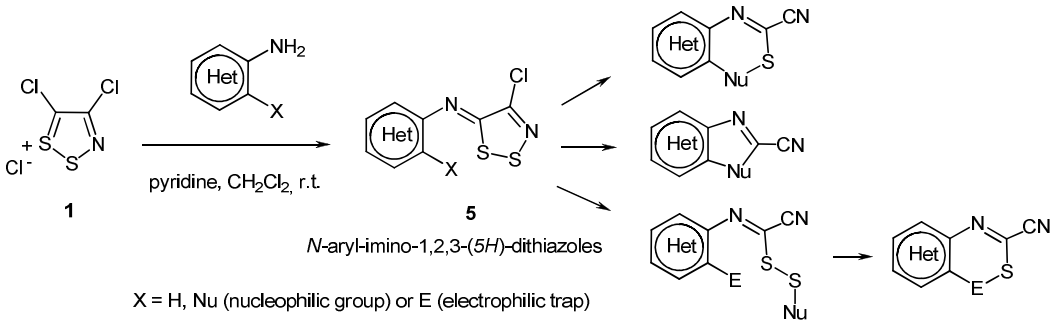
Thiéry and Rakitin described the synthesis and antibacterial evaluation of 4-substituted-5-*N*-phenylimino-1,2,3-dithiazoles, 5-thieno and 5-oxo-1,2,3-dithiazoles (*e.g.*, compounds **2** and **3** in Scheme 3). The authors suggested that these molecules were obtained then disulfur dichloride, pyridine and various ethanoneoximes were mixed in acetonitrile to give an intermediate 5-chloro-1,2,3-dithiazolium chloride which then reacted (in one-pot) with either anilines, thioacetamides and formic acid (Scheme 7).[42]



Scheme 7

3. Synthesis of heterocyclic systems *via* 5-*N*-arylimino-4-chloro-1,2,3-dithiazoles

The reaction of neutral 5-*N*-arylimino-4-chloro-1,2,3-dithiazoles **5** with nucleophilic reagents involves extra- or intra-molecular attacks at either C-5 or S-1, leading to the cleavage of the dithiazole ring and to the formation of various nitrogen- and/or sulfur-containing heterocyclic rings (Scheme 8). 1,2,3-Dithiazoles **5** can also take part in ANRORC style ring transformations: various soft nucleophiles can attack the dithiazole at S-2 affording a disulfide intermediate that may rearrange into a cyclized ring after a second attack. In each case, the final structure presents a carbonitrile group which is latent in the 1,2,3-dithiazole ring, generated after extrusion of chloride and loss of sulfur.



Scheme 8

Taking in account all these mechanistic possibilities, it is easy to understand that *N*-5-arylimino-4-chloro-1,2,3-dithiazoles **5** and their chemistry constitute very interesting tools for the access to novel heterocyclic systems of therapeutic importance. Various examples of bioactive molecules are described in the next paragraphs.

3.1. Five membered rings

3.1.1. Thiazoles

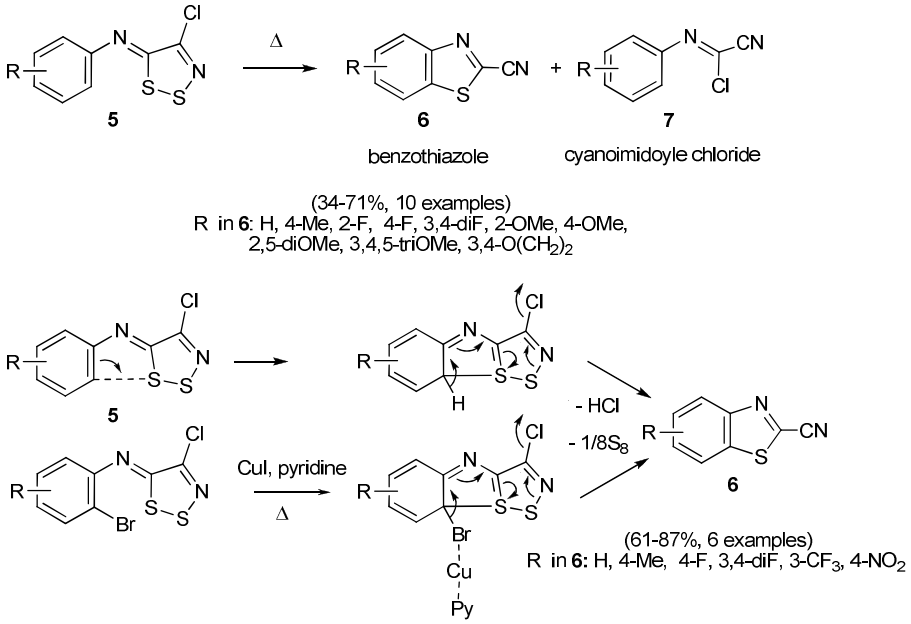
3.1.1.1. Benzothiazoles and derivatives

Rees and his co-workers demonstrated that thermolysis of 4-chloro-5*H*-1,2,3-iminodithiazoles **5** gave benzothiazoles **6** in good yields and in very short times.[7,19,20] Depending on the nature of the subtituents present on the aromatic ring, this procedure provided a number of benzothiazoles in 30–70% yields.[43,44] Besson's group studied this reaction under microwave irradiation and by varying parameters like power input, pressure, time and temperature. They identified well-defined conditions and described methods for scale-up.[43] Comparisons were made between reactions performed under solvent free conditions and in the presence of solvent.[44] In all cases, the focused microwave methodologies were more productive than the traditional thermal reactions (Scheme 9).

The major draw-back in the electrocyclization and fragmentation processes is the presence of strong electron withdrawing groups in the benzenic part. It prevents cyclization and results in the formation of a large number of by-products (*e.g.*, cyanoimidoyle chloride **7** in Scheme 9). Benzothiazoles **6** possessing strong electron withdrawing substituents can be obtained from appropriate *o*-bromo-substituted anilines in the presence of copper(I) iodide in pyridine at reflux (Scheme 9).[45]

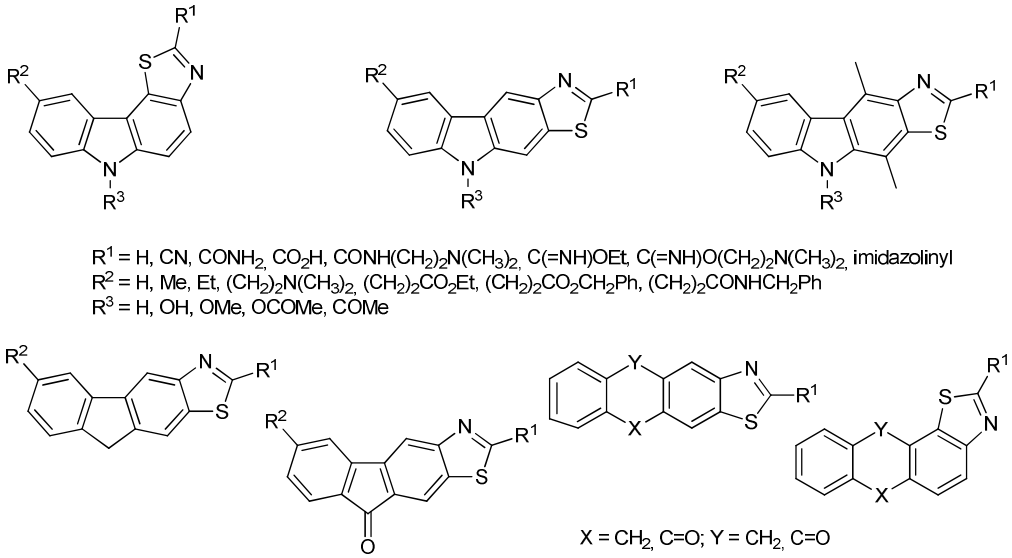
The mechanism may be facilitated by halogen complexation as described previously for the cyanation of aryl halides by copper(I) cyanide, where 2-cyanobenzothiazoles are also formed in the presence of

copper(I) cyanide or copper(0). This reaction was performed with a focused microwave reactor at atmospheric pressure. Important reduction of the reaction time and comparable yields with those obtained under oil bath conditions were observed.[43–45]



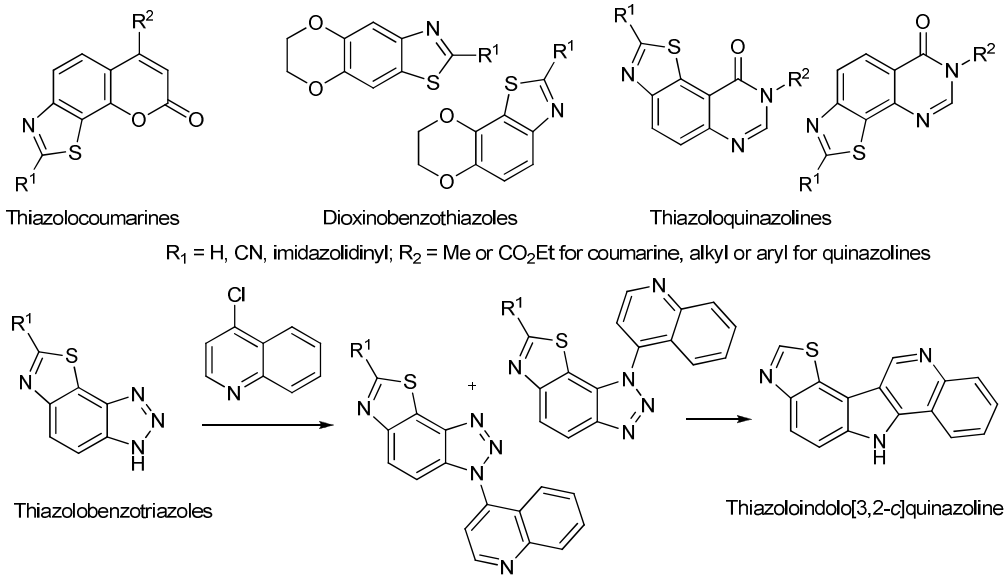
Scheme 9

Possessing a large variety of microwave-assisted strategies to build the benzothiazole ring, the authors extended their work and launched a research program dealing with the preparation and pharmacological evaluation of some original thiazolo-derivatives. They focused their studies on the regio-controlled synthesis of substituted heterocyclic fused benzothiazoles mainly related to marine or terrestrial alkaloids (*e.g.*, dercitine, kuanoniamine and ellipticine) in the hope to detect interesting cytotoxicity profiles and anticancer activity. Pursuing their efforts, they reported the microwave-assisted synthesis of a series of thiazole rings fused with carbazoles,[29–32] naphthalenes, fluorene, fluorenone and anthraquinones[39] (Scheme 10).



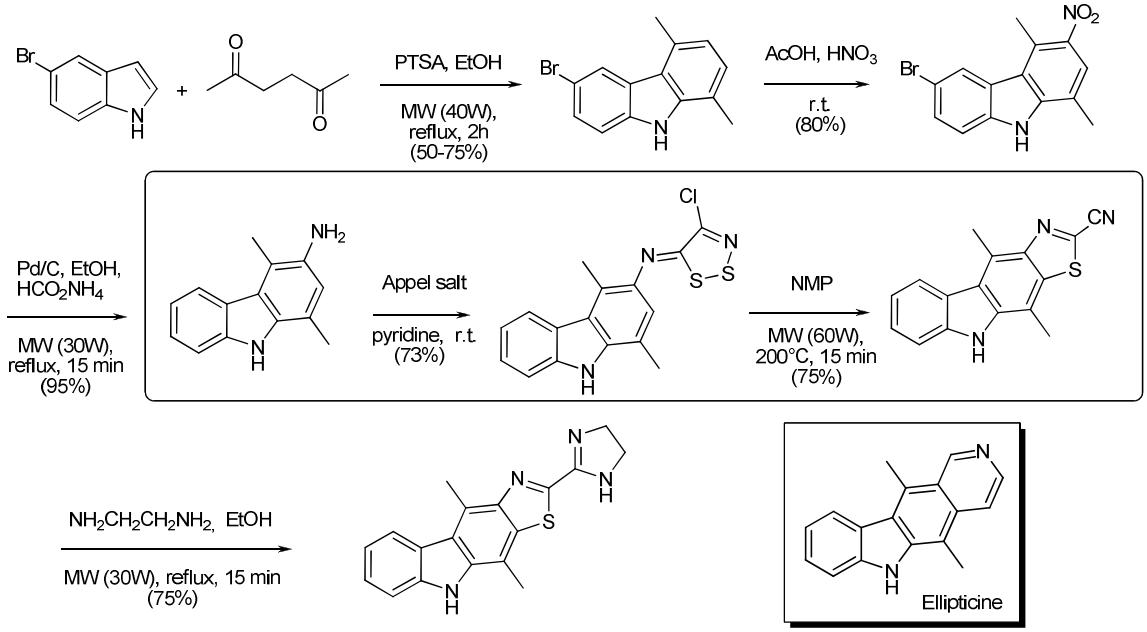
Scheme 10

Coumarins,[33] benzodioxines,[34] quinazolines[35,36] and benzotriazoles[37,38] were also thermally cyclized into the corresponding thiazolo derivatives[33–36] and thiazoloindolo[3,2-*c*]quinolines[37,38] (Scheme 11). In all cases, besides resulting in good to excellent yields, the microwave-assisted multistep syntheses resulted in much faster reactions compared to earlier published procedures at atmospheric pressure under conventional heating conditions.



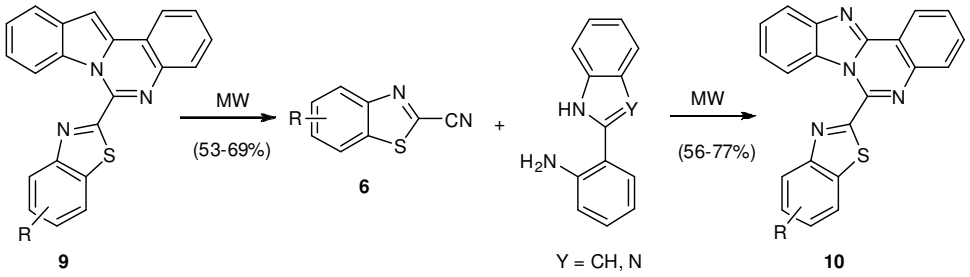
Scheme 11

It is also noteworthy that in some cases the strong thermal effect due to graphite/microwave interactions, can efficiently be used for the synthesis of heterocyclic skeletons, especially benzothiazoles[33,44] but, in fact, there is no general rule and some reactions performed in the presence of solvent may sometimes be more convenient than the same dry-media conditions. The example described in Scheme 12 shows the multistep synthesis of a thiazolocarbazole analog of ellipticine, a naturally occurring heterocyclic alkaloid known for its anticancer activity.[30]



Scheme 12

Exploring the transformation of the cyano group present in position 2 of the thiazole ring, Besson's group described the synthesis of novel benzothiazolyl indolo[1,2-*c*]quinazolines **9**[46] or benzimidazo-[1,2-*c*]quinazolines **10**[46,47] which were obtained by condensation of the 2-cyanobenzothiazoles **6** with 2-(2-aminophenyl)indole or benzimidazole. Microwave irradiation (150 °C) of the reactants at atmospheric pressure in the presence of graphite as energy sensitizer (10% by weight) afforded the expected products in good yields and in short times (Scheme 13).[46]



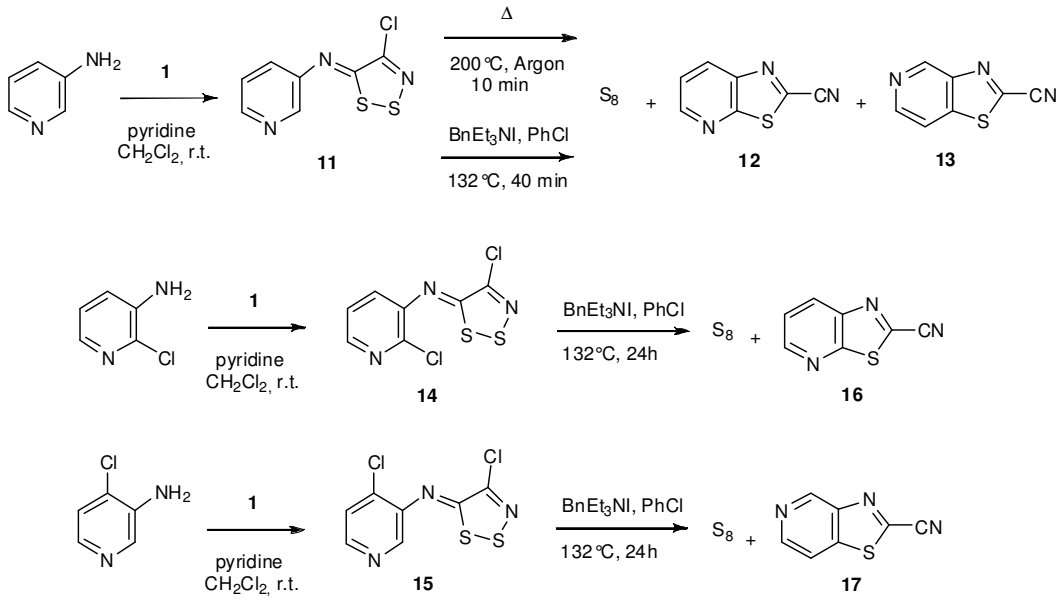
MW : graphite (10 % by weight), µw (150°C, 150 W), 30-240 min.

6 examples : R = H, 6-F, 6-Me, 6-OMe, 4,7-diMe, 4,7-diOMe

Scheme 13

3.1.1.2. Thiazolopyridines

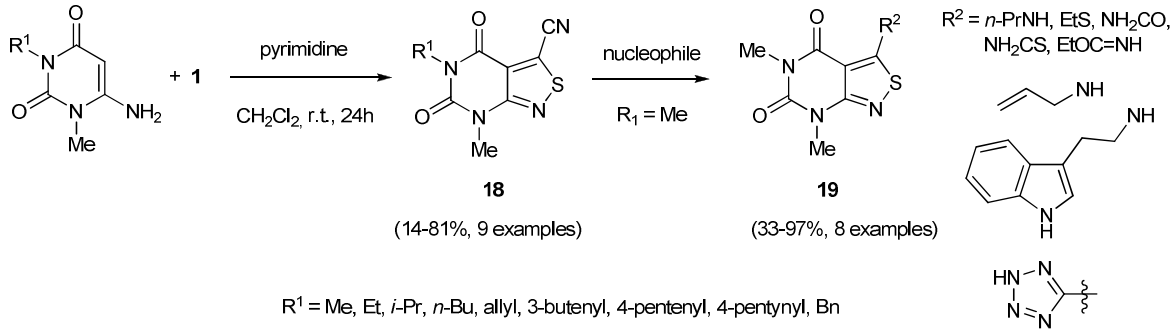
Thermolysis of *N*-(pyrid-3-yl)-4-chloro-1,2,3-dithiazol-*5H*-imine **11** gave thiazolo[5,4-*b*]pyridine-2-carbonitrile **12** and thiazolo[5,4-*c*]pyridine-2-carbonitrile **13** in low yields. Repeating the reaction in the presence of a soft nucleophile like benzyltriethylammonium iodide at 132 °C in chlorobenzene gave improved but still moderate yields of both isomers. The 2-chloro and 4-chloro-derivatives **14** and **15** were prepared and treated with catalytic iodide (5 mol%) to give the expected single isomers **16** and **17** in near quantitative yields. In this case, the chlorine substituent was expected to assist in directing the ring closure (Scheme 14).[9]



Scheme 14

3.1.1.3. Isothiazolopyrimidines

Kim's group described the synthesis of novel isothiazolo[3,4-*d*]pyrimidine-3-carbonitriles **18** from 6-amino-1,3-dialkyluracils and salt **1** in dichloromethane at room temperature for 24 hours. The cyano group of **18** was readily displaced or transformed by reactions with various nucleophiles, rapidly affording a short library of substituted 3-aminoisothiazolo[3,4-*d*]pyrimidine-4,6-diones **19** which constitute an interesting class of compounds since some of them have been reported to be useful as sedatives and inflammation inhibitors (Scheme 15).[48]

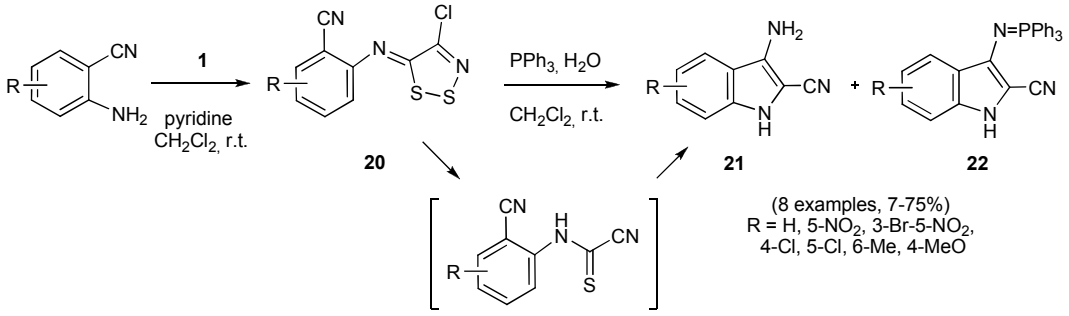


Scheme 15

3.1.2. Indoles, benzimidazoles, benzoxazoles and derivatives

3.1.2.1. Indoles

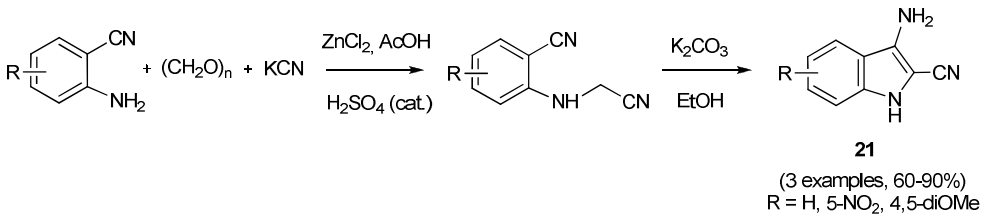
3-Aminoindole-2-carbonitriles **21** were obtained by reacting 2-(4-chloro-*5H*-1,2,3-dithiazolylidene-amino)benzonitriles **20** with triphenylphosphine (4 equiv.) in the presence of water (2 equiv.). The major product was accompanied by various amounts of (2-cyanoindol-3yl)iminotriphenylphosphorane **22**, together with triphenylphosphine and oxide. The use of polymer bound triphenylphosphine provided cleaner reaction mixtures. Electron withdrawing substituents gave the indoles **21** in relatively high yields (75 and 71% for 5-nitro and 4-chloro, respectively) whilst electron rich methoxy-substituted starting compounds gave little to no yield of the expected products (Scheme 16).[49]



Scheme 16

Pursuing their investigations, Koutentis and his co-workers identified 2-cyanothioformanilides as possible intermediates for this transformation. They discovered that the attempted indoles **21** can be efficiently synthesized from isolated substituted formanilides (an efficient route to this class of derivatives was described by treating **20** with 4 equivalents of DBU in dichloromethane[50]) and triphenylphosphine (2 equiv.) in the presence of 1 equivalent of *para*-toluenesulfonic acid (PTSA).[51]

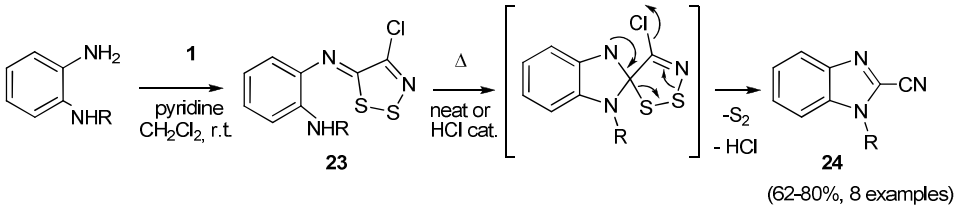
An alternative route to these cyanated amino-indoles was recently described by the same group from anthranilonitriles (either NO_2 and OMe substituted) *via* the *N*-unprotected Thorpe-Ziegler cyclization of the starting 2-(cyanomethylamino)benzonitriles at elevated temperatures under pressurized microwave-assisted experiments (Scheme 17).[52]



Scheme 17

3.1.2.2. Benzimidazoles

N-Monosubstituted *o*-phenylenediamines reacted with Appel salt **1** in dichloromethane at room temperature to give the corresponding 2-cyanobenzimidazoles **24** *via* thermal or acid-catalyzed rearrangement of intermediate *N*-arylimino-4-chloro-1,2,3-dithiazoles **23**.[53,54] The mechanism of this rearrangement involves a reversible attack of the *ortho*-amino group on the C-5 atom of the heterocycle. The spiro compound obtained is then aromatized with elimination of HCl and formally a molecule of diatomic sulfur (Scheme 18). Formation of the diatomic sulfur was supported by Rakitin and Rees *via* isolation of Diels-Alder cycloadducts with norbornene and 2,3-diphenyl butadiene,[54] although these S_2 traps can also react with S_8 at elevated temperatures.



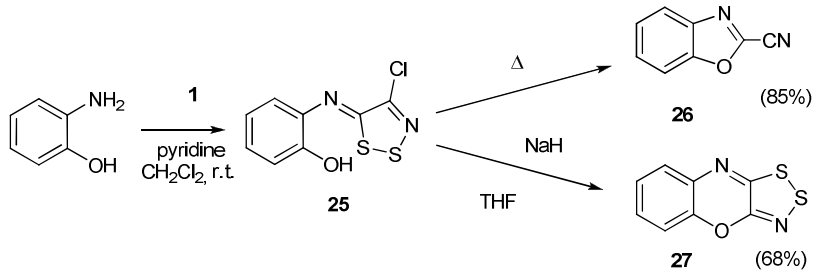
R = H, Me, Ph, 4-ClC$_6$H$_4$, 2,4-diNO$_2$-C$_6$H$_3$, 4-Me-2-pyridyl, 3-NO$_2$-2-pyridyl, cyclohexyl

Scheme 18

It is interesting to note that poorly nucleophilic intermediates failed to undergo rearrangement at temperature up to 180 °C. Addition of pyridine (2 equiv.) to the reaction mixture can suppress the spontaneous rearrangement. By omission of pyridine, it is possible to convert in one step the starting diamines into the expected benzimidazoles, without isolation of the imine intermediate.[54]

3.1.2.3. Benzoxazoles

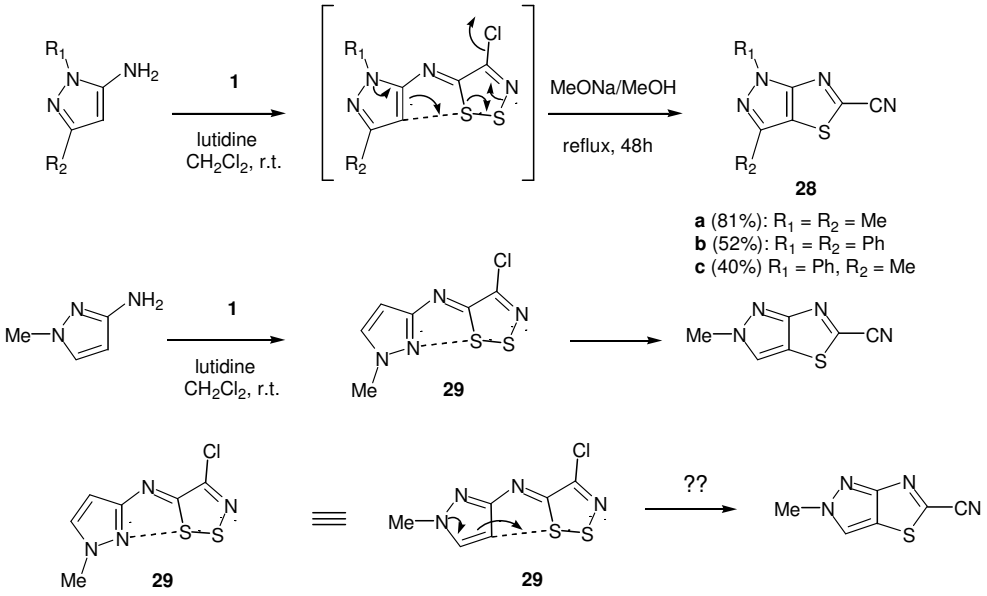
The mechanism suggested above for the benzimidazoles **24** is also implied for the reaction of the salt **1** with *o*-aminophenols which affords *o*-hydroxyphenylimines **25** which cyclize under heating to give the corresponding 2-cyanobenzoxazoles **26** (Scheme 19).[7,11] It should be noticed that treatment of the starting imine **25** with sodium hydride in THF leads to a thermally stable dithiazolobenzoxazine **27** probably *via* a very rare nucleophilic attack on the carbon 4 of the 1,2,3-dithiazole ring.



Scheme 19

3.1.2.4. Pyrazolo[3,4-*d*]thiazole

The reaction of Apple salt with 5-aminopyrazoles at room temperature in the presence of lutidine (2 equiv.) led to condensed *1H*-pyrazolo[3,4-*d*]thiazoles **28**. L'abbé and co-workers assumed that the bicyclic products result of spontaneous intramolecular cyclization of intermediates imines, accompanied by extrusion of sulfur and hydrogen chloride.[55] This mechanism was confirmed by the fact that the stable imine **29** formed from the salt **1** and 3-amino-1-methylpyrazole was not able to form a bicylic product; the S---N intramolecular interaction hinders the cyclization (Scheme 20).



Scheme 20

Previous methods for the synthesis of *1H*-pyrazolo[3,4-*d*]thiazoles also used 5-aminopyrazoles as starting materials but required multi-steps reactions.[56] The method described by L'abbé and his group has the advantage of introducing the S–C–N unit directly onto the aminopyrazole under mild conditions and in one step from Appel salt.

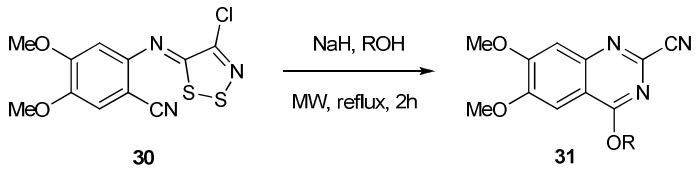
3.2. Six membered rings

3.2.1. Quinazolines and derivatives

3.2.1.1. Quinazolines

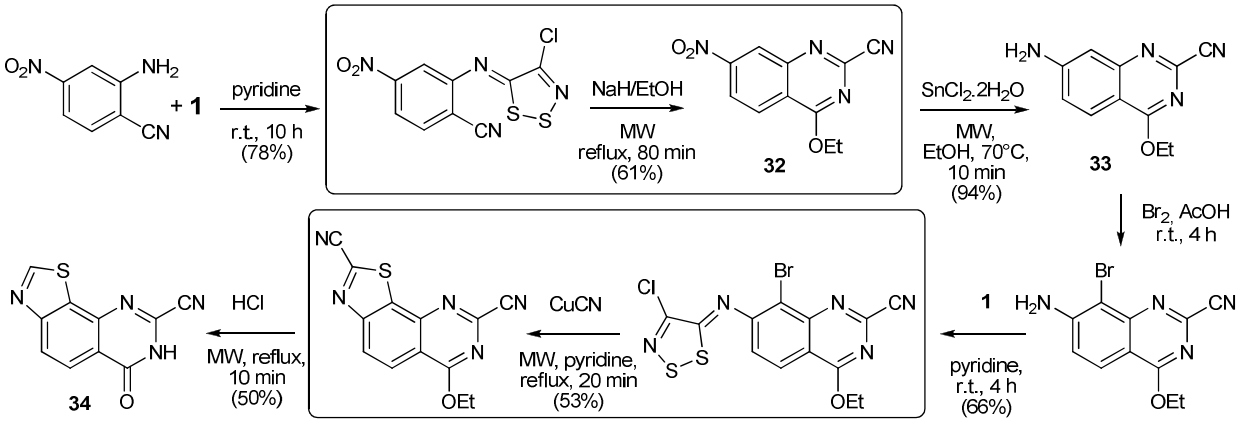
The first paper relating the synthesis of the 4-alkoxyquinazoline-2-carbonitrile **31** was published in 1996 by Rees and Besson[57] who studied the chemical transformation of the 4-chloro-5*H*-1,2,3-dithiazole **30**

itself obtained from condensation of salt **1** and anthranilonitrile. Besson and his co-workers described later the microwave-assisted conversion of *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazoles **30** into 4-alkoxy-quinazoline-2-carbonitriles **31** in the presence of sodium alkoxide, using the corresponding alcohols, as solvents. Microwave irradiation of the solutions at atmospheric pressure in monomode systems with focused irradiation and continuous temperature control (IR pyrometer) gave cleaner, faster and higher yielding reactions compared to conventional conditions (Scheme 21).[58]



Scheme 21

It is important to note that these experiments could be safely scaled up to multigram quantities minimizing the risk of explosion and hazardous bumping reported in multimode domestic ovens.[58] Continuing its search for interesting bioactive quinazolines, the same group described the synthesis of 6-nitro and 6-amino-4-alkoxyquinazoline-2-carbonitrile derivatives[35] **32** and **33**, respectively which served as intermediates in the synthesis of novel thiazoloquinazolin-4-ones **34** (Scheme 22).



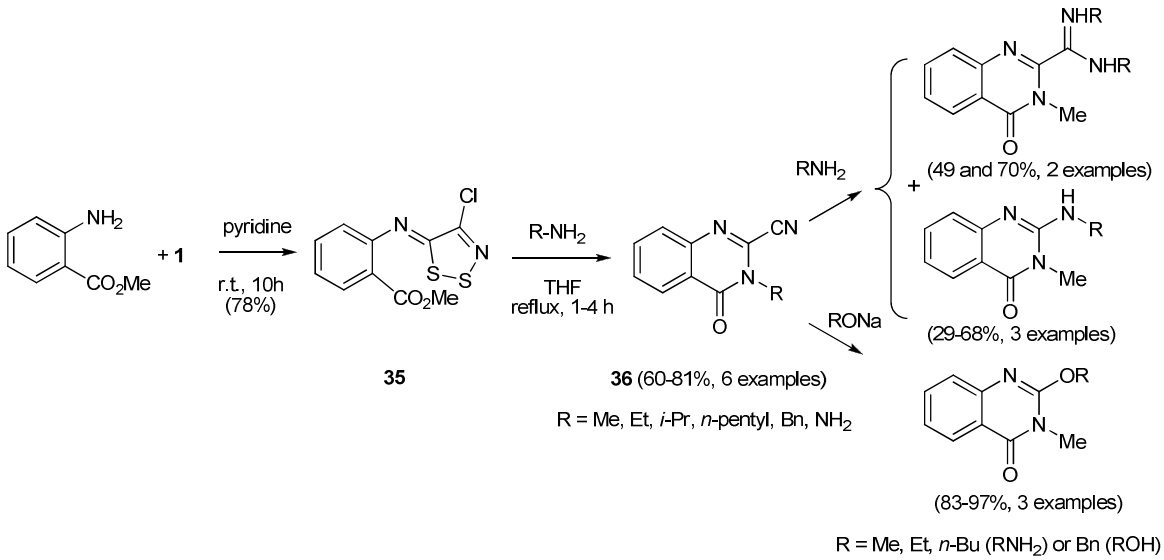
Scheme 22

Another route to thiazoloquinazoline isomers ([4,5-*f*] and [5,4-*h*]) was described latter by fusion of the thiazole and the quinazoline ring *via* microwave-assisted Appel salt chemistry.[59]

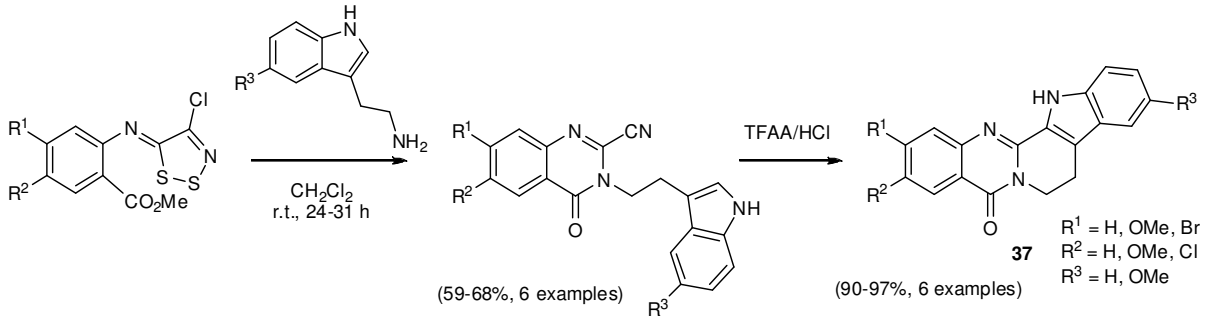
During the same period, Kim's group studied the reaction of methylanthranilate with Appel salt **1** in the presence of pyridine.[60] The (*N*-4-chloro-*5H*-1,2,3-dithiazol-5-ylidene)anthranilate **35** obtained was reacted with primary alkylamines to give directly 2-cyanoquinazolin-4(*3H*)ones **36** in moderate to good yields (scheme 23).[60–64] In his studies, Kim has demonstrated that the cyano group present in C-2 of the quinazoline ring may be displaced by nucleophiles like primary amino groups and alcohols or attacked on its carbon to generate amidines.[61,62]

Then, looking for access to various polyheterocyclic molecules with potent biological activity, Kim and Mohanta described a short and rapid synthesis of quinazolinocarboline analogs of Rutaecarpine **37**, an

alkaloid found in certain herbs including *Evodia rutaecarpa*, a well-known herb called Wu-Chu-Yua used in traditional Chinese medicine (Scheme 24).[62,63]

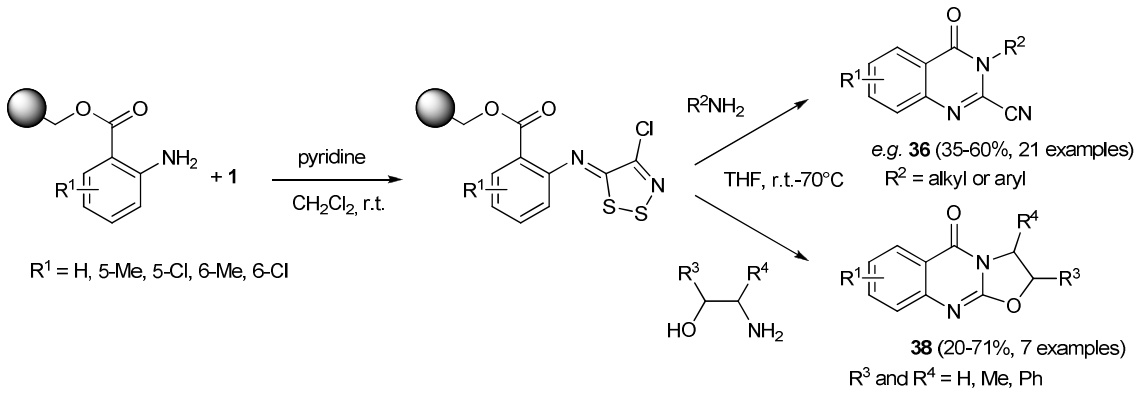


Scheme 23



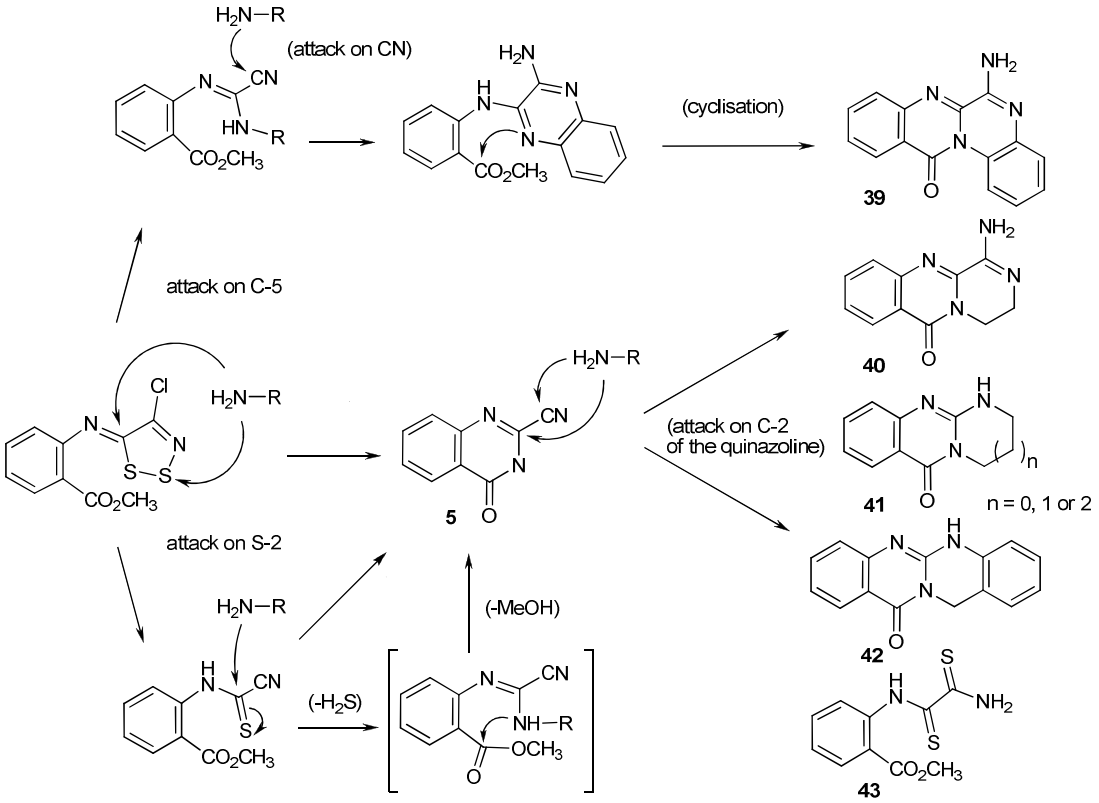
Scheme 24

More recently, Gong and his co-workers published the conversion of anthranilic acid derivatives linked by an ester bound with a polymeric matrix.[64] The immobilized 5-arylimino-1,2,3-dithiazoles reacted efficiently with aromatic or alkylamines to afford a library of twenty quinazolin-4-one-2-carbonitriles (*e.g.*, **36** in Scheme 23). Condensation of α-amino-alcohols with the immobilized imines was experimented with success to give 2,3-dihydrooxazolo[2,3-*b*]quinazolin-5-one **38** which was obtained *via* intramolecular cyclization of the intermediate 2-cyanated quinazoline (Scheme 25).[64]

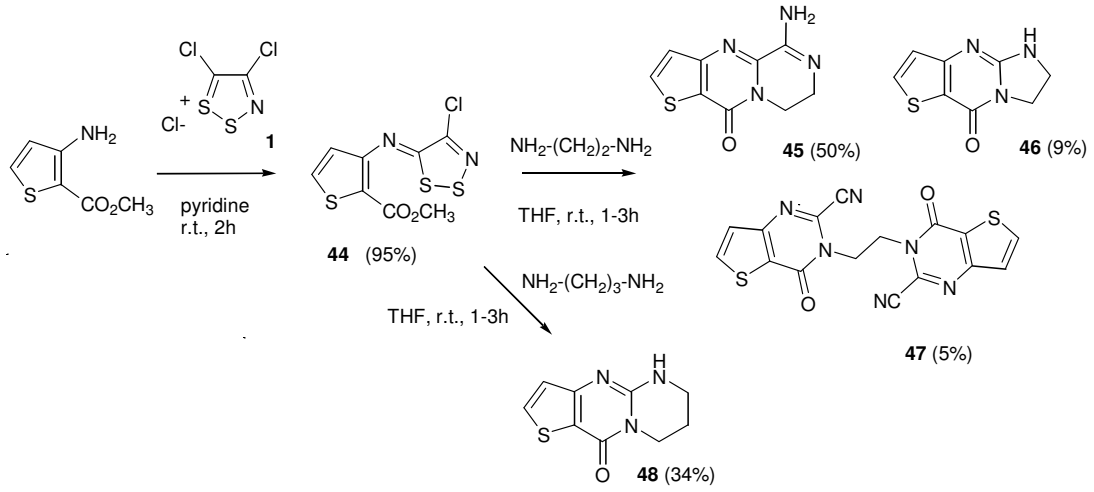


Scheme 25

Confirming the utility of Appel salt chemistry in the conception of novel heterocyclic rings, Besson and his co-workers studied the condensation of alkyl or aromatic diamines with methyl *N*-(4-chloro-*5H*-1,2,3-dithiazol-5-ylidene)anthranilate to afford a novel family of 2,3-condensed quinazolines (**39–42**) which are structurally closed to model natural products (*e.g.*, rutaecarpine, luotonine, tryptanthrine and vasicinone) (Scheme 26).[65–68] In these studies, the authors suggest that most nucleophilic amines (alkaneamines or alkanediamines) attack firstly on C-5 of the dithiazole ring and then give **39** and **40**; on the other hand, less nucleophilic amines (areneamines) and bulky amines attack on S-2 of the ring and lead to intermediate cyanothioformamides which can be transformed into the polycyclic compounds **40–42** or into unexpected thiooxamides **43** (Scheme 26).



Scheme 26

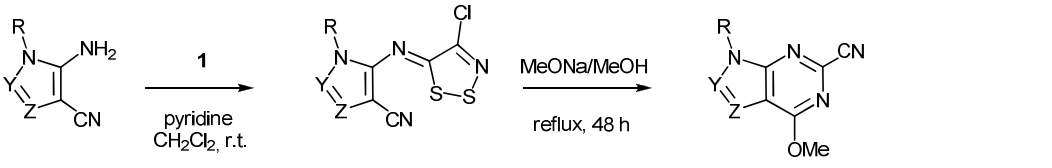


Scheme 27

Investigating the chemistry of imino-1,2,3-dithiazoles possessing a thiophene ring, Pereira and co-workers described the synthesis of novel 2,3-condensed thieno[2,3-*d*]pyrimidine derivatives **45–48** (Scheme 27).[68] This work also confirmed the interest to use methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-thiophene carboxylate **44** as a good precursor of a variety of novel thiophene-containing bioisosters of pharmaceutically active quinazolines.

3.2.1.2. Triazolo-, imidazo- and pyrazolopyrimidines

The reaction of Appel salt with *o*-aminonitrile heterocycles in methylene chloride at room temperature gave the corresponding 4-chloro-5-heteroimine-5*H*-1,2,3-dithiazole **49** which reacted with sodium methoxide in methanol at reflux to give the 1-substituted 2-cyano-pyrazolo[3,4-*c*]pyrimidines **50** in acceptable yields (52–72%) (Scheme 28).

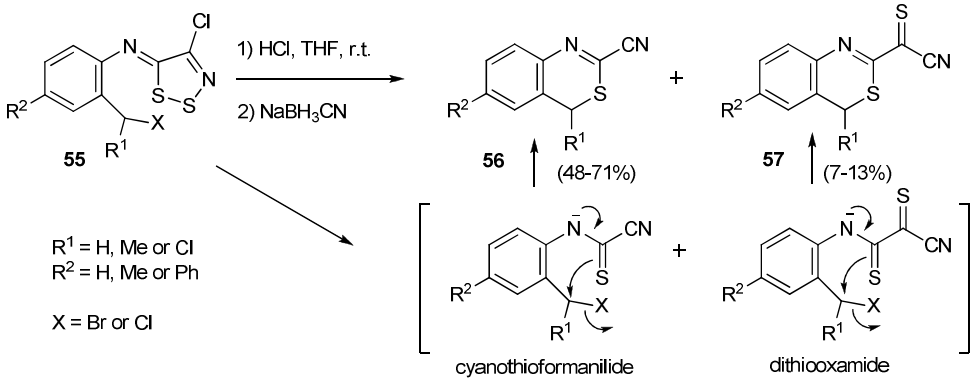


Scheme 28

The method described by Baraldi and co-workers[69] was extended to the imidazole and triazole precursors giving the imines **51** and **53** which were treated with sodium methoxide in methanol to give corresponding imidazolo[3,4-*c*]pyrimidine **52** and the triazolo[4,5-*c*]pyrimidine **54** in 52 and 69% yields, respectively.[69] As demonstrated before for the quinazoline[35] or benzothiazole[29–32] congeners, the cyano group can be easily removed by hydrolysis and decarboxylation with hot concentrated hydrochloric acid.

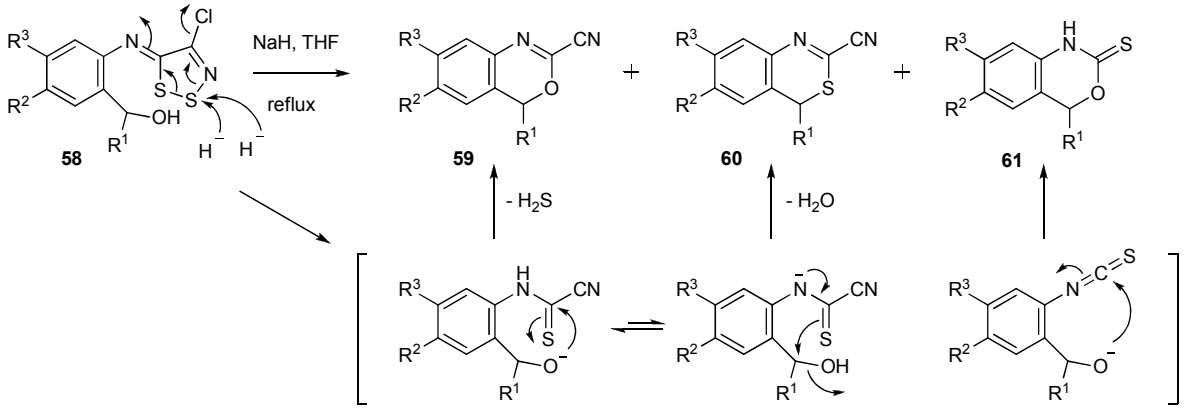
3.2.2. Benzoxazines and benzothiazines

Studying the chemistry of 1,2,3-dithiazoles, Kim and his co-workers[70] discovered that treatment of the hydrochloride salt of 4-chloro-5-(2-halomethylarylimino)-5*H*-1,2,3-dithiazoles **55** with cyanoborohydride in THF at room temperature gave 2-cyano-4*H*-3,1-benzothiazines **56** and **57** in good to moderate yields (Scheme 29).



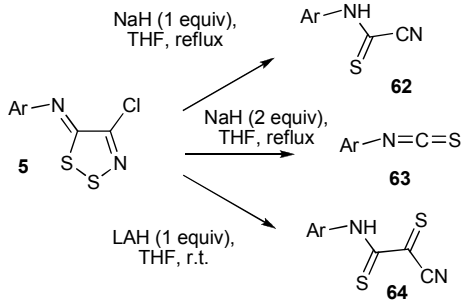
Scheme 29

2-Cyano-4*H*-3,1-benzoxazines **59** and their sulfur-containing analogs **60** were also obtained by refluxing 4-chloro-5-(2-hydroxymethylarylimino)-5*H*-1,2,3-dithiazoles **58** with sodium hydride in THF.[52] In this process and depending of the R^2 and R^3 substituents, 4*H*-3,1-benzoxazine-2-thiones **61** were also identified (Scheme 30).



Scheme 30

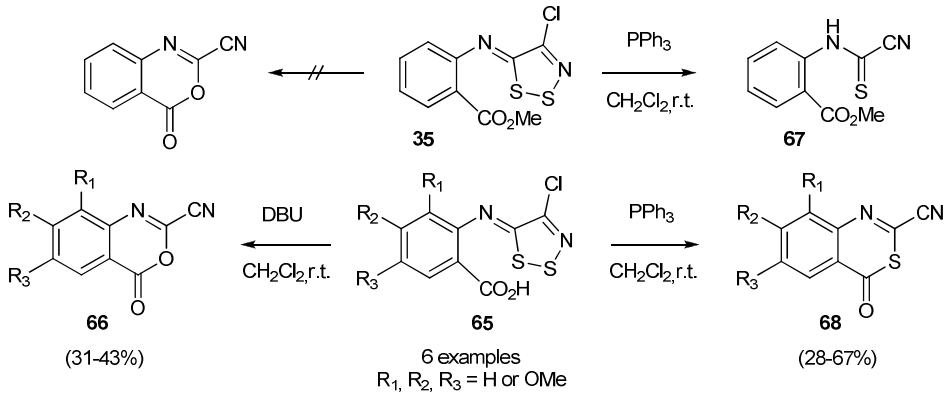
In these experiments, the authors suggested the presence of cyanothioformanilide, dithiooxamide or isothiocyanate derivatives but were not able to prove their existence in the reaction media.[70] Six years later, Besson and his group demonstrated that treatment of arylimino-1,2,3-dithiazoles with sodium hydride in THF at reflux gave the *N*-arylcyanothioformanilides (Scheme 30, bottom part, and **62** in Scheme 31) which reacted with sodium hydride to give aryl isothiocyanates **63**.[71,72] The latter can also be directly obtained by treating the starting imines with 2 equiv. of sodium hydride. Pursuing its studies the same group revealed that dithiooxamide derivatives **64** are available in interesting yields from the starting imino-1,2,3-dithiazoles (*e.g.*, **5**) by treatment with lithium aluminium hydride in THF at room temperature (Scheme 31).[73]



Scheme 31

This part of Appel salt chemistry was extended to the synthesis of analogs of Dapsone, one of the main drugs for the treatment of leprosy, although its action is only bacteriostatic.[74]

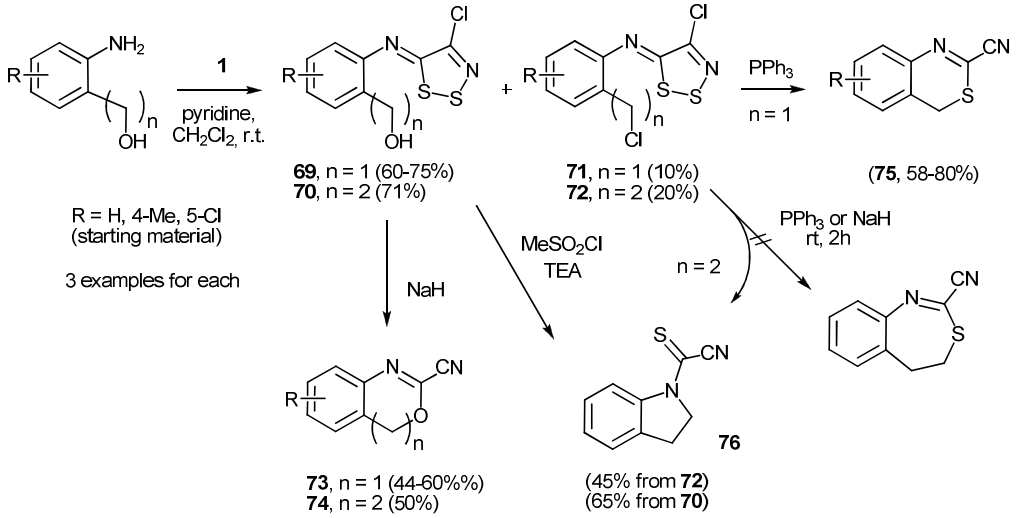
Two years after Kim's work, Besson and Rees described that treatment of methyl anthranilate with 4,5-dichloro-1,2,3-dithiazolium chloride **1** in dichloromethane at room temperature, followed by addition of pyridine, gave the expected imino derivative **35**, while anthranilic acid derivative **65** gave 4-oxo-4*H*-3,1-benzoxazine-2-carbonitrile **66**. If triphenylphosphine was added to the reaction mixture instead of pyridine, methyl anthranilate gave methyl *N*-(cyanothioformyl)anthranilate **67** while anthranilic acid gave 4-oxo-4*H*-benzo-3,1-thiazine-2-carbonitrile **68** (Scheme 32).[75,76]



Scheme 32

These differences were explained mechanistically. When anthranilic acid was treated with the dithiazolium chloride **1** without the addition of pyridine, the delicate imino derivative **65** of the free carboxylic acid could be isolated (60%). This, when heated in boiling toluene,[75] or stirred at room temperature in the presence of DBU,[76] gave the benzoxazinone **66** quantitatively. With triphenylphosphine, at room temperature, it gave the benzothiazinone **68** quantitatively. These reactions provide a good route to benzo-substituted 2-cyanooxazinones and 2-cyanothiazinones from the corresponding anthranilic acids.[75,76] It can be noticed that ten years later the chemistry of such a compounds was then investigated by Alexandre and co-workers who prepared novel benzo[1,3,4]benzotriazepine derivatives for which biological activity was expected.[77]

Studying novel synthetic routes to 2-cyano-4*H*-3,1-benzoxazines **66** and its sulfur containing analogs **68**, Besson and co-workers discovered that conversion of 2-hydroxymethyl- and 2-hydroxyethylaniline with Appel salt **1** into the arylimines **69** and **70** was accompanied by formation of the chloromethyl and chloroethyl derivatives **71** and **72**.[78,79] The *o*-aminobenzyl alcohol **69** and the *o*-aminophenethyl derivative **70** were converted into the corresponding 3,1-benzoxazine **73** and the 3,1-benzodiazepine **74**, respectively, in the presence of sodium hydride. Triphenylphosphine converted compound **69** into the benzothiazine **75** but the chloroethyl compound **72** gave *N*-(cyanothioformyl)indoline **76** (55%) rather than the analogous benzothiazepine.



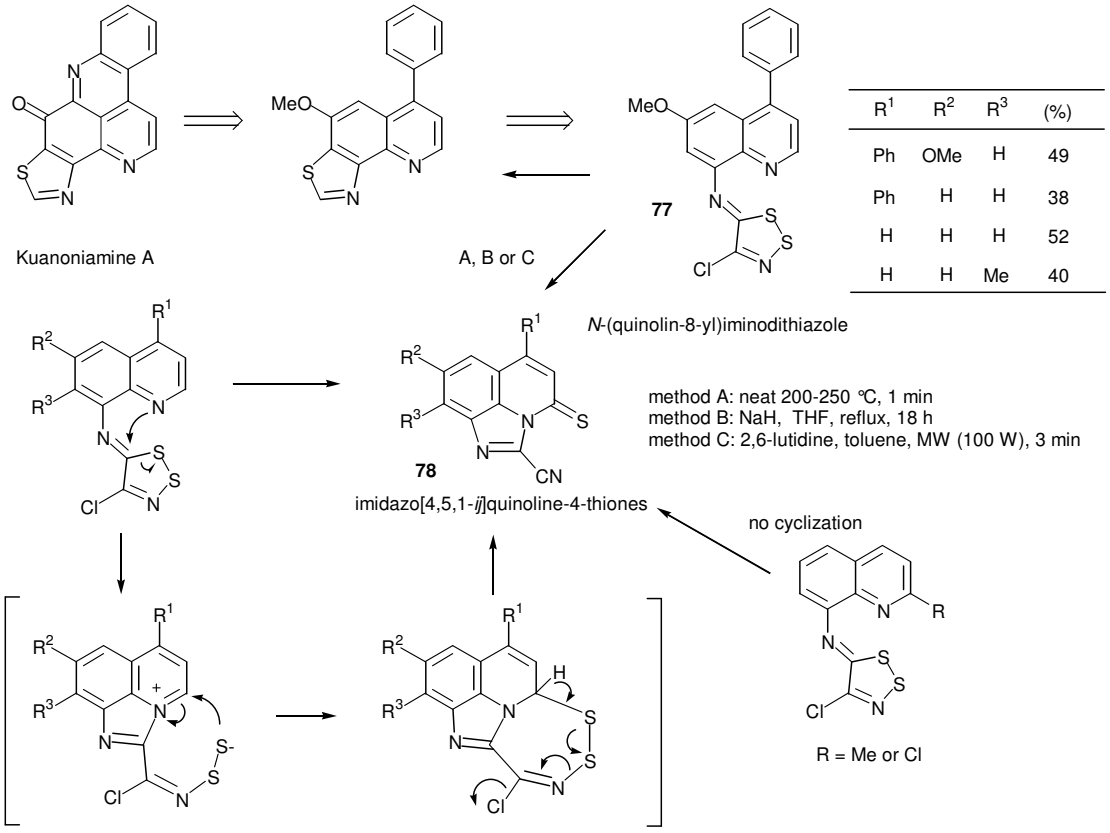
Scheme 33

Indoline **76** was also formed from **72** with sodium hydride (45%) and from the hydroxyethyl compound **70** with mesyl chloride and triethylamine (65%)[79] (Scheme 33).

^{1}H and ^{13}C NMR spectra show that the final product **76** exists in solution as two rotamers (the form drawn in Scheme 33 is the major one).[79] In this study, the structure of this unknown indoline was confirmed by an independent synthesis by the method which Lee and Kim have described for *N*-alkyl- and *N,N*-dialkyl-cyanothioformamides.[80]

3.2.3. Imidazo[4,5,1-*ij*]quinoline-4-thiones

Exploring new routes to cytotoxic marine natural products (*e.g.*, kuanoniamine A and dercitins), Rees and Thiéry demonstrated that condensation of 8-aminoquinolines with 4,5-dichloro-1,2,3-dithiazolium chloride **1** provided *N*-(quinolin-8-yl)iminodithiazoles **77** which underwent a novel thermal rearrangement to give imidazo[4,5,1-*ij*]quinoline-4-thiones **78**.[81] Normal cyclization of the dithiazolo group onto the carbocyclic ring to form a benzothiazole was averted by *peri*-participation of the quinoline ring nitrogen. This participation results in the formation of the imidazole ring and the delivery of a sulfur atom to the quinoline 2-position. Delivery of this sulfur appears to be intramolecular and possibly involves a [1,3] sigmatropic shift of a carbon–sulfur bond (Scheme 34).[80,81]



R^1	R^2	R^3	(%)
Ph	OMe	H	49
Ph	H	H	38
H	H	H	52
H	H	Me	40

Scheme 34

The same overall reaction was observed, at much lower temperature, during treatment of the quinolinyliminodithiazoles with sodium hydride in THF (method B) or after short microwave irradiation in the presence of 2,6-lutidine and toluene (method C), thus providing a ready route to imidazo[4,5,1-*ij*]quinoline-4-thiones **78**.

4. Conclusion

The work presented in this review demonstrates that *N*-arylimino-1,2,3-dithiazole derivatives (*e.g.*, **5**) are very versatile intermediates in heterocyclic chemistry, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the 1,2,3-dithiazole ring. Since the first paper of Appel in 1985, several hundreds of compounds were synthesized from 4,5-dichloro-1,2,3-dithiazolium chloride and its derivatives. Today the literature contains more than hundred papers covering the last twenty years of intensive research mainly introduced by C. W. Rees and his co-workers The utility of Appel salt in the conception of novel heterocyclic skeletons is of growing interest and it is particularly good for the direct preparation of nitrile bearing heteroarenes (*e.g.*, benzothiazoles and quinazolines) with broad applications in materials and biological sciences.

Acknowledgments

T.B. is most grateful to his able coworkers who are mentioned in the references for their many contributions. We thank the *Ministère de l'Enseignement Supérieur et de la Recherche* (MESR) (AF PhD grant) and the *Ligue Nationale contre le Cancer* for financial support.

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α,β-UNSATURATED TRIFLUOROMETHYL KETONES IN THE SYNTHESIS OF FLUORINATED HETEROCYCLES

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Abstract. *The review is devoted to the application of α,β-unsaturated trifluoromethyl ketones in the synthesis of 3–7 membered fluorinated heterocycles. The literature up to 2010 is highlighted.*

Contents

1. Introduction

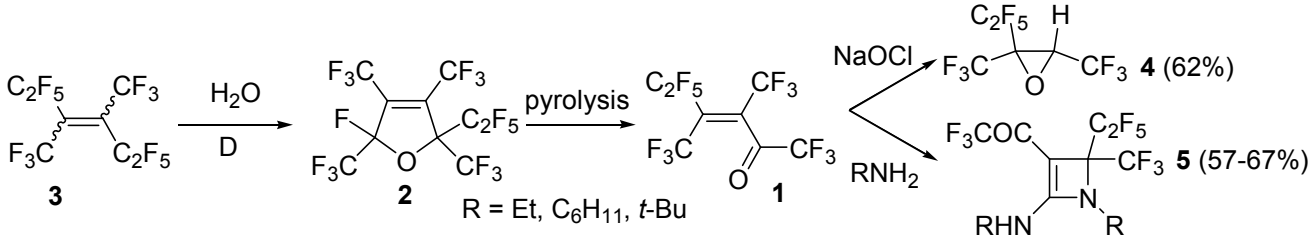
Trifluoromethyl group, due to its unique stereo and electronic properties, is a very important substituent in medicinal chemistry. Trifluoromethyl group usually enhances lipophilicity of the molecules, thus improving their transport characteristics *in vivo*. Furthermore, the durability of C–F bond comparing with C–H one (116 and 100 kcal/mol, respectively) allows to avoid undesirable metabolic transformations. The incorporation of trifluoromethyl group into bioactive molecules becomes very important direction in pharmaceutical studies that stimulates the works aimed at the elaboration of synthetic methodologies for various

classes of compounds containing trifluoromethyl group. Due to all these factors, the fluorine chemistry has been vigorously developing during the last two decades.

Most of the known approaches to the synthesis of CF_3-containing organic compounds suffer from serious drawbacks. First of all, initial compounds applied by these methods are rather difficult to obtain or they are fairly toxic and it is inconvenient to work with them. Additionally, the methods for the direct fluorination and trifluoromethylation do not always allow to introduce the CF_3-group in the required position of the molecule. As the result, more flexible "synthon" approach based on the application of simple and available fluorine containing compounds gains substantial interest. α,β-Unsaturated trifluoromethyl ketones are easily available compounds which can be prepared by various methods[1] and fairly convenient building blocks to prepare a variety of heterocyclic compounds bearing trifluoromethyl group.

2. Synthesis of three- and four-membered heterocycles

Several reactions of perfluorinated CF_3-enone **1** were studied.[2] This ketone was produced by pyrolisis of perfluorodihydrofuran **2** which in turn was prepared by high temperature hydrolysis of tetrafluoroethene tetramer **3**. The fluorinated oxirane **4** and azetidine **5** were prepared in good yields using the reaction of **1** with sodium hypochlorite and the corresponding primary amines (Scheme 1).

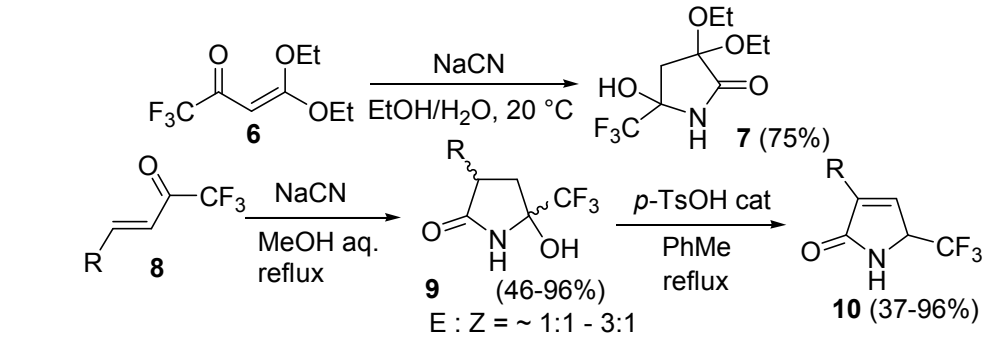


Scheme 1

3. Synthesis of five-membered heterocycles

3.1. Synthesis of pyrrole derivatives

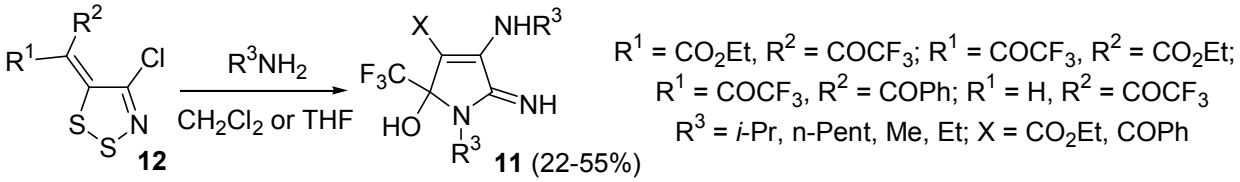
The reaction of diethoxyenone **6** with sodium cyanide was described for the synthesis of the corresponding pyrrolidone **7**.[3] It was shown that various enones **8** react with sodium cyanide similarly to give the corresponding pyrrolidones **9** as the mixture of diastereomers.[4] Subsequent dehydration proceeded with migration of double bond and led to the formation of pyrroline-3-one-2 **10** (Scheme 2).



R = Ph, 4-MeC_6H_4; 3-MeC_6H_4; 3-$MeOC_6H_4$; 2-thienyl; 2,5-$(MeO)_2C_6H_3$; 3-(2-methylindolyl)

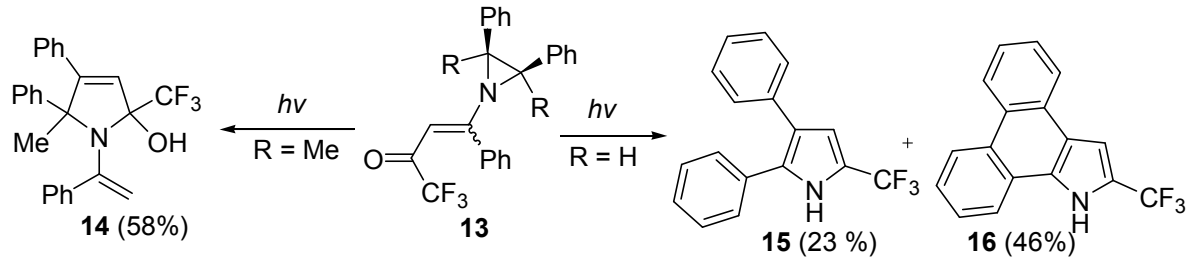
Scheme 2

Other derivatives of trifluoromethyl pyrrole **11** were prepared using reaction of dithiazole **12** (prepared from Appel salt[5]) with primary amines. A possible reaction mechanism was suggested (Scheme 3).



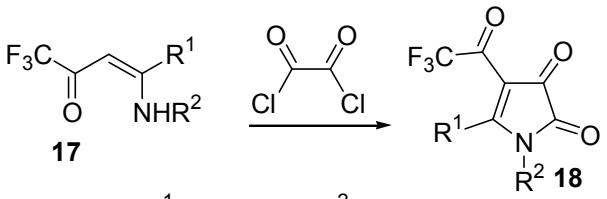
Scheme 3

Photolytic rearrangement of aziridine-substituted enaminoketones **13** was used for the preparation of the CF_3-pyrrole derivatives.[6] Depending on the substituents of starting ketone **13**, the pyrrole **14** or the mixture of diphenylpyrrole **15** and dibenzoindole **16** were formed (Scheme 4).



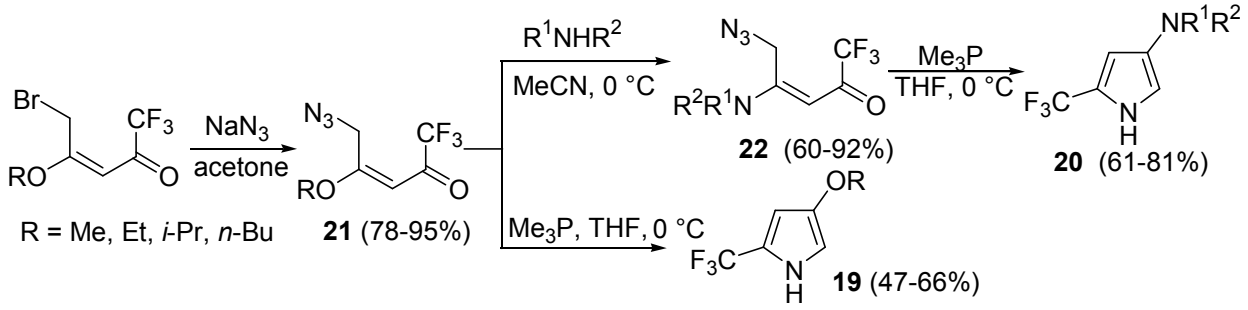
Scheme 4

The acylation of enaminoketones **17** with oxalyl chloride was applied for the preparation of 1*H*-pyrrole-2,3-diones **18**.[7] The reaction proceeded at room temperature but the yields of the products were not given (Scheme 5).



Scheme 5

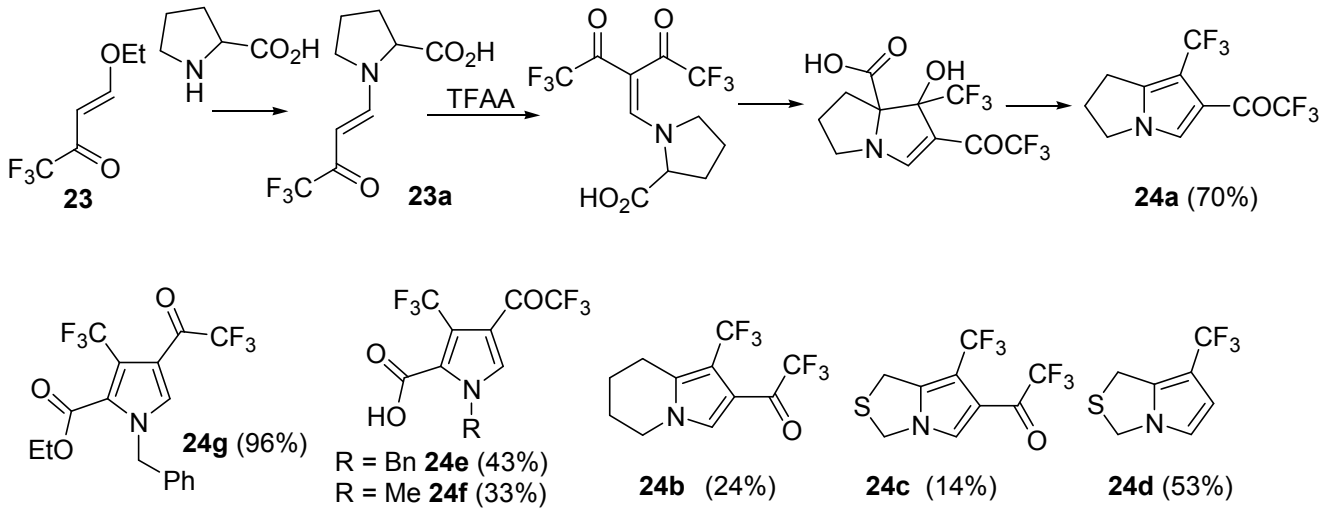
Novel approach for the synthesis of alkoxy- and amino-pyrrole derivatives **19** and **20** has been elaborated using the reaction of azidomethylenones **21** and **22** with trimethylphosphine (Scheme 6).[8]



R^1, R^2 = Me, Et; $-(CH_2)_4-$; $-(CH_2)_5-$; $-(CH_2)_2-O-(CH_2)_2-$; Bn

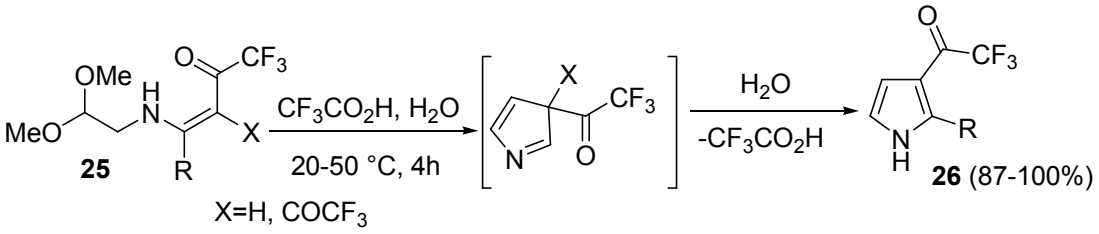
Scheme 6

The viability of a reaction sequence based on the reaction of α-amino acids with the alkoxy enone **23** followed by a cyclization promoted by TFAA was established.[9] All steps of the synthesis can be done in one-pot to give various CF_3-pyrroles **24**, including condensed pyrrole systems (Scheme 7).



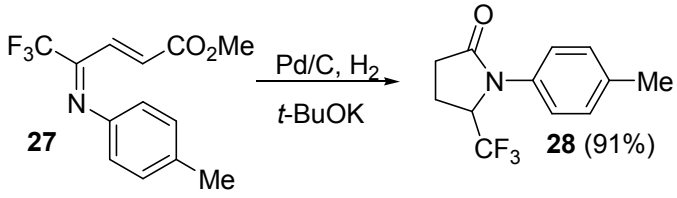
Scheme 7

Dimethoxyethylamine substituted enaminones **25** can be cyclized easily to the corresponding 3-trifluoroacetylpyrroles in good yield. The transformation is promoted by CF_3COOH (Scheme 8).[10]



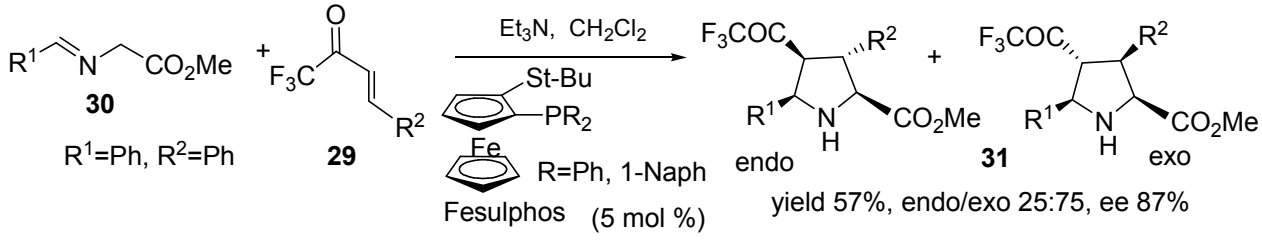
Scheme 8

Imino-derivative of unsaturated trifluoromethyl-containing ketones **27** was cyclized in the presence of palladium on carbon to 5-trifluoromethylpyrrolidone **28** (Scheme 9).[11]



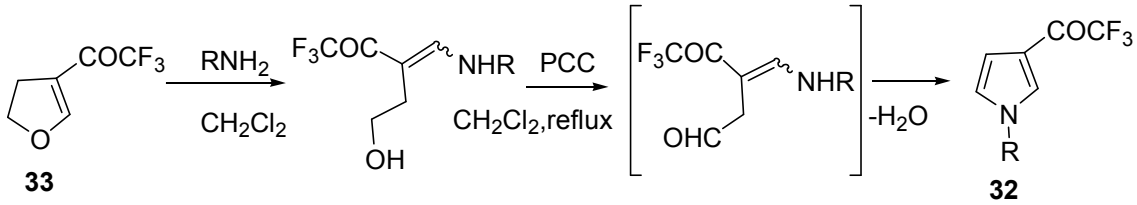
Scheme 9

α,β-Unsaturated ketones **29** were demonstrated to be efficient dipolarophiles in catalytic asymmetric 1,3-dipolar cycloaddition with azomethine ylides **30**. The efficiency of this protocol strongly relies on the use of CuI-Fesulphos catalysts, leading to highly functionalized CF_3-substituted pyrrolidine **31** in good yields, moderate to high *endo*/*exo*-selectivities and high enantiocontrol (81–96% ee) (Scheme 10).[12]



Scheme 10

A new one-pot strategy for the synthesis of *N*-substituted 3-trifluoroacetyl pyrroles **32** was elaborated recently.[13] The reaction of 3-trifluoroacetyl-4,5-dihydrofuran **33** with primary amines followed by oxidation with PCC leads to 1,1,1-trifluoro-3-(2-ethanal)-4-alkylaminobut-3-en-2-ones that cyclize to pyrroles **32** (Scheme 11).

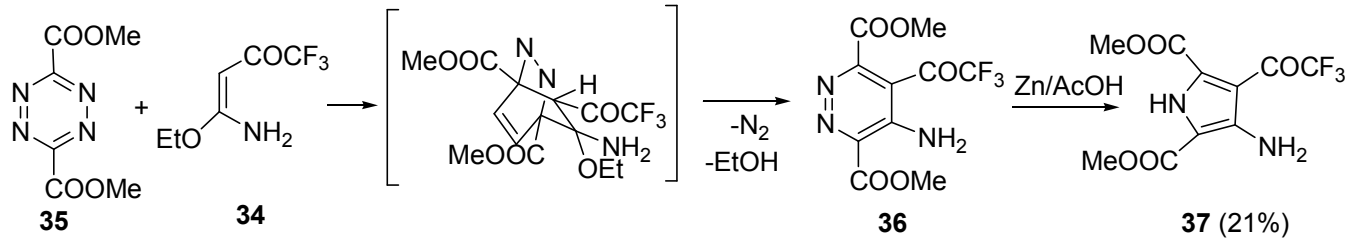


33 **32**

R=Alk (41-52%);R=Aryl (50-55%); R=Hetaryl (39-51%)

Scheme 11

Reaction of CF_3CO-substituted primary ketene *N,O*-acetals **34** with tetrazine-3,6-dicarboxylate **35** yielded, by [4+2] cycloaddition, tetrafunctionalized pyridazines **36**, that were converted into aminopyrrole derivatives **37** in reductive conditions (Scheme 12).[14]

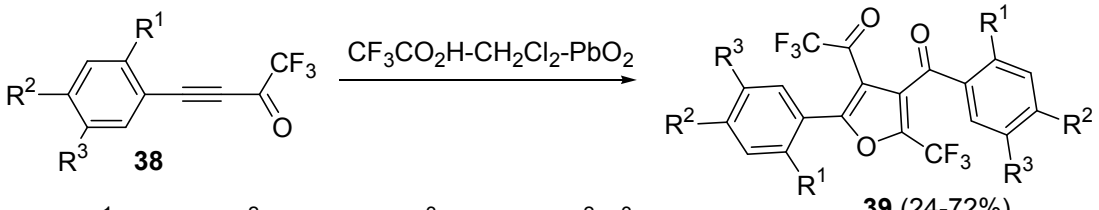


35 **34** **36** **37** (21%)

Scheme 12

3.2. Synthesis of furan derivatives

The oxidative dimerization of acetylenic ketone **38** under the treatment with lead dioxide resulted in the formation of substituted furan **39** bearing CF_3 and $COCF_3$ groups in moderate yields (Scheme 13).[15]

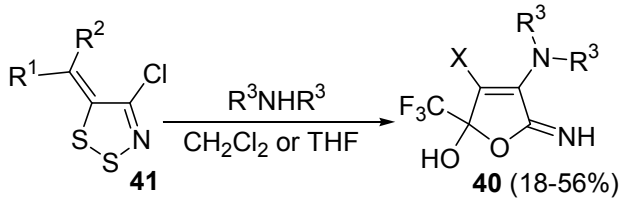


38 **39** (24-72%)

R^1 = H, Me; R^2 =Me, MeO; R^3 =MeO, F; R^2,R^3 = -OCH_2O-

Scheme 13

Trifluoromethyl furan derivatives **40** were prepared by reaction of dithiazole **41** with secondary amines (Scheme 14).[5]

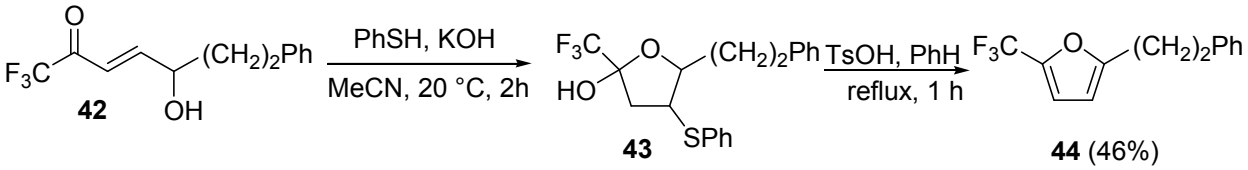


41 **40** (18-56%)

R^1 = CO_2Et, R^2 = $COCF_3$;
R^1 = $COCF_3$, R^2 = CO_2Et;
R^1 = $COCF_3$, R^2 = COPh;
R^1 = H, R^2 = $COCF_3$
R^3 = *i*-Pr, n-C_5H_{11}, Me, Et

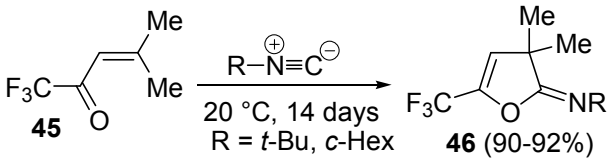
Scheme 14

The reaction of γ-hydroxyenone **42** with thiophenol led to tetrahydrofuran derivative **43**. The compound **43** eliminated water and thiophenol being thus converted into the corresponding furan **44** (Scheme 15).[16]



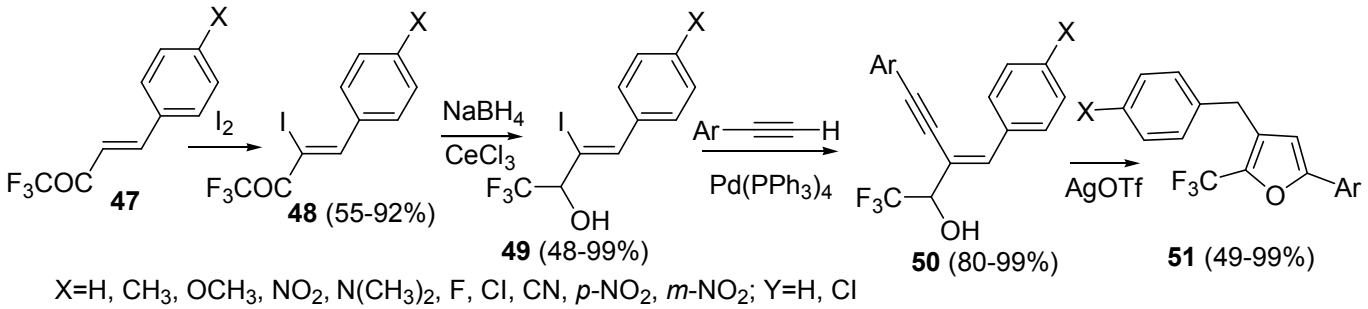
Scheme 15

The reaction of 1,1,1-trifluoro-4-methylpent-3-en-2-one **45** with isocyanides occurred at room temperature without catalysts to give stable 1,4-cycloaddition products, the substituted dihydrofurans **46** (Scheme 16).[17]



Scheme 16

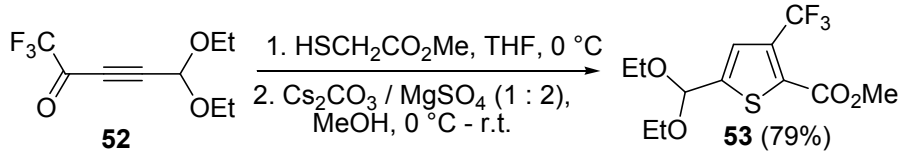
The readily available trifluoromehtyl ketones **47** were iodinated and subsequently reduced to give the corresponding alcohols **49** which were then subjected to coupling with phenylacetylene to furnish alcohols **50**. Final cyclization by means of AgOTf led to 2-(trifluoromethyl)furans **51** in fair yield (Scheme 17).[18]



Scheme 17

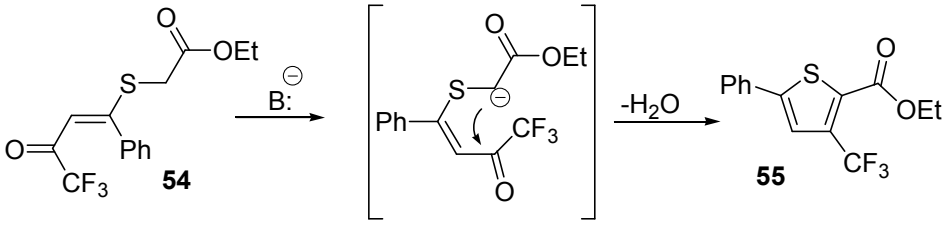
3.3. Synthesis of thiophene derivatives

Acetylenic ketone **52** was successfully applied as starting compound for the preparation of 3-CF_3-thiophene-2-carboxylates **53**. Treatment with methyl thioglycolate in THF and cesium carbonate in methanol led to the target ester of thiophen-2-carboxylic acid **53** in good yield (Scheme 18).[19]



Scheme 18

The cyclization of sulfide derivatives **54** in the presence of a base demonstrated the formation of trifluoromethyl-containing 3-trifluoromethylthiophenes **55** (Scheme 19).[20]

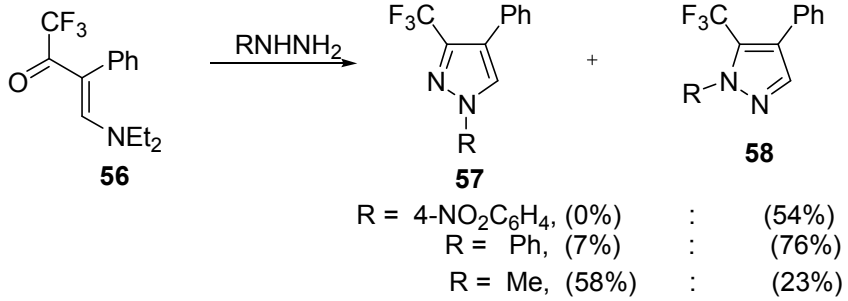


Scheme 19

3.4. Synthesis of pyrazoles and their derivatives

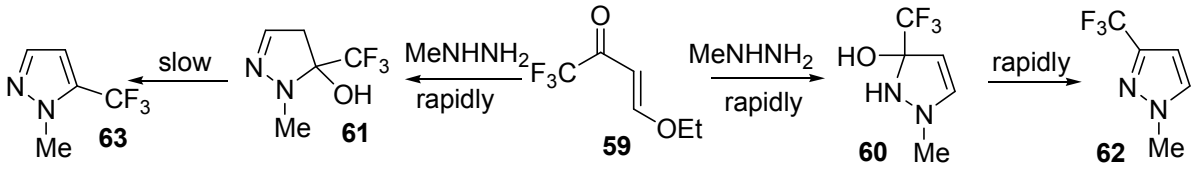
The first example of using a trifluoromethyl enone (β-trifluoroacetylstyrene) for the synthesis of pyrazole derivatives dates back to 1959.[21] However, vigorous studies along the reactions of CF_3-enones, predominantly for those having an eleminting group in β-position, have been investigated till last years.

β-Enaminoketones react with substituted hydrazines opening simple and effective way to various pyrazoles.[22] The reactions of ketone **56** with *N*-substituted hydrazines depending on structure of starting hydrazine led to individual pyrazole or to the mixture of regioisomers **57** and **58** (Scheme 20).[22]



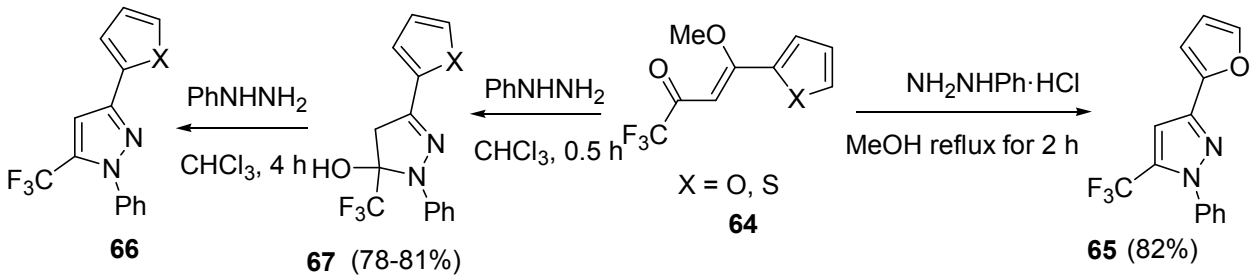
Scheme 20

The reactions of hydrazines with β-alkoxy-substituted trifluoromethyl enones has been investigated.[23] The reaction of **59** with *N*-methylhydrazine gave two isomeric dihydropyrazoles **60** and **61** in various ratio. These pyrazolines underwent dehydration to form pyrazoles **62** and **63** (Scheme 21).



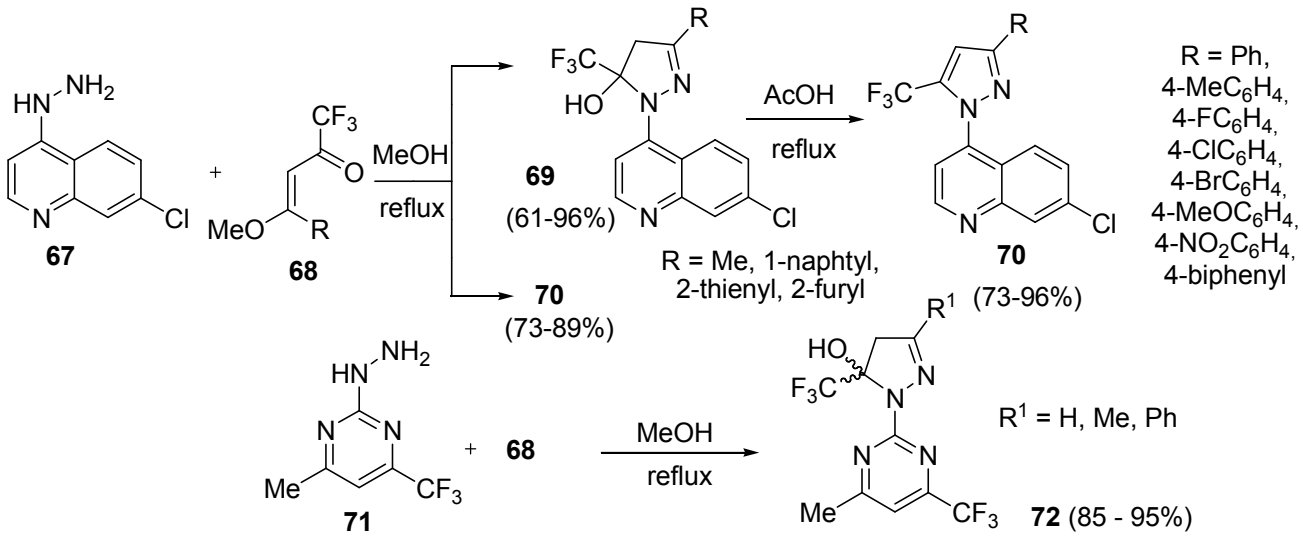
Scheme 21

Depending on condition applied, the reactions of β-methoxy-CF_3-enones **64** with phenylhydrazine gave isomeric pyrazoles **65,66** or pyrazoline **67** (Scheme 22).[24]



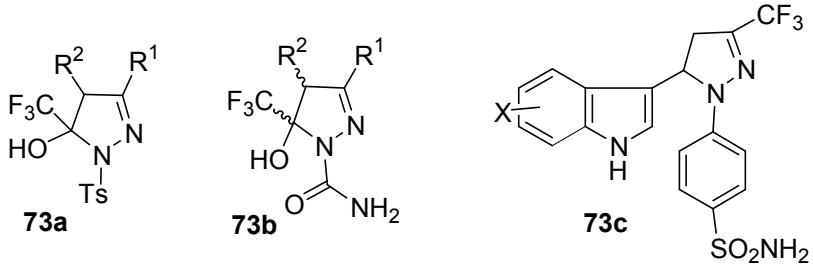
Scheme 22

The reaction of 4-hydrazo-7-chloroquinoline **67** with various β-methoxy-CF_3-enones **68** was investigated for antimalarial screening. Dihydropyrazoles **69** and pyrazoles **70** were obtained in good yields.[25,26] The reaction of enones **68** with 2-hydrazo-derivatives of pyrimidine **71** proceeded in analogous way. The corresponding pyrimidine derivatives **72** containing dihydropyrazole substituent in the position 2 of pyrimidine ring were prepared.[27] These products are potential analgesics and antipyretics (Scheme 23).



Scheme 23

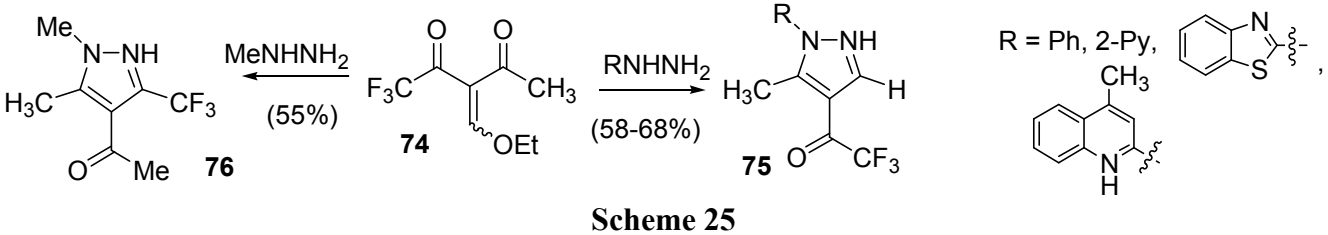
Similarly prepared trifluoromethyl substituted pyrazolines **73a,b** exhibit antimicrobial activity against yeast, fungi, bacteria and alga.[28] The compounds bearing indole moiety **73c** were found dual inhibitors of cyclooxygenases (COXs) and lipoxygenases (LOXs) (Scheme 24).[29]



R^1= H,Ph,4-MePh,4-OMePh,4-BrPh,4-ClPh,4-FPh; R^2 =H,Ph
X= H, Hal, NO_2, NH_2, CN, OMe, COOH, CH_3

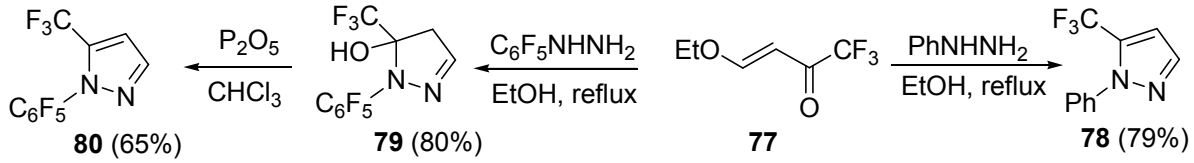
Scheme 24

The reactions of various aryl- and hetaryl-substituted hydrazines with β-ethoxy-CF_3-enone **74** containing acetyl group in α-position were investigated. It was established that the heterocyclization is directed to acetyl-group for arylhydrazines and to trifluoroacetyl-group for methylhydrazine to form pyrazoles **75** and **76** (Scheme 25).[30]



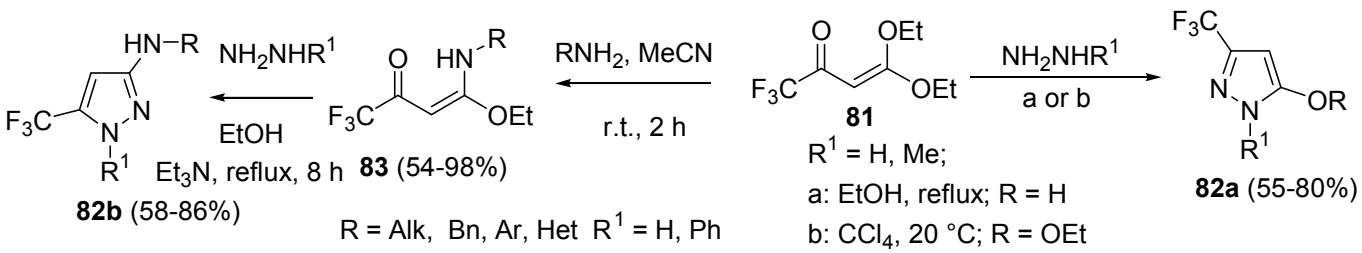
Scheme 25

It was noted that the pathway of the reaction for ketone **77** with perfluorophenylhydrazine due to its reduced basicity differs from that of reaction with phenylhydrazine. For example, the reaction of **77** with phenylhydrazine leads to the corresponding pyrazole **78** while the same reaction with pentafluorophenylhydrazine leads to the formation of pyrazoline **79**. The pyrazolines **79** can be dehydrated into pyrazoles **80** using phosphorus pentoxide (Scheme 26).[31]



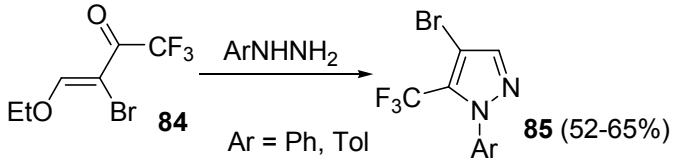
Scheme 26

Ethoxy-, hydroxy- and amino-pyrazole derivatives **82** were obtained in good yields by the reaction of diethoxyenone **81** (*O*,*N*-acetals-aminals of trifluoroacetylketene **83**) with hydrazine and methylhydrazine. Depending on the solvent, used the formation of hydroxy- or ethoxy-derivatives **82a** was observed (Scheme 27).[32,33]



Scheme 27

The reaction of α-bromo-β-ethoxy-CF_3-enone **84** with aryl hydrazines proceeds 100% regioselectively to open new effective way to the synthesis of 4-bromo-5-CF_3-pyrazoles **85** (Scheme 28).[34]

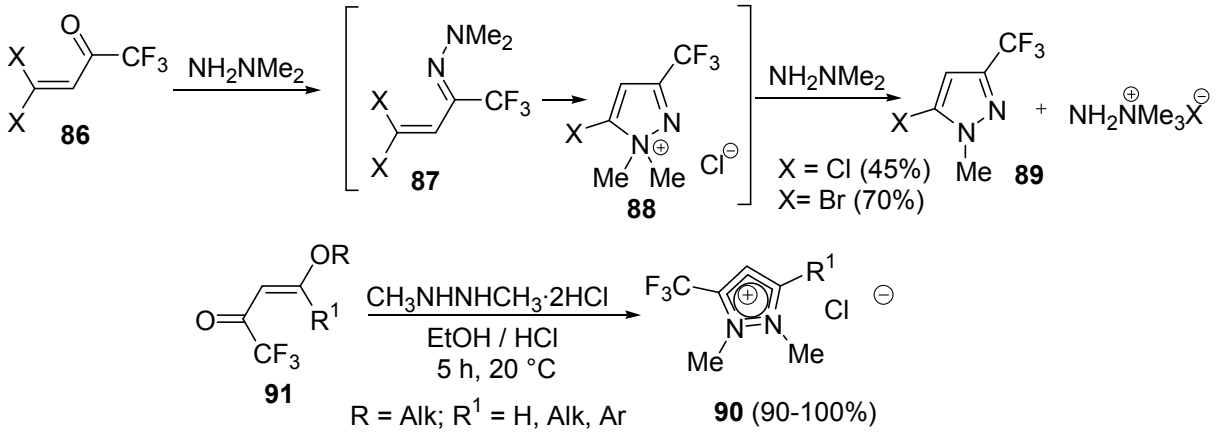


Scheme 28

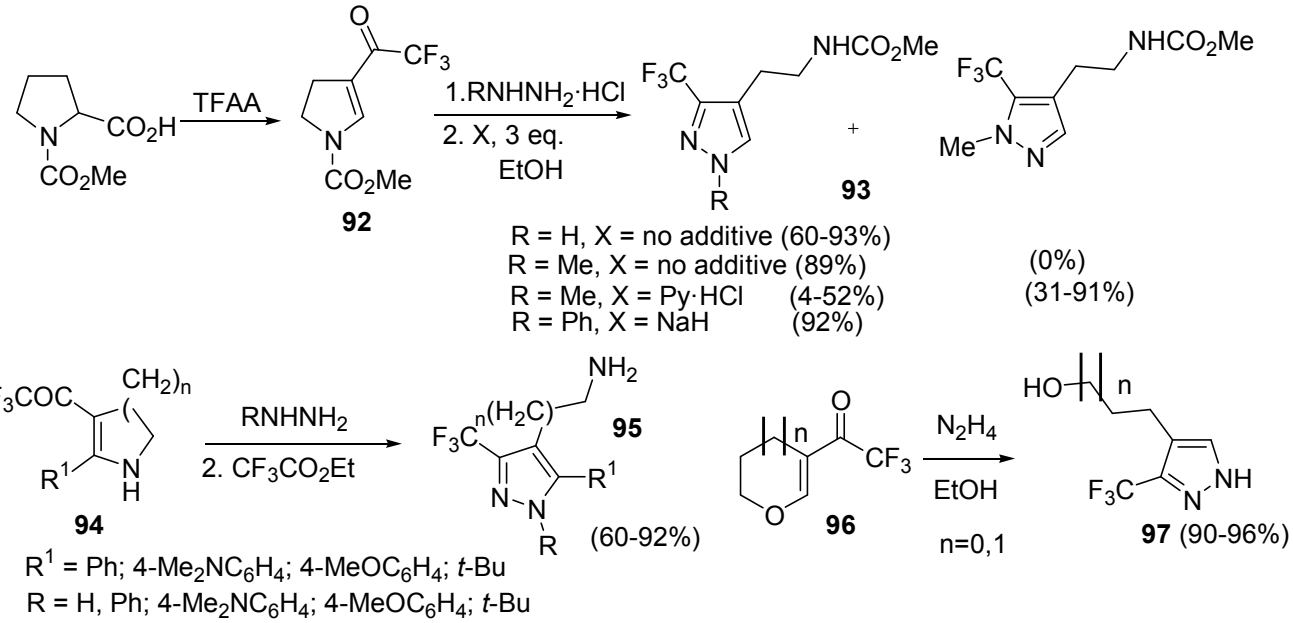
Isomeric 3-chloro (bromo) substituted pyrazoles **89** were prepared by the reaction of β,β-dihalogen-substituted trifluoromethylketones **86** with *N*,*N*-dimethylhydrazine.[35] The mechanism of the reaction consists of initial dimethylhydrazone **87** formation with subsequent intramolecular attack of nucleophilic fragment on β-carbon atom of vinyl group and demethylation of the intermediate *N*,*N*-dimethylpyrazolium chloride **88** with second mole of dimethylhydrazine. Isomeric *N*,*N*'-dimethylpyrazolium salts **90** with potential high herbicide activity were prepared in the reaction of enones **91** with *N*,*N*'-dimethylhydrazine (Scheme 29).[36]

An interesting example of application of trifluoroacetyl pyrroline **92** for the preparation of pyrazoles **93** was described.[37] It was found that pyrroline **92** is a new 1,3-ambident electrophile reacting with bifunctional *N*-nucleophiles such as hydrazines and amidines to give CF_3-substituted pyrazoles bearing the β-aminoethyl side chain. The reaction sequence represents a special type of ring transformation by ring-chain-transfer where a ring and a chain moiety in the product are transformed to each other giving the

product. In view of the pharmacological interest in heterocycles bearing both CF_3-appendage and β-aminoethyl side chain the method is very attractive. The reaction of cyclic enaminoketones **94** with hydrazine led to pyrazoles **95** containing aminoalkyl side chain.[38] The reaction of hydrazine with β-trifluoroacetyldihydropyran and β-trifluoroacetyldihydrofuran **96** led to the corresponding pyrazole **97** (Scheme 30).[39]

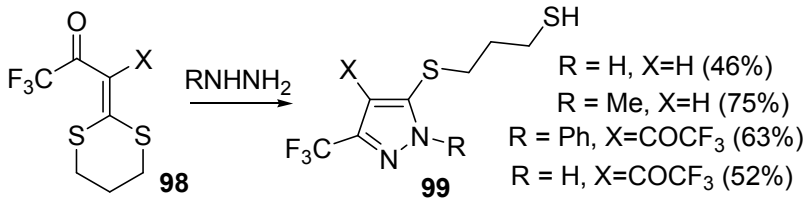


Scheme 29



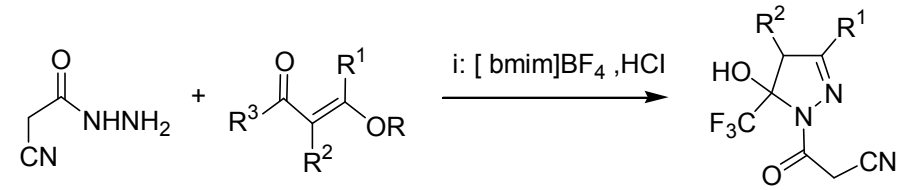
Scheme 30

Similarly, the pyrazoles **99** containing 1,3-dithiopropyl substituent were prepared from CF_3-enones containing dialkyldithio-fragment in β-position **98** (Scheme 31).[40]



Scheme 31

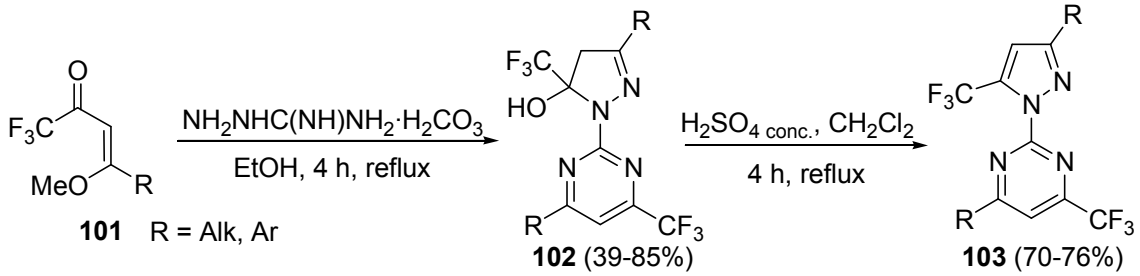
An efficient synthesis of 1-cyanoacetyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles **100** was reported in the ionic liquid ([bmim][BF_4]) (Scheme 32).[41]



R=Me, Et ; R^2= H, -$(CH_2)_4$-, Me ;R^3=CF_3,CCl_3,$CHCl_2$,CO_2Et

Scheme 32

Using double excess of ketones **101** in the reaction with aminoguanidine carbonate, the formation of pyrazolinepyrimidines **102** was observed. These compounds can be easily dehydrated into the corresponding pyrazolylpyrimidines **103** (Scheme 33).[42]



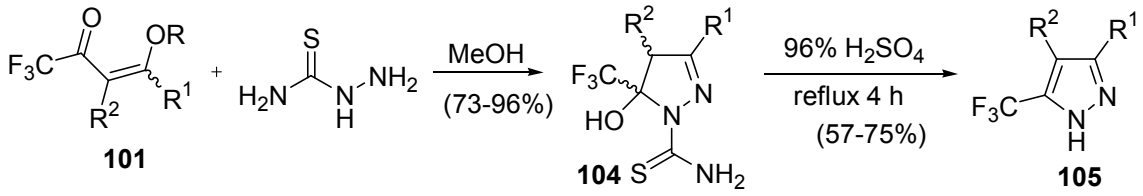
101 R = Alk, Ar

102 (39-85%)

103 (70-76%)

Scheme 33

The reaction of β-alkoxy-β-aryl-CF_3-enones **101** with thiosemicarbazide led to the corresponding hydroxy-derivatives of dihydropyrazoles **104** in high yields.[43] They can be transformed into *N*-unsubstituted pyrazoles **105** in high yields using acidic hydrolysis. The ketone **106** has the hidden bromoketone fragment; it was applied for forming thiazole connected with pyrazoline **108** (Scheme 34).[44]

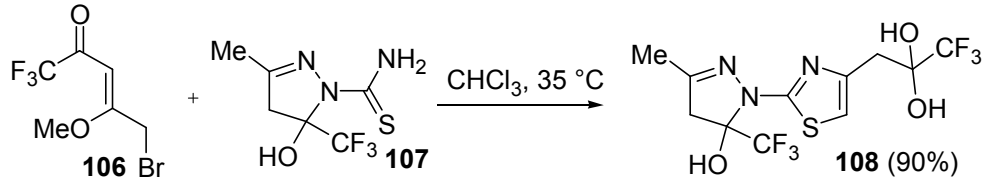


101

104

105

R = Me, Et; R^1 = H, Me, Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$; R^2 = H, Me



106 Br

107

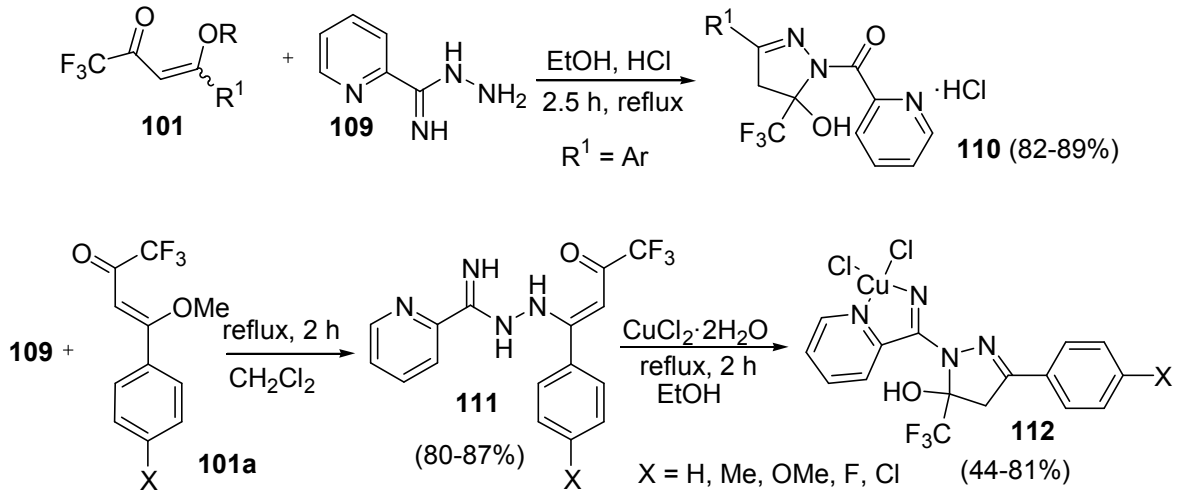
108 (90%)

Scheme 34

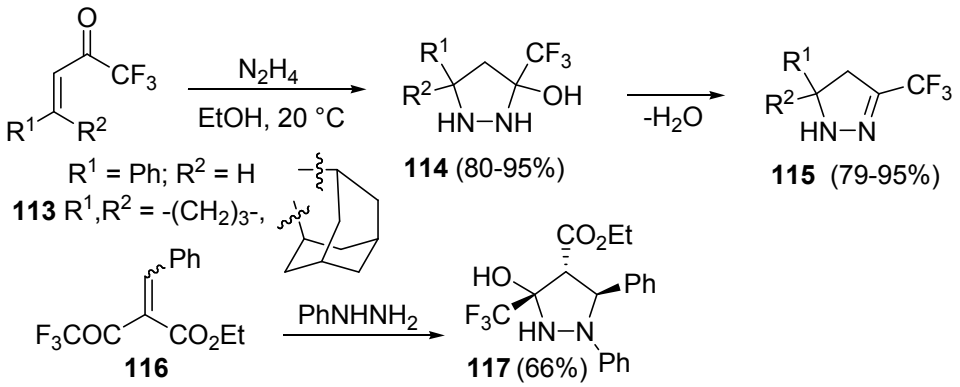
The reaction of ketones **101** with 2-pyridylcarboxamidrazone **109** led to predominant formation of pyrazoline derivatives **110** regardless of the fact that amidrazone possesses three reactive nitrogen atoms.[45] Reaction was accompanied with imine fragment of amidrazone hydrolysis. The preparation of copper(II) amidrazone complexes **112** was described recently. The compounds **111** reacted with copper(II) chloride to give 1:1 adducts in which the donor molecules were shown to isomerize into their cyclic pyrazolic forms (Scheme 35).[46]

Trifluoromethyl enones **113** containing no replaceable β-substituents reacted readily with hydrazine to form pyrazolidines **114**. Dehydration of the pyrazolidines **114** gave the corresponding pyrazolines **115**.[47] An

interesting example is the reaction of ketone **116** with phenylhydrazine. The derivative of tetrahydropyrazole **117** was obtained in moderate yield 100% stereoselectively (Scheme 36).[48]

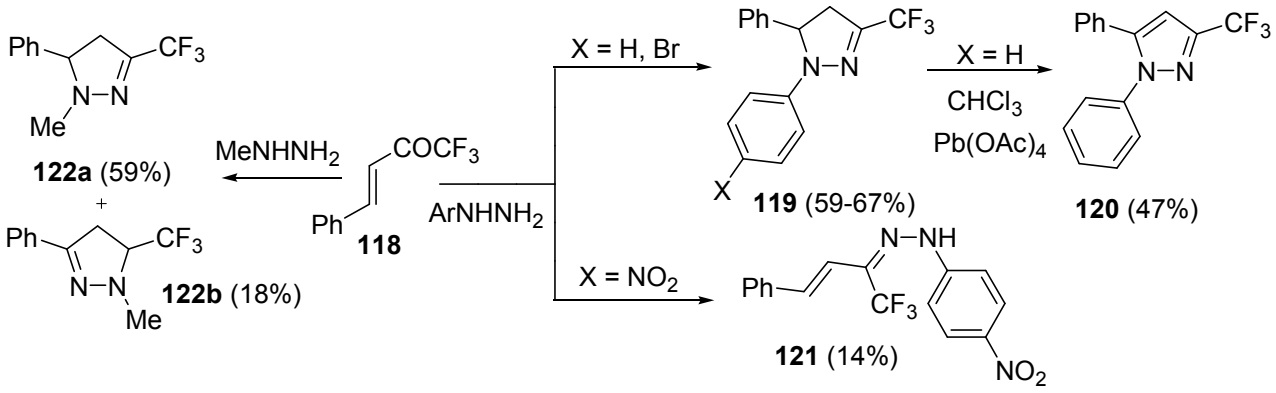


Scheme 35



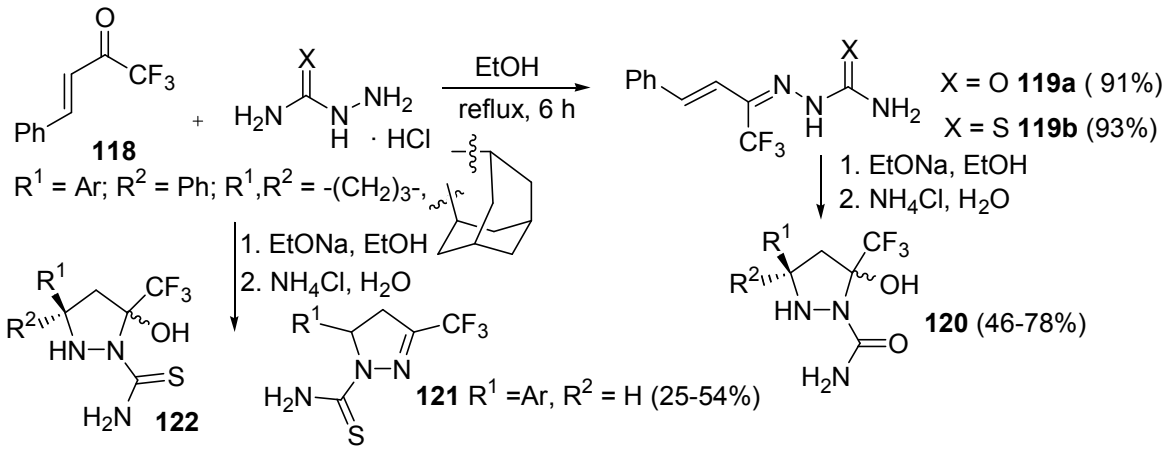
Scheme 36

β-Trifluoroacetylstyrene **118** reacted with substituted aryl- or alkyl-hydrazines to afford pyrazolines **119**. Oxidation of the compound **119** with X=H with led tetraacetate affords the corresponding pyrazole **120** in a moderate yield.[49] The reaction with *p*-nitrophenylhydrazine did not give pyrazoline; in this case, only *p*-nitrophenylhydrazone **121** is formed in a low yield. When β-trifluoroacetylstyrene **118** reacted with methylhydrazine, a mixture of isomeric pyrazolines **122a,b** (in ~1:3 ratio) was formed. The reaction with 1,2-dimethylhydrazine gives pyrazolidine apparently due to the fact that elimination of water yielding a C=C bond is substantially hampered (Scheme 37).[47]



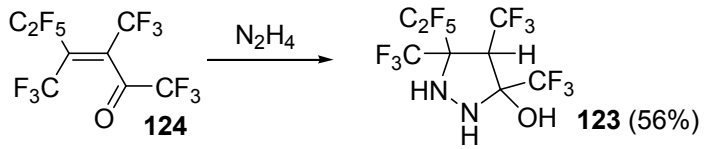
Scheme 37

Enone **118** similarly to ketones having alkoxy-substituents in β-position reacted with semicarbazide or thiosemicarbazide in an acid medium to afford semicarbazone **119a** or thiosemicarbazone **119b**. These compounds were cyclized in the presence of an equimolar amount of sodium ethoxide to give 5-trifluoromethylpyrazolidine-1-carboxamide **120**. When CF_3-enones reacted with thiosemicarbazide under the same conditions, either 3-trifluoromethyl-2-pyrazolidinethiocarboxamides **122** or 5-trifluoromethyl-2-pyrazoline-thiocarboxamides **121** were obtained (Scheme 38).[50]



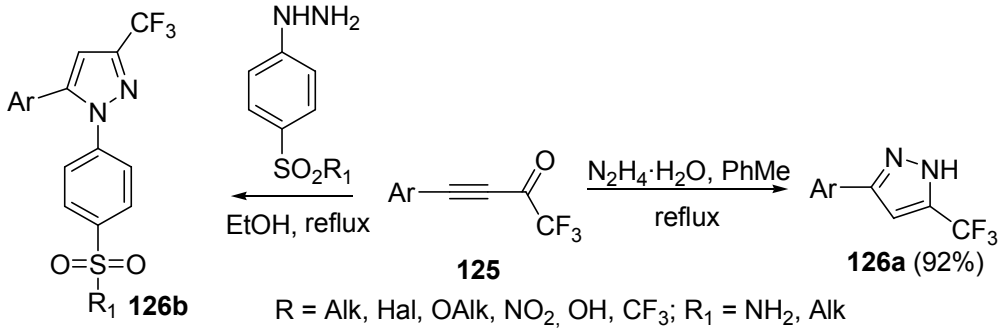
Scheme 38

The perfluorinated derivative pyrazolidine **123** was obtained by the reaction of perfluorinated CF_3-enone **124** with hydrazine. This product **123** is stable solid sublimating in vacuum without decomposition (Scheme 39).[51]



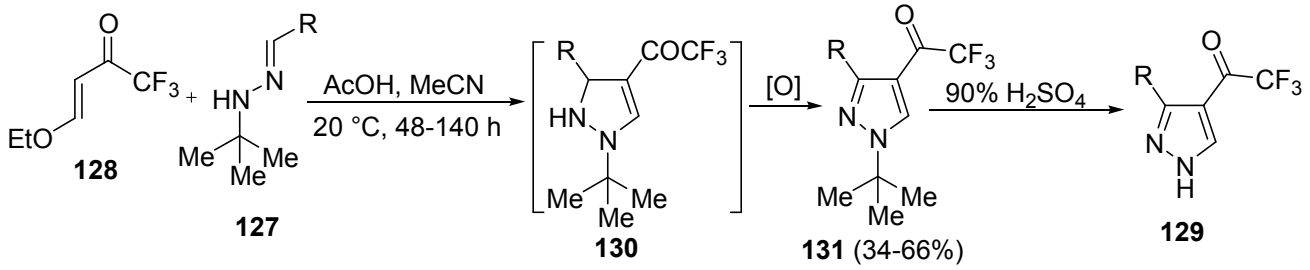
Scheme 39

The reaction of acetylenic CF_3-ketones **125** with hydrazines is also used for the preparation of CF_3-substituted pyrazoles **126** in excellent yield (Scheme 40).[52]



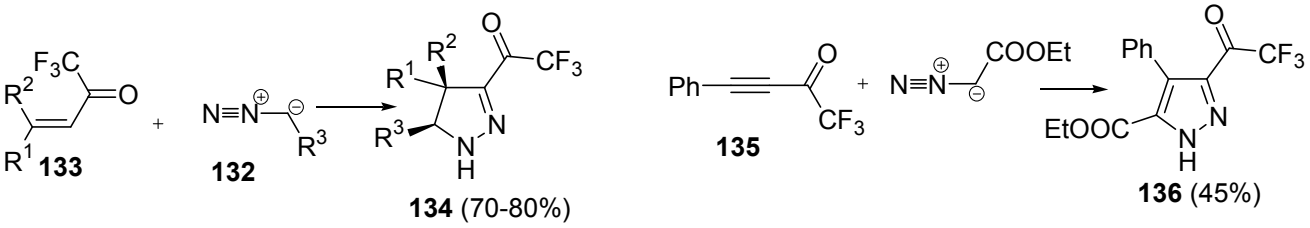
Scheme 40

tert-Butylhydrazones of various aldehydes **127** reacted with β-ethoxy enone **128** giving rise to 4-trifluoroacetylpyrazoles **131**. A possible mechanism of this reaction includes replacement of the ethoxy group by the hydrazone, subsequent cyclization to pyrazolines **130** and oxidation to pyrazoles **131** by atmospheric oxygen. *tert*-Butyl group can be removed easily by sulfuric acid (Scheme 41).[53]



Scheme 41

[2+3]-Dipolar cycloaddition of various diazocompounds **132** to α,β-unsaturated trifluoromethylketones **133** has been investigated. The ketones **133** reacted with diazoalkanes **132** forming pyrazolines **134** 100% regioselectively and highly stereoselectively. In the case of phenyldiazomethane, the exclusive formation of *cis*-isomers of pyrazolines was observed. Using the trifluoroacetylated acetylene **135** in the reaction with ethyl diazoacetate allowed to the preparation of the pyrazole **136** (Scheme 42).[54]

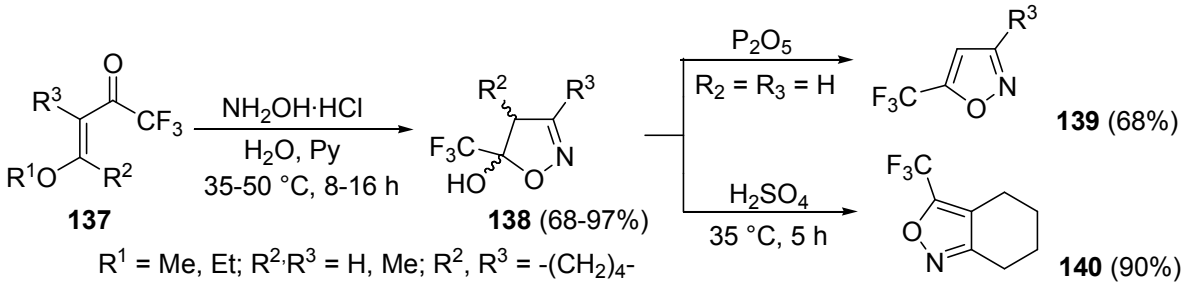


R^1 = Alk, Ar; R^2 = H, Alk; R^3 = Ar, Het, CO_2Et

Scheme 42

3.5. Synthesis of isoxazoles (isoselenoazoles) and their derivatives

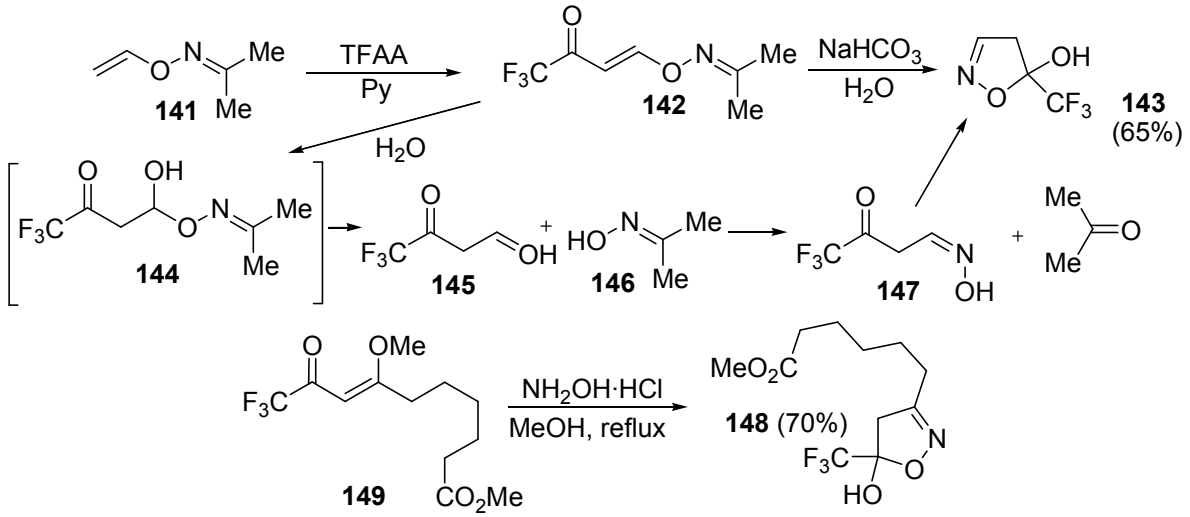
The reactions of β-alkoxy-substituted enones **137** with hydroxylamine follow different pathways depending on the structure of the enone. Thus acyclic enones and enones containing no oxygen atom in the ring are converted into isoxazolines **138**,[3,55] which can be dehydrated on treatment with P_2O_5 or concentrated H_2SO_4 to give the corresponding isoxazoles **139** or **140** (Scheme 43).



R^1 = Me, Et; R^2,R^3 = H, Me; R^2, R^3 = -$(CH_2)_4$-

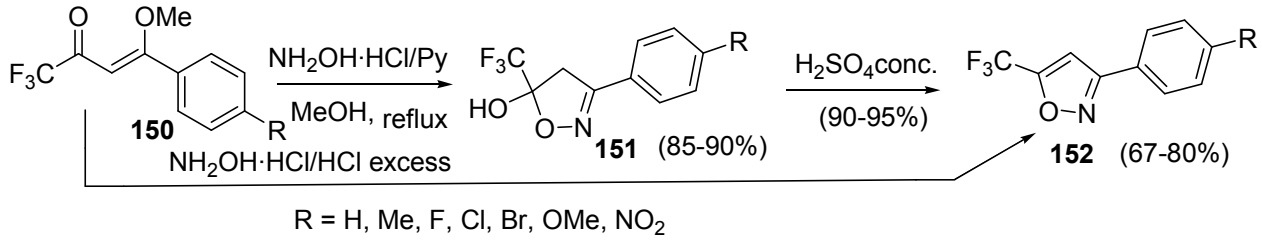
Scheme 43

O-Vinyl oximes **141** reacted readily with trifluoroacetic anhydride to give CF_3-enones **142**. 4,5-Dihydro-1,2-oxazole **143** was isolated as the single product when the reaction mixture was treated after trifluoroacylation with aqueous $NaHCO_3$.[56] The formation of **143** implied the hydrolysis of **142** *via* intermediate semi-acetal-like adduct **144** which decomposed to **145** and acetoxime **146**. The reoximation resulted in the formation of the corresponding aldoxime **147** and acetone. The isoxazoline **148** was synthesized starting from CF_3-enone **149**.[57] The presence of methoxycarbonyl group in the isoxazole obtained makes possible the further transformations (Scheme 44).



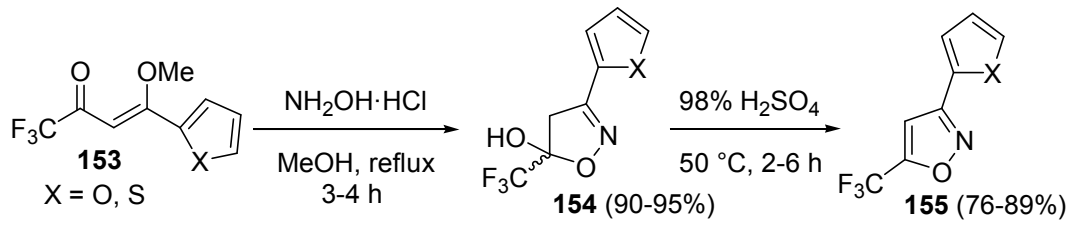
Scheme 44

The reaction of a number of β-methoxy-β-aryl-CF_3-enones **150** with hydroxylamine hydrochloride was investigated.[58,59] 4,5-Dihydroisoxazoles **151** were obtained in high yields and they can be transformed into the corresponding isoxazoles **152** in yields nearly to quantitative using concentrated sulfuric acid. Furthermore, compounds **152** can be directly obtained by the reaction of β-methoxy-β-aryl-CF_3-enones **150** with hydroxylamine hydrochloride using the excess of HCl (Scheme 45).



Scheme 45

Analogous reactions were carried out for β-methoxy-CF_3-enones **153** containing 2-thienyl or 2-furyl substituents. Similarly, the intermediate dihydroisoxazole **154** can be easily dehydrated with concentrated sulfuric acid to form the corresponding isoxazoles **155** (Scheme 46).[60]

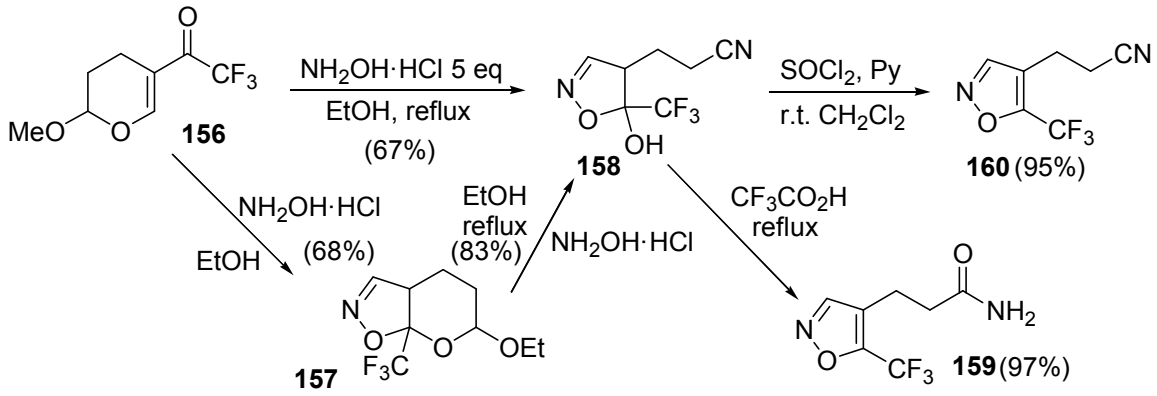


Scheme 46

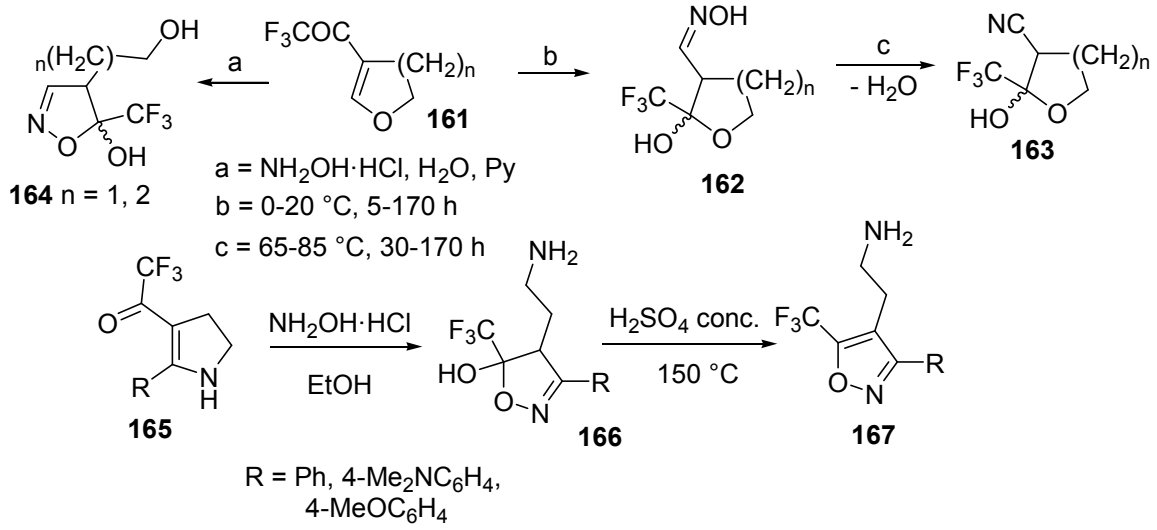
The use of cyclic β-alkoxy-CF_3-enone **156** allowed to the preparation of isoxazoles **159** and **160** and their dihydro-derivatives **157** and **158** containing functional groups in high yields (Scheme 47).[61]

Analogously enones **161** were converted into isoxazolines **164**, which resulted from opening of the furan or pyran ring. However, when the reaction was carried out at higher temperatures, it gave rise to tetrahydrofuran and tetrahydropyran derivatives **163**, formed apparently upon dehydration of aldehyde oximes **162**, resulting from recyclization of the starting enones. The reactions of cyclic enaminoketones **165**

with hydroxylamine led to dihydroisoxazoles **166** containing aminoalkyl side chain as the single diastereomers. Compounds **166** can be dehydrated with sulfuric acid into isoxazoles **167** in high yields (Scheme 48).[38]

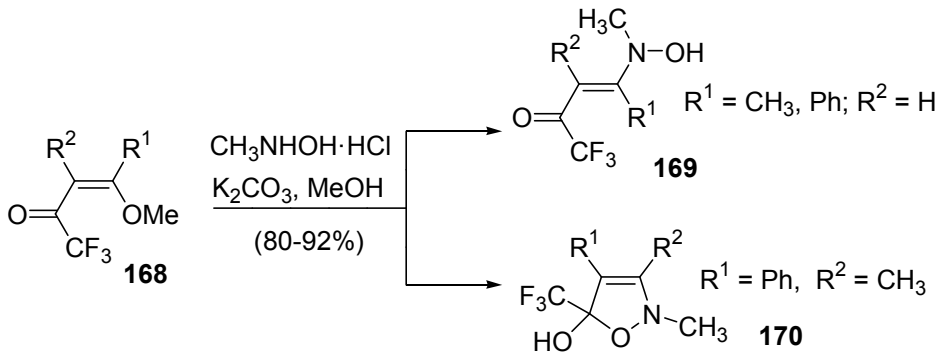


Scheme 47



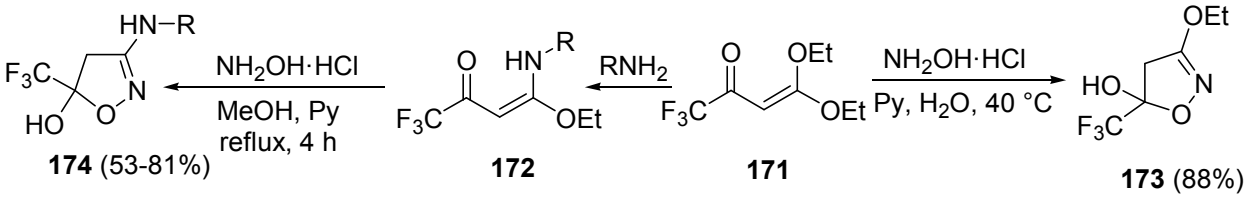
Scheme 48

The reaction of β-methoxy-CF_3-enones **168** with *N*-methylhydroxylamine hydrochloride proceeded as Michael addition forming **169** or the isoxazoles **170** depending on the substituent in **168** (Scheme 49).[62]



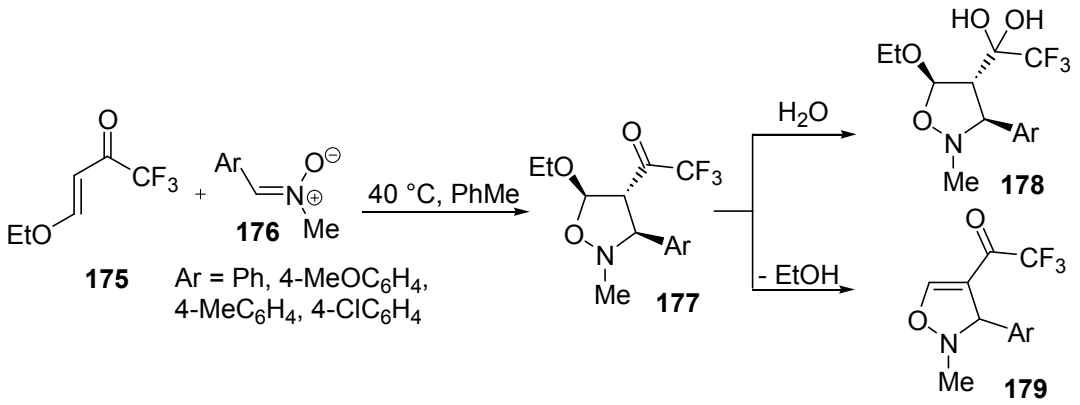
Scheme 49

The reaction of diethoxyenone **171** or *O,N*-acetals-aminals of trifluoroacetylketene **172** with hydroxylamine hydrochloride gave the corresponding ethoxy-derivative of isoxazoline **173** or amino-substituted isoxazoles **174** in good yield (Scheme 50).[32]



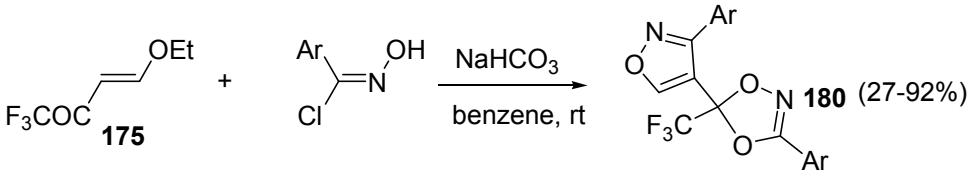
Scheme 50

[2+3]-Cycloaddition of β-ethoxy-CF_3-enone **175** with *N*-methyl-C-arylnitrones **176** resulted in the isoxazolidines **177**. These compounds can not be isolated in pure form due to transformation to diol **178** and ethanol elimination product **179** under column chromatography purification (Scheme 51).[63]



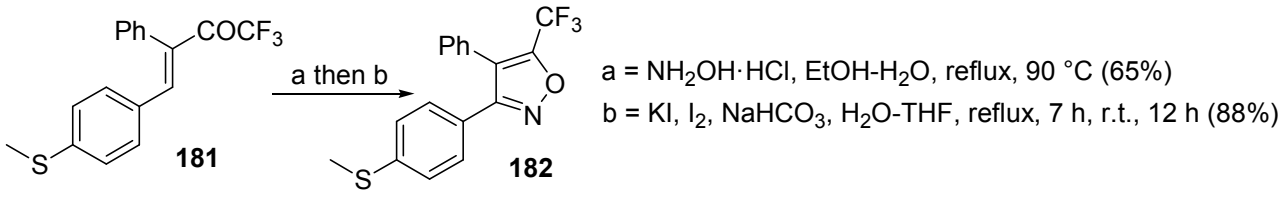
Scheme 51

In the case of 1,3-dipolar cycloaddition of β-ethoxy-CF_3-enone **175** with nitrile oxides, both C=C and C=O participate in the formation of isoxazole rings to afford 1,4,2-dioxazoles **180** (Scheme 52).[64]



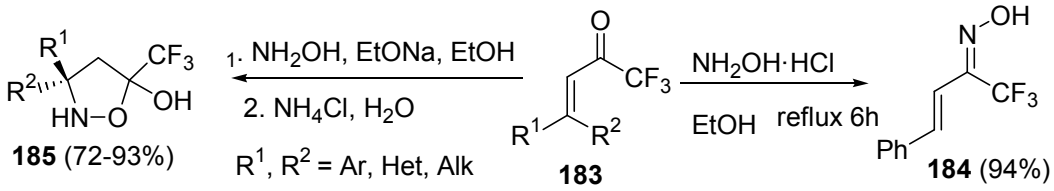
Scheme 52

Ketones containing no alkoxy-groups in β-position **181** can also be used for the preparation of isoxazoles **182**. Diaryl-substituted isoxazole with unusual regiochemistry **182** was synthesized using the reaction with hydroxylamine with further aromatization by treatment with iodine (Scheme 53).[65]



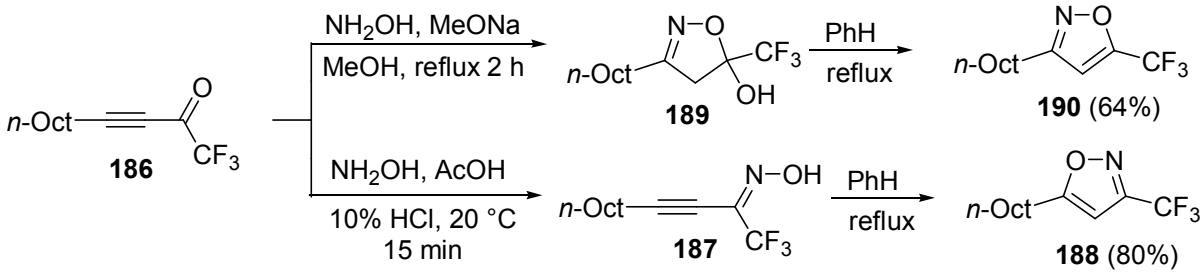
Scheme 53

The reaction of β-trifluoroacetylstyrene **183** with hydroxylamine in an acidic medium gave rise to oxime **184**, which did not tend to cyclize in either acid or alkaline medium. The reaction with hydroxylamine in the presence of an equimolar amount of sodium ethoxide gave isoxazolidines **185** in good yields (Scheme 54).[66]



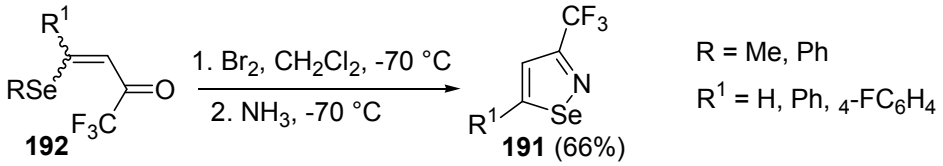
Scheme 54

Isoxazolines **189** and isoxazoles **190** were also obtained in good yields in the reaction of alkynyl ketones **186** with hydroxylamine; the regiochemistry of the reaction depends on the reaction conditions. This reaction performed in an acid medium gave oxime **187**, which cyclized to isomeric isoxazole **188** (Scheme 55).[52]



Scheme 55

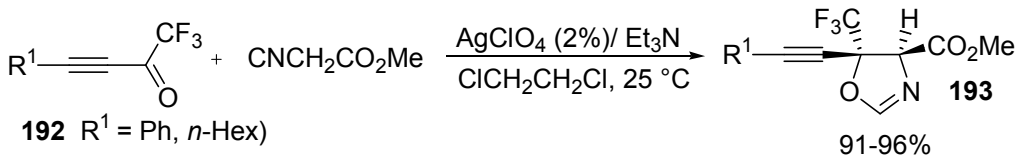
Hardly available isoselenoazoles **191** can be easily prepared by consequent treatment of enones **192** with bromine and ammonia (Scheme 56).[67]



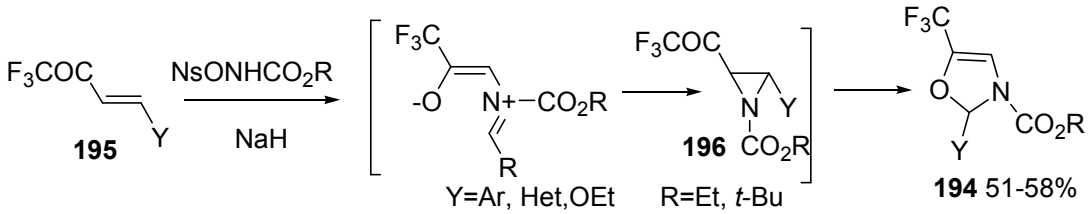
Scheme 56

3.6. Synthesis of oxazoles

The reaction of acetylenic CF_3-ketones **192** with methyl isocyanoacetate catalyzed with silver perchlorate led to the formation of the dihydrooxazole **193** in high yields and 100% stereoselectively (Scheme 57).[68]



Scheme 57

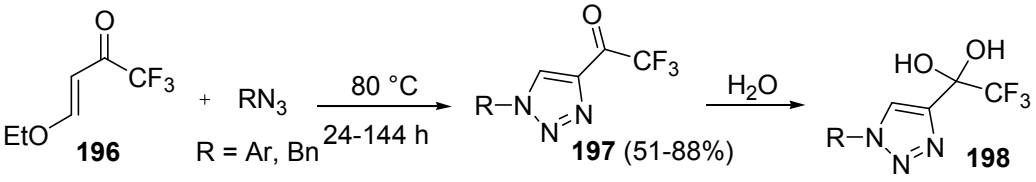


Scheme 58

4-Oxazolines **194** were obtained by the amination of CF_3-enones **195** with nosyloxycarbamates through a domino reaction involving a fast rearrangement of unstable 2-trifluoroacetyl aziridines **196** (Scheme 58).[69]

3.7. Synthesis of triazoles

The reaction of ketone **196** with various azides led to the formation of the corresponding trifluoroacetyl triazoles **197** hydrated to diols **198** (Scheme 59).[70]

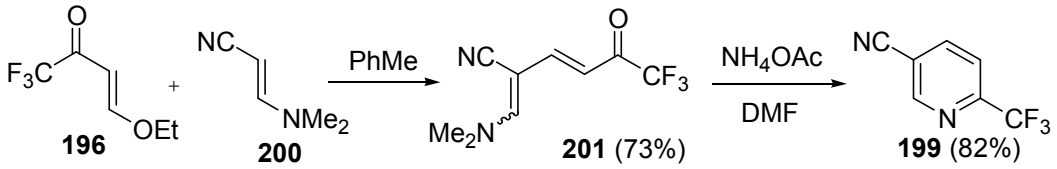


Scheme 59

4. Synthesis of six-membered heterocycles

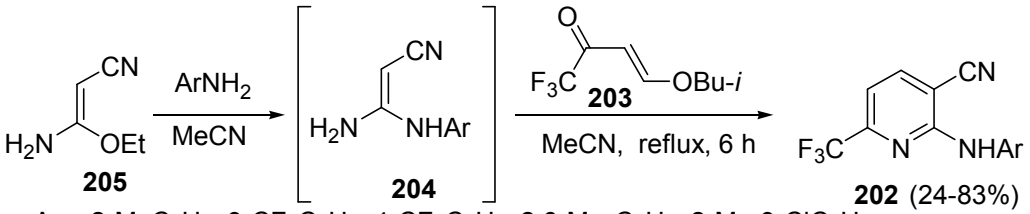
4.1. Synthesis of pyridines and their derivatives

Pyridines are very important class of heterocyclic compounds. There are plenty of methods for their synthesis, though there are few methods for preparation of CF_3-containing pyridines. The method for synthesis of the 6-CF_3-nicotinonitrile **199** based on the reaction of β-ethoxy CF_3-enone **196** with β-dimethyl-aminoacrylonitrile **200** followed by the treatment of intermediate product **201** with ammonium acetate was proposed. The sequence represents the convenient method for the regioselective preparation of 6-CF_3-nicotinonitrile **199** (Scheme 60).[71]



Scheme 60

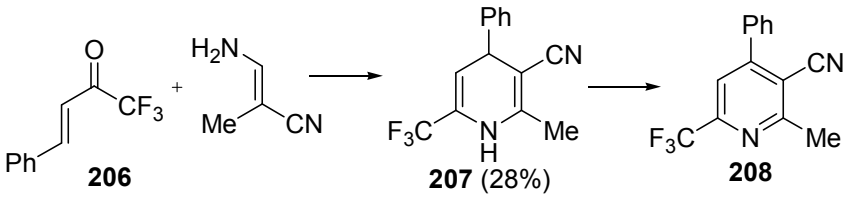
Recently, the synthesis of 2-arylamino 6-CF_3-derivatives of the nicotinonitrile **202** was elaborated using β-*i*-butoxy CF_3-enone **203**. The key step of the method is the cyclization of ketone **203** with β,β-di-aminosubstituted acrylonitrile **204** generated *in situ* by the reaction of **205** with anilines (Scheme 61).[72]



Ar = 2-MeC_6H_4, 3-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 2,6-$Me_2C_6H_3$, 2-Me-3-ClC_6H_3, 2-Me-4-ClC_6H_3, 2-Me-5-ClC_6H_3, 2-Me-6-ClC_6H_3

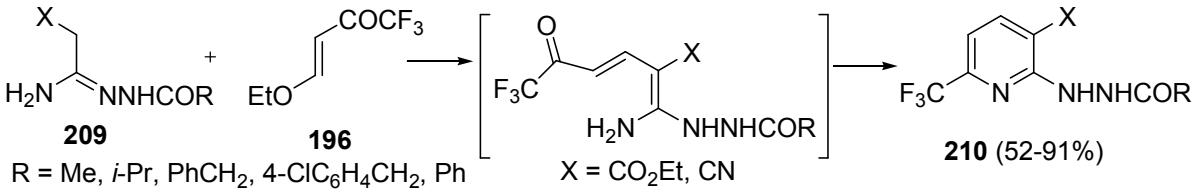
Scheme 61

The reaction of the enone **206** with β-aminocrotononitrile resulted in the formation of 6-trifluoro-methyldihydropyridine **207** in a low yield; oxidation of this product led to the corresponding aromatic derivative **208** (Scheme 62).[73]



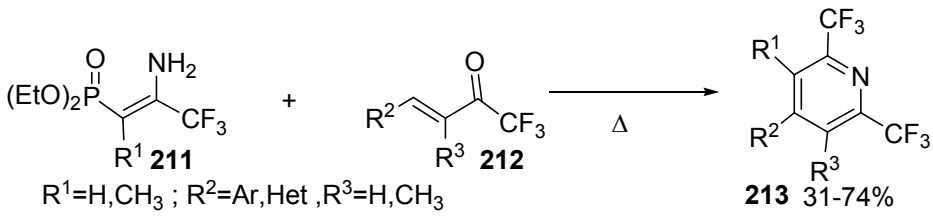
Scheme 62

The reaction of enone **196** with *N*-acylacetamidrazones **209** allowed to prepare various 2-hydrazo-derivatives of ethyl 6-trifluoromethylnicotinate and 6-trifluoromethylnicotinonitrile **210** in good yields (Scheme 63).[74]



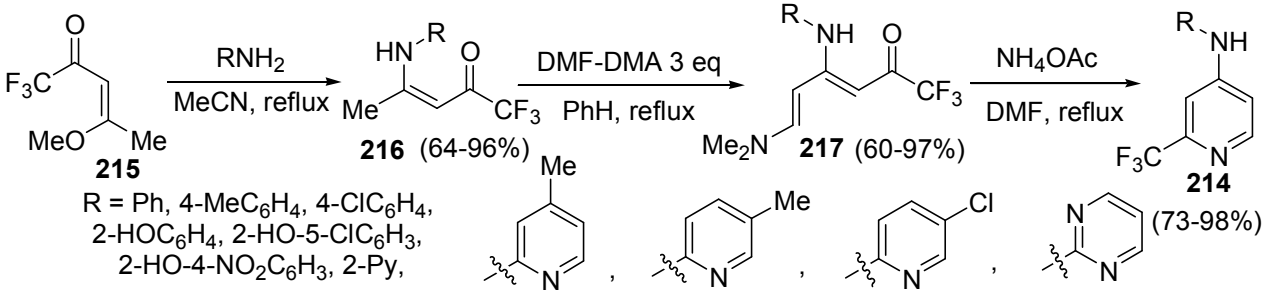
Scheme 63

Phosphorylated enamines containing fluoroalkyl substituents **211** were used for the regioselective preparation of polysubstituted pyridine derivatives **213** by their reaction with fluorinated α,β-unsaturated ketones **212** at high temperature in the absence of solvent (Scheme 64).[75]



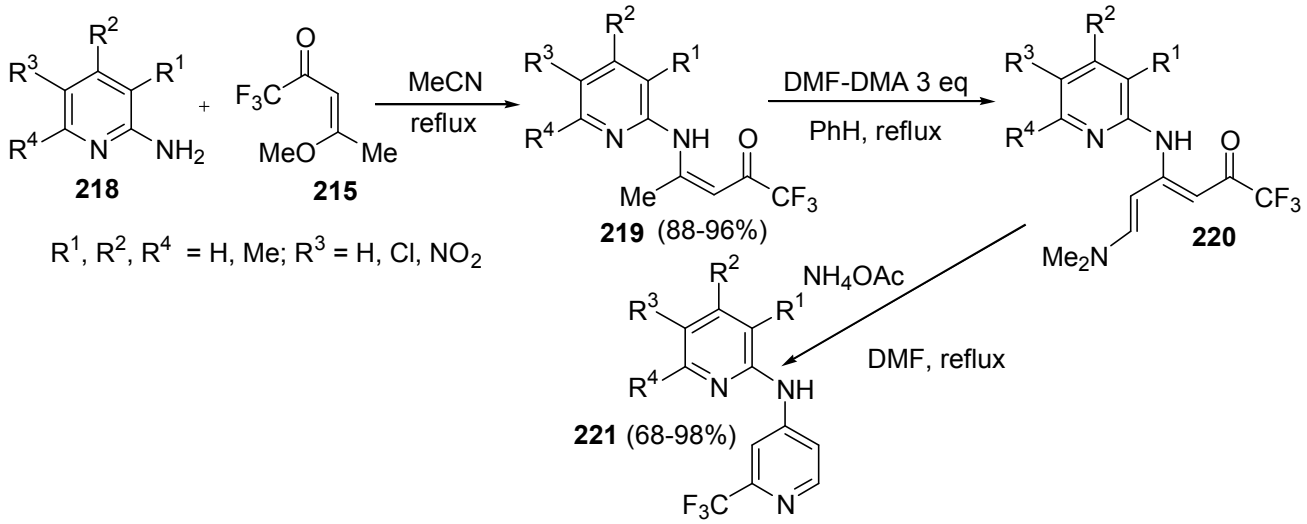
Scheme 64

New approach for the synthesis of 2-CF_3-pyridines **214** containing various arylamino-substituents in the 4-position exploits the reaction of CF_3-enone **215** with various aromatic amines including heterocyclic ones. The subsequent reaction of formed enaminoketone **216** with the DMF dimethylacetal led to dienones **217** which underwent cyclization in high yields to the targeted 2-CF_3-4-arylaminopyridines **214** with ammonium acetate (Scheme 65).[76]



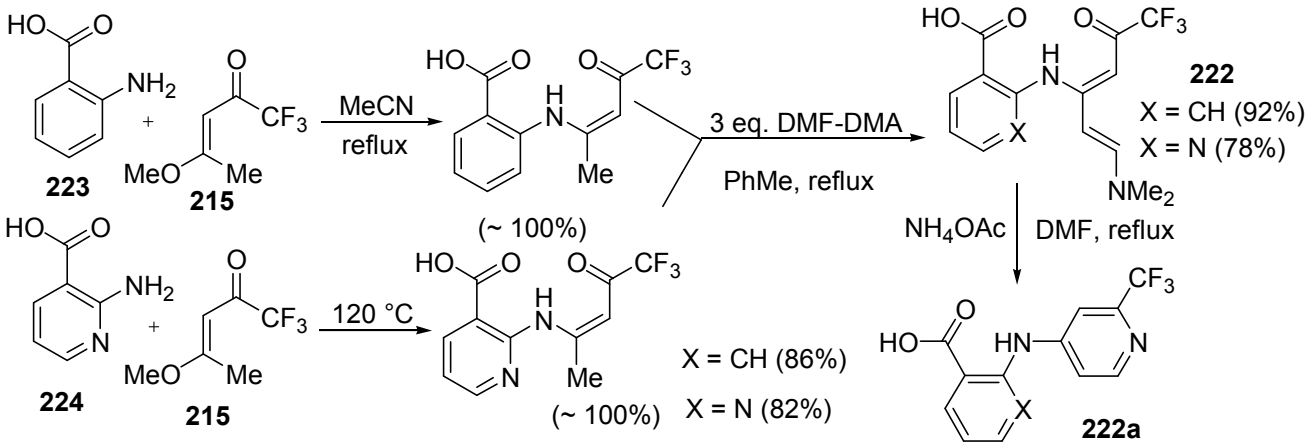
Scheme 65

Analogous approach is based on the use of 2-aminopyridine derivatives **218** as aromatic amines for the synthesis of the 2-CF_3-4-pyridylaminopyridine derivatives **221**. The target products **221** were formed in high yields by reflux of dienone **220** obtained from enaminoketone **219** with ammonium acetate (Scheme 66).[77]



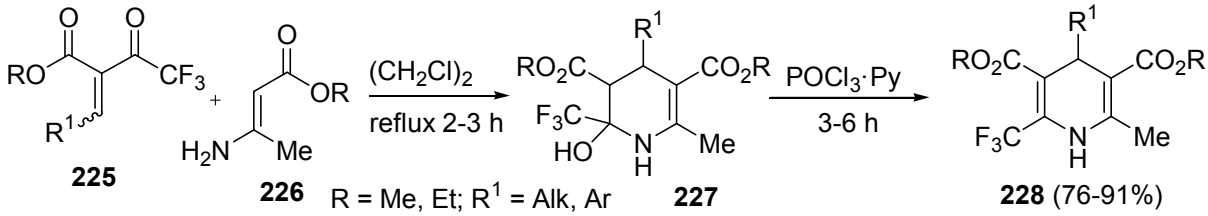
Scheme 66

The same method was used for the preparation of 2-CF_3-pyridine derivatives **222a** possessing anticancer activity. 2-Aminobenzoic acid **223** and 2-aminonicotinic acid **224** were used as the aromatic amines (Scheme 67).[78]



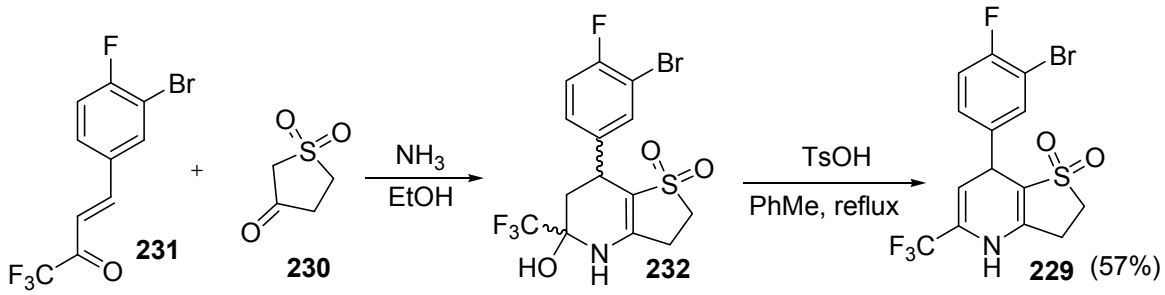
Scheme 67

α-Alkoxycarbonyl-substituted CF_3-enones **225** reacted with enamino esters **226** to afford fairly stable hydroxypyridines **227**. The hydroxypyridines **227** were dehydrated to form dihydropyridines **228** (Scheme 68).[79]



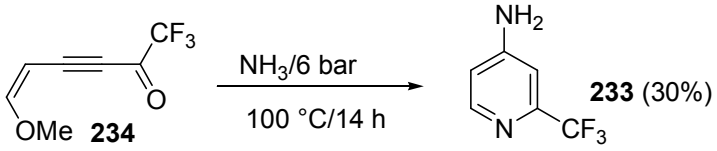
Scheme 68

The Gantsch-type synthesis of the 1,4-dihydropyridines derivatives **229** was suggested. The method uses the reaction of dihydrothiophene-3(2*H*)-one-1,1-dioxide **230** with CF_3-enone **231**. The intermediate compound **232** was isolated as the mixture of diastereomers and without further purification utilized in the next step. The target 1,4-dihydropyridine derivative **229** was prepared in good yield (Scheme 69).[80]



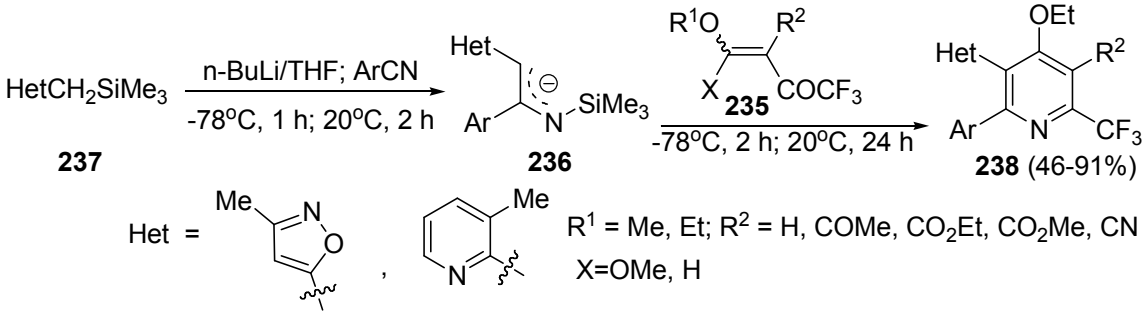
Scheme 69

4-Amino-2-CF_3-pyridine **233** was prepared in moderate yield using the reaction of ketone **234** with ammonia under heating at high pressure (Scheme 70).[81]



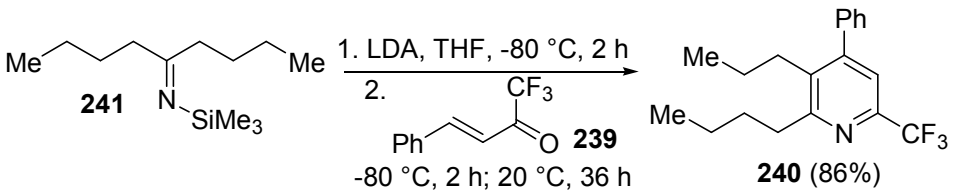
Scheme 70

Several works are devoted to the methods for the synthesis of the pyridine derivatives using iminates. For instance, ketone **235** was involved in the reaction with iminate **236** prepared from lithiated alkyltrimethylsilanes **237** and aromatic nitriles (Scheme 71).[82]



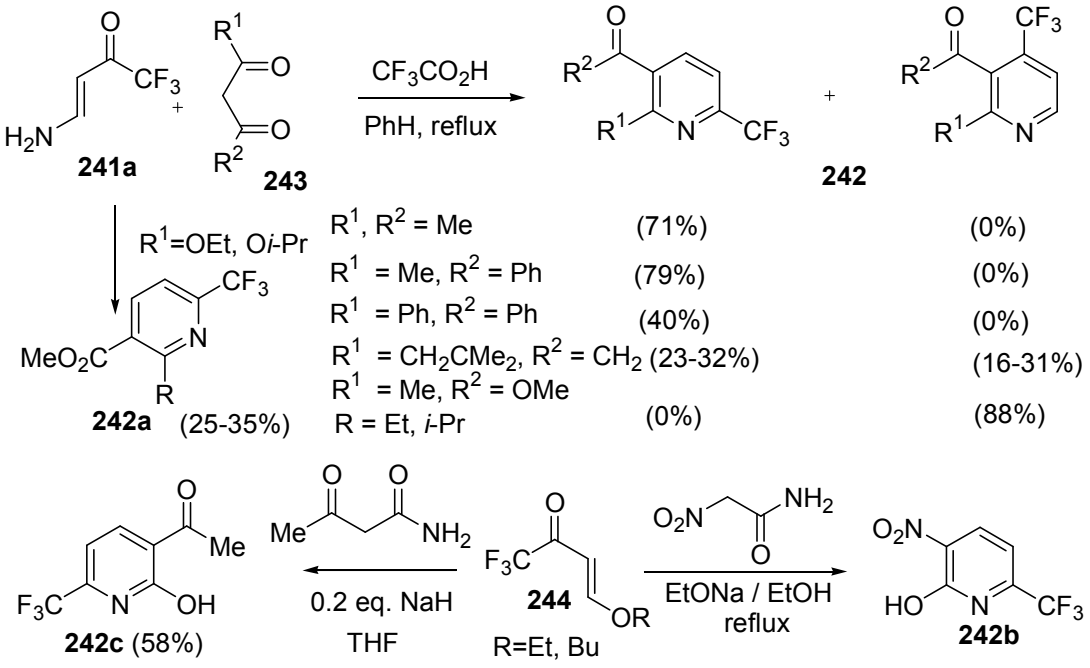
Scheme 71

The method is general and other α,β-unsaturated ketones react similarly. For example, the ketone **239** was used for the synthesis of the trifluoromethylpyridine **240** by the reaction with lithiated imine **241** (Scheme 72).[83]



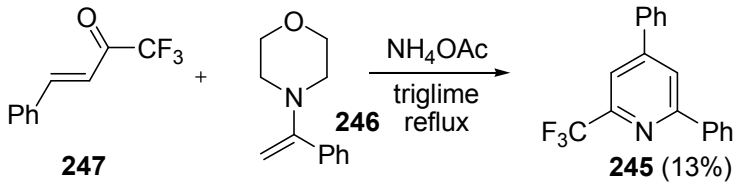
Scheme 72

Enaminoketone **241** was studied as the building block for preparation of 4-CF_3-containing pyridines **242a**. Ketone **241** reacted easily with various CH-acids **243** in the presence of trifluoroacetic acid under mild conditions to give α-trifluoromethylpyridines **242a** in moderate to high yields. In several cases, the formation of mixture of regioisomers **242a** was observed. Similar methods for preparation of pyridines **242b,c** involving the reaction of alkoxyenones **244** with CH-acids were described (Scheme 73).[84]



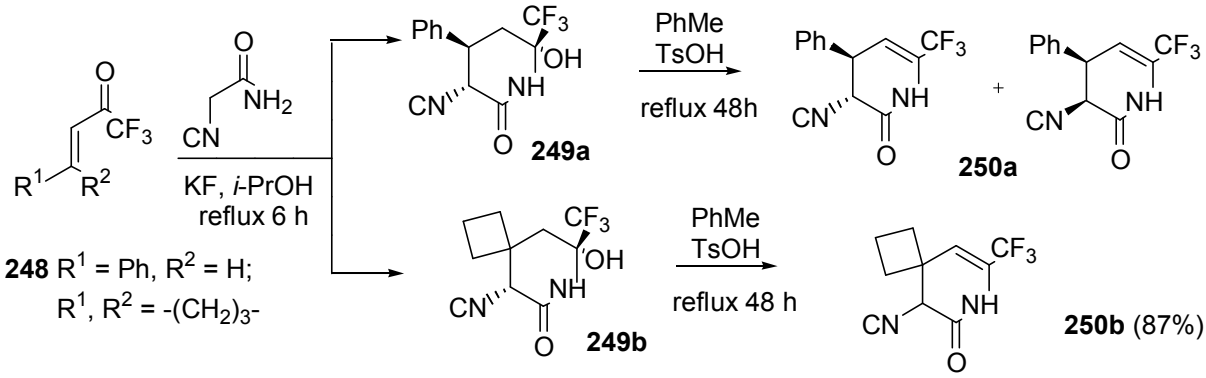
Scheme 73

2-CF_3-pyridine **245** was prepared in very low yield by the reaction of the enamine **246** with ammonium acetate and the ketone **247** by reflux in triglime (Scheme 74).[85]



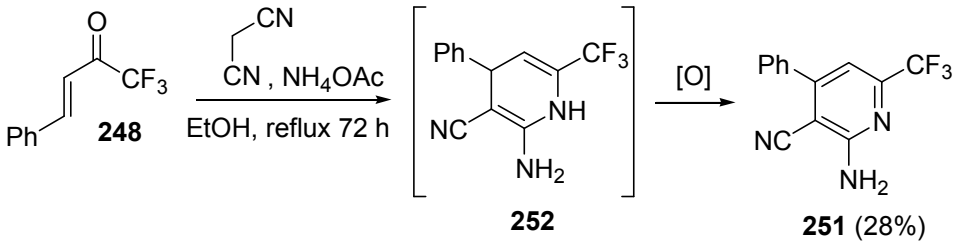
Scheme 74

It was found that reflux of benzylidene- and cyclobutylidene- trifluoromethyl ketones **248** with cyano-acetamide in isopropanol in the presence of calcinated KF leads to stereoselective formation of piperidones **249** in high yields. Dehydration gave dihydropyridines **250a,b** (Scheme 75).



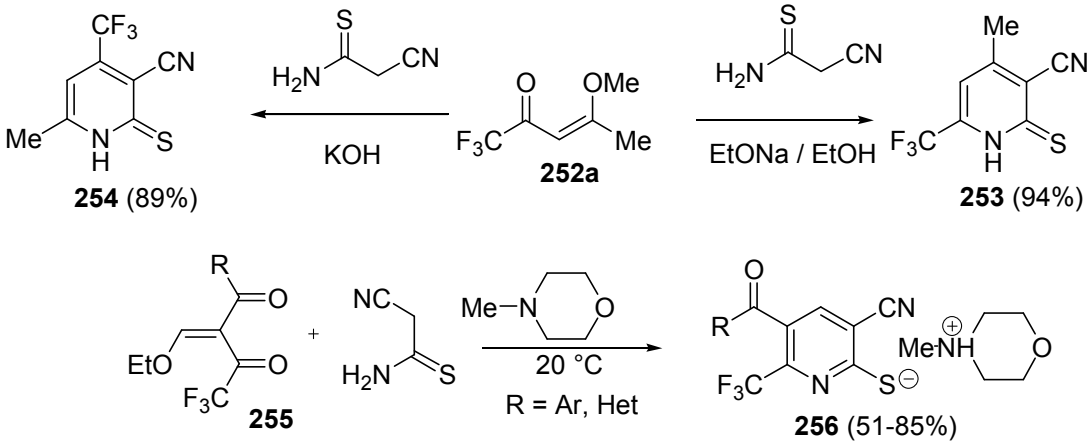
Scheme 75

The reactions of trifluoromethyl enones with malonodinitrile in the presence of ammonium acetate occurred ambiguously. Only in the case of the trifluoroacetylstyrene**248**, pyridine derivative **251**, resulting from oxidation of the corresponding dihydropyridine **252** with atmospheric oxygen, was isolated in a low yield (Scheme 76).[86]



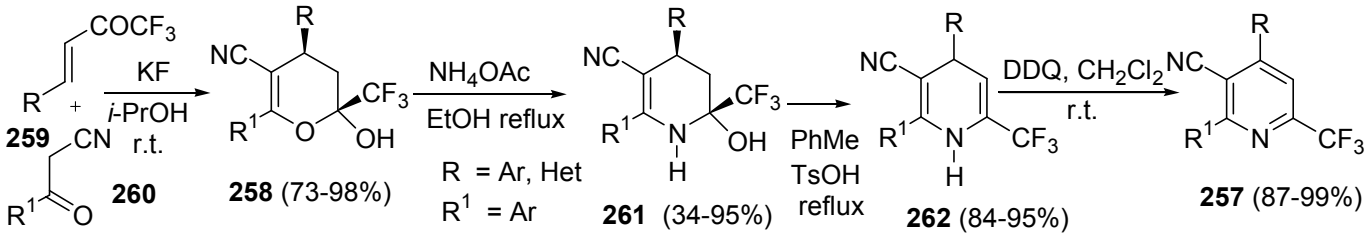
Scheme 76

The reaction of CF_3-enone **252a** with cyanothioacetamide depending on conditions permits preparation of the isomeric pyridinethiones **253** and **254** in good yields.[87] The similar method for preparation of pyridine-2-thiols as *N*-methylmorpholine salts **256** is based on the reaction of enones **256** and cyanothioacetamide in the presence of double excess of *N*-methylmorpholine (Scheme 77).[88]



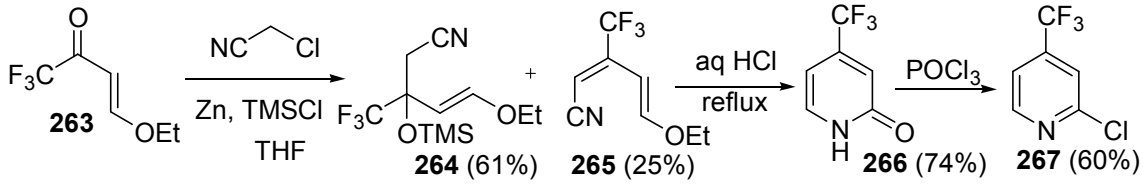
Scheme 77

A novel method for the preparation of CF_3-containing pyridines **257** was elaborated recently. First step is the synthesis of α-hydroxydihydropyrans **258** by reaction of α,β-unsaturated ketones **259** and α-cyanoacetophenones **260**. The second step is the transformation of **258** with ammonium acetate to form tetrahydropyridines **261**. The third one is the dehydration of **261** to give dihydropyridines **262**. The final stage is oxidation into the target pyridines **257** with DDQ. The sequence is very effective and useful method for preparation of CF_3-containing nicotinonitriles **257** and all compounds were prepared in good yields (Scheme 78).[89]



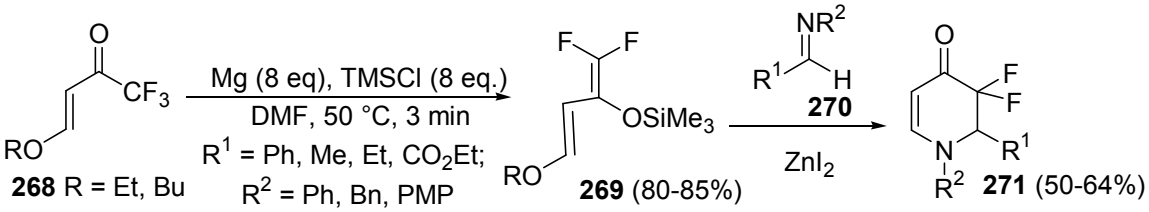
Scheme 78

It has been found that chloroacetonitrile reacts with **263** in the presence of zinc and trimethylchlorosilane to produce the β-trimethylsilyloxynitrile **264** and the elimination product **265**. 4-Trifluoromethyl-2-pyridone **266** was prepared in good yield after reflux of **264** and **265** mixture in concentrated HCl. 2-Chloro-4-trifluoromethylpyridine **267** was prepared by chlorination of **266** with $POCl_3$ (Scheme 79).[90]



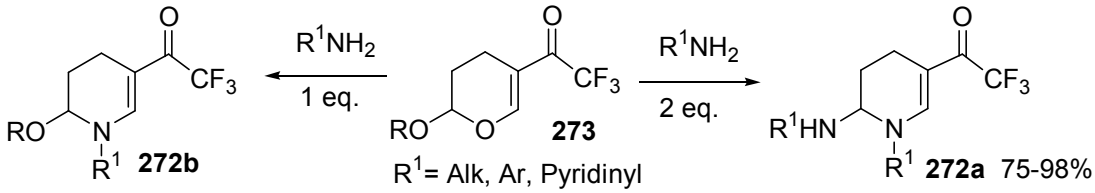
Scheme 79

Treatment of enones **268** with eight equivalents of magnesium and chlorotrimethylsilane in DMF led to the formation of difluoro-derivative of Danishefsky-diene **269** which can be used in Diels-Alder reaction with various dienophiles. Hardly available 5,5-difluoro-derivatives of dihydropyridone-4 **271** were obtained in good yields using various aldimines **270** as dienophiles (Scheme 80).[91]



Scheme 80

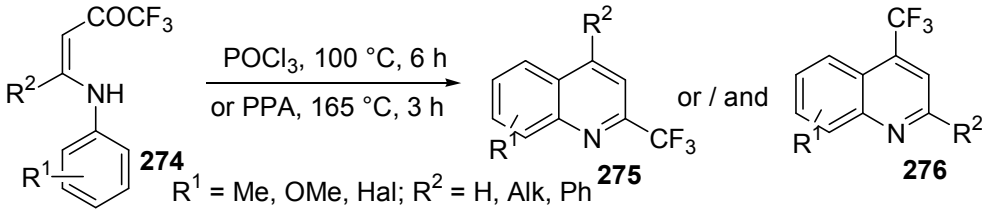
A simple and chemoselective synthesis of alkoxy- or alkylamino-substituted tetrahydropyridines bearing trifluoroacetyl group **272a,b** was elaborated by reaction of primary amines with ketone **273** (Scheme 81).[92]



Scheme 81

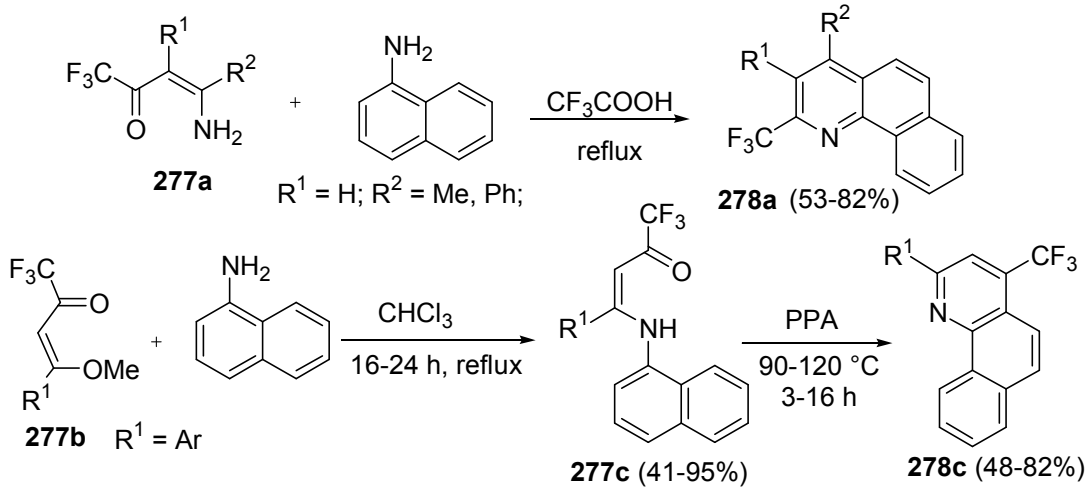
4.2. Synthesis of quinolines and benzoquinolines

β-Arylamino-substituted CF_3-enones **274** were cyclized to 2-trifluoromethyl- **275** and 4-trifluoromethylquinolines **276** under treatment with acids.[52,93] Phosphorus oxochloride, zinc chloride and polyphosphoric acid (PPA) were used as catalysts. Quinolines **276** are the products of "normal" cyclization, while the mechanism for the formation of 2-trifluoromethylquinolines **275** is the question of further investigations. The ratio of the products depends on the nature of acidic catalyst applied and the structure of the initial enone. Cyclization of enones with R_2=H gave only 2-trifluoromethylquinolines **275**. When R_2=Alkyl or Ph, 4-trifluoromethylquinolines **276** were formed predominantly. The presence of electron-donating substituents in the meta-positions of the aromatic amine facilitates cyclization and increases the total yield (Scheme 82).[94]



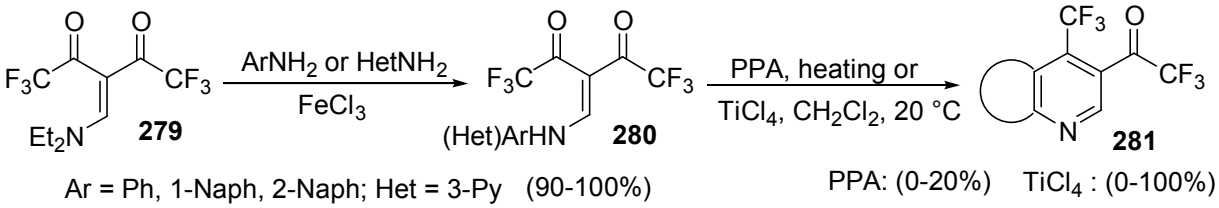
Scheme 82

Various enaminoketones **277a** were used for preparation of benzo[h]quinolines **278a**. The target heterocycles **278** were obtained in good yields using TFA as cyclizing agent.[95] The alkoxyketones **277b** can be used for the synthesis of isomeric 4-CF_3-benzo[*h*]quinolines **278c**.[96] The intermediate enaminoketones **277c** prepared from the enone **277b** and 1-naphtylamine were treated with polyphosphoric acid (Scheme 83).



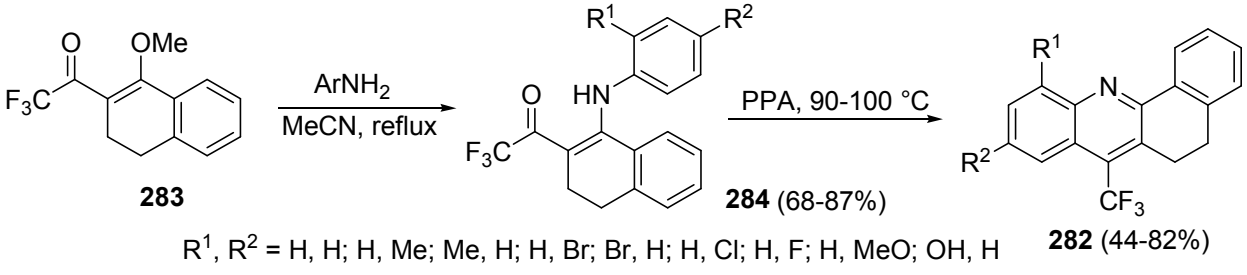
Scheme 83

The enaminodione **279** reacted with aromatic amines in the presence of catalytic amount of $FeCl_3$; the diethylamino group was substituted to give *N*-aryl-substituted enaminodiones **280**, which cyclized on treatment with PPA or $TiCl_4$; the yields of the reaction products **281** were substantially higher in the case of $TiCl_4$ catalysis (Scheme 84).



Scheme 84

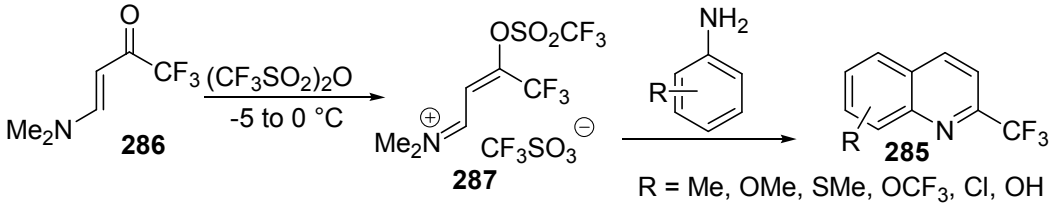
The method for the synthesis of CF_3-derivatives of dihydrobenzo[c]acrydine **282** is based on the application of β-methoxy CF_3-enone **283** obtained from tetralone-1.[97] In the reaction of **283** with substituted anilines, the formation of enaminoketones **284** was observed. Compounds **284** were cyclized into target dihydrobenzo[c]acrydines **282** in high yields under the treatment with polyphosphoric acid (Scheme 85).



Scheme 85

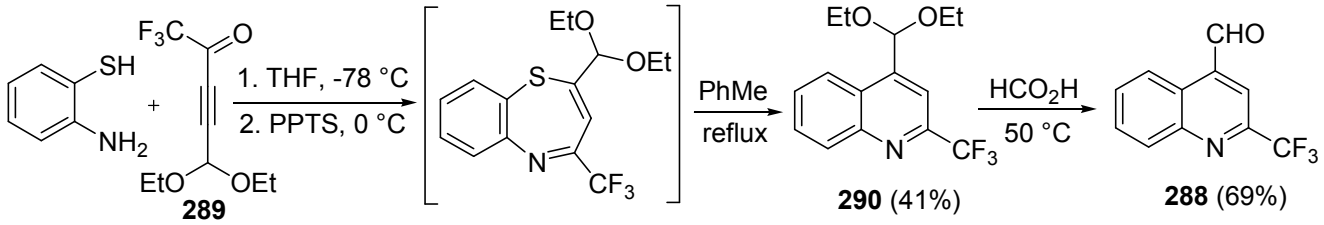
A simple and general one-pot synthesis of 2-trifluoromethylquinolines **285** from anilines and enaminoketone **286** was elaborated. Treatment of **286** with triflic anhydride caused the formation of 3-trifloxy-3-

trifluoromethylpropeniminium triflate **287** which was found to react with electron-rich aromatic compounds to give corresponding trifluoromethyl quinolines **285** in excellent yields (Scheme 86).[98]



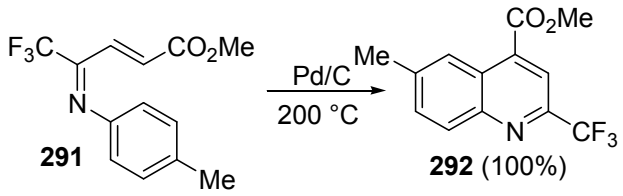
Scheme 86

The effective method for the preparation of 2-substituted 4-quinolinecarbaldehydes **288** is based on the reaction of acetylenic ketones **289** with 2-aminothiophenol. The reaction proceeds through the formation of diacetal **290** which is hydrolyzed with formic acid. Unfortunately, the yield of **288** is moderate (Scheme 87).[99]



Scheme 87

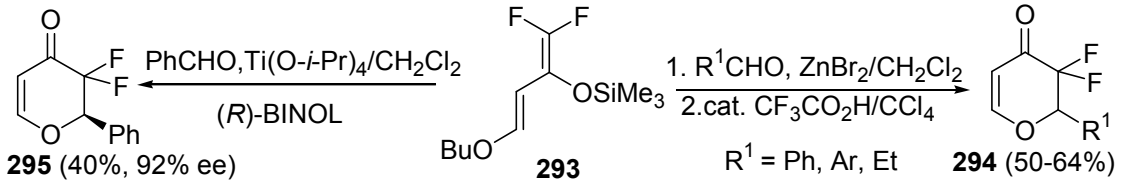
Imino-derivatives of α,β-unsaturated trifluoromethyl-containing ketones **291** can be also applied for the synthesis of quinolines **292** in good yield under dehydrogenation (Pd/C) (Scheme 88).[100]



Scheme 88

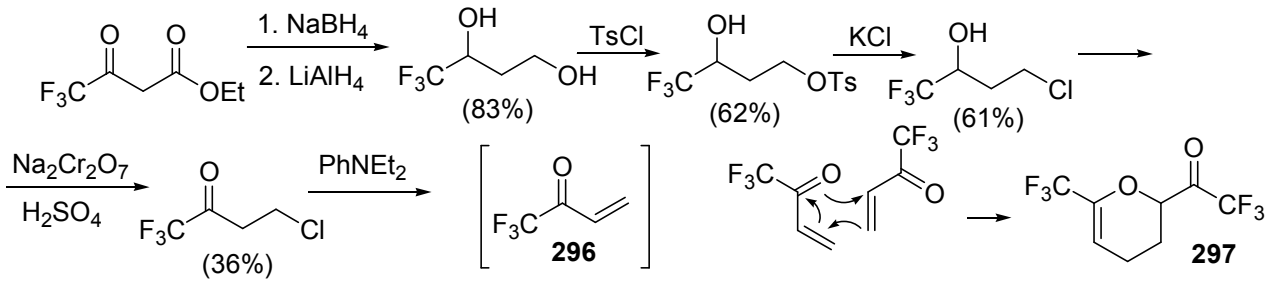
4.3. Synthesis of pyrans, thiopyrans and their derivatives

Diels-Alder reaction of difluorinated Danishefsky-diene **293** with various aldehydes was studied. The corresponding pyran-4-ones **294** were obtained in moderate yields. The asymmetric synthesis of dihydropyrone **295** using Ti(IV)-(*R*)-BINOL catalyst was demonstrated (Scheme 89).[91]



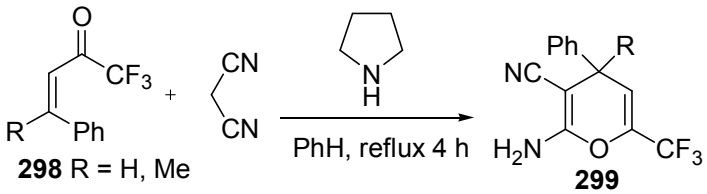
Scheme 89

An attempt has been made to prepare unsubstituted CF_3-enone **296** from ethyl trifluoroacetoacetate. However, **296** dimerized spontaneously at above –30 °C to give dihydropyran **297** (Scheme 90).[101]



Scheme 90

The reactions of trifluoromethyl enones **298** with malonodinitrile in the presence of pyrrolidine as a catalyst gave the corresponding pyrans **299** (Scheme 91).[86]

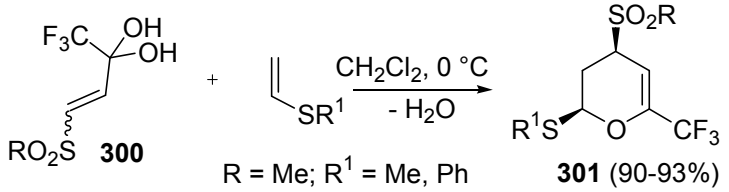


298 R = H, Me

299

Scheme 91

The ketone and diol form of compounds **300** can be used as heterodiene in the Diels-Alder reaction to reveal the stereoselective approach for dihydropyrans **301** (Scheme 92).[102]



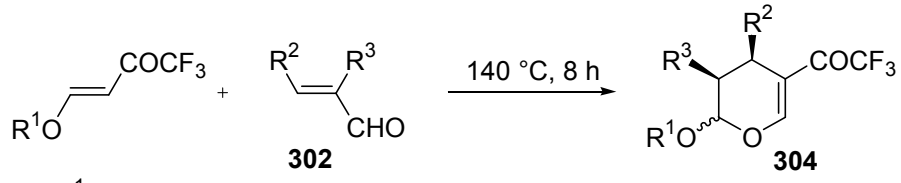
300

R = Me; R^1 = Me, Ph

301 (90-93%)

Scheme 92

The cycloaddition of α,β-unsaturated aldehydes **302** with β-alkoxy-CF_3-enones **303** led to unexpected products, the cycloadducts **304**, having alkoxy-group migrated as a mixture of *cis*-/*trans*-isomers (Scheme 93).[63]



303 R^1 = Et, *i*-Bu

302

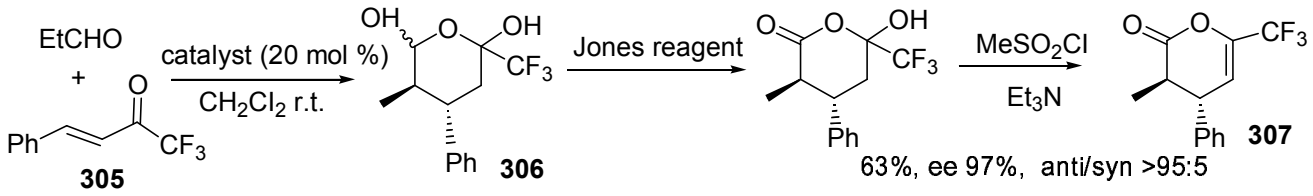
304

R^2 = H, Me; R^3 = H, Me

R^1 = Et, R^2 = R^3 =H (46%);
R^1 = Et, R^2 = Me, R^3 = H (cis / trans mixture) (40%);
R^1 = Et, R^2 = H, R^3 = Me (35%);
R^1 = *i*-Bu, R^2 = H, R^3 = H (cis / trans mixture) (39%);
R^1 = *i*-Bu, R^2 = H, R^3 = Me (36%)

Scheme 93

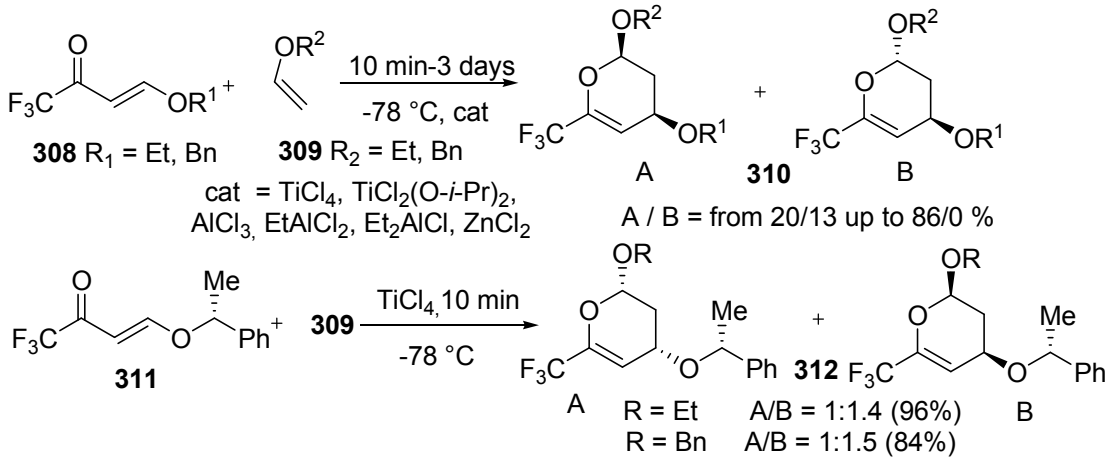
The inverse-electron-demand hetero-Diels-Alder reaction of α,β-unsaturated CF_3- ketones **305** occurred under mild conditions using a chiral diphenylprolinol silyl ether as the catalyst. The corresponding trifluoromethyl-dihydropyan-2-ones **306** were obtained with high ee and transformed to **307** (Scheme 94).[103]



305 306 307

Scheme 94

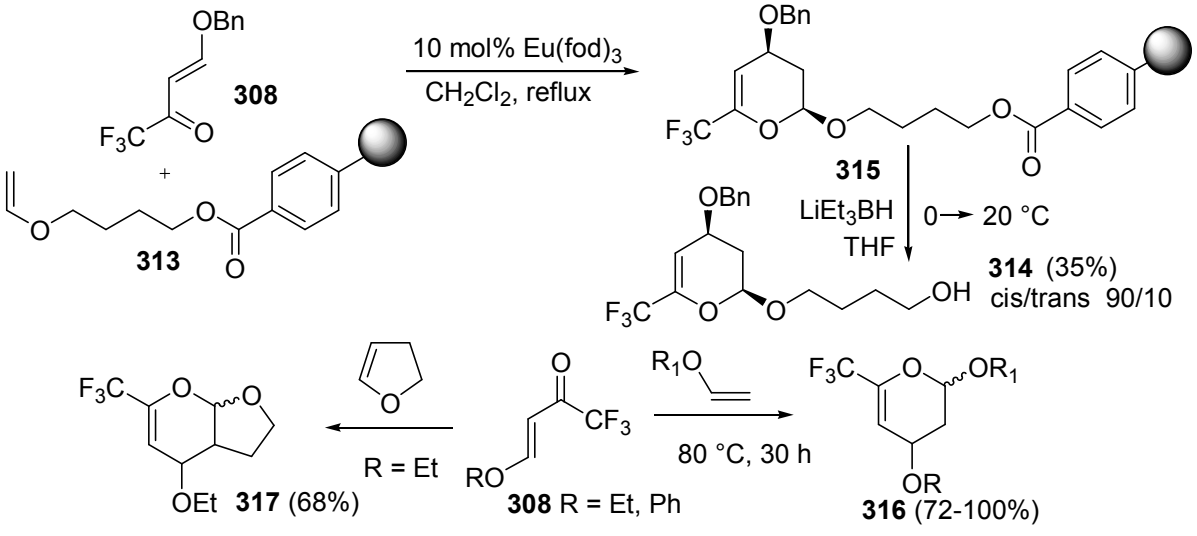
The influence of various Lewis acids additives on the cycloaddition reaction of β-alkoxy CF_3-enones **308** with vinyl ethers **309** was investigated. The best results (the highest ratio of diastereoisomers of compound **310**) were obtained using titanium(IV) chloride. The preparation of chiral CF_3-dihydropyrans **312** was also investigated. In this case the reaction of CF_3-enone **311** containing chiral substituent in β-position was used. The application of titanium(IV) chloride as the catalyst has permitted the preparation of the target pyrans **312** in high yields; however the diastereoselectivity of the reaction was very low (Scheme 95).[104]



308 R_1 = Et, Bn 309 R_2 = Et, Bn 310 311 312

Scheme 95

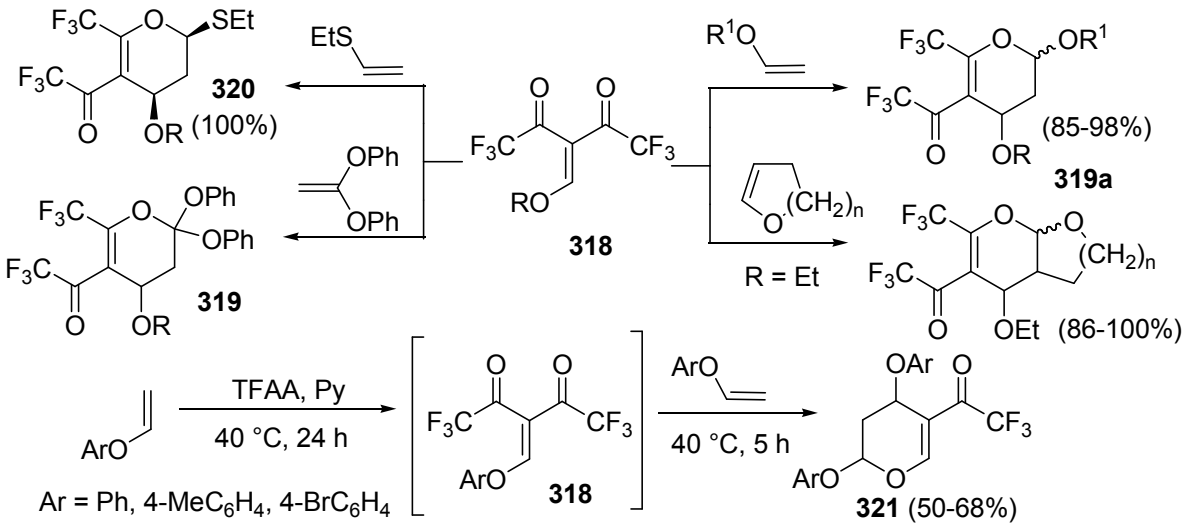
The solid-phase methodology can be successfully applied to the cycloaddition reaction of β-benzyl-oxy-CF_3-enone **308** and vinyl ether **313**. The reaction was catalyzed with europium(III) complex and proceeded in rather moderate yield though with high stereoselectivity. The target pyran **314** was obtained after the treatment **315** with lithium triethylborohydride. The reaction of β-ethoxy(phenoxy)-substituted enones **308** with vinyl ethers afforded 3,4-dihydro-2*H*-pyrans **316** and **317** in good yields (Scheme 96).[105]



308 313 315

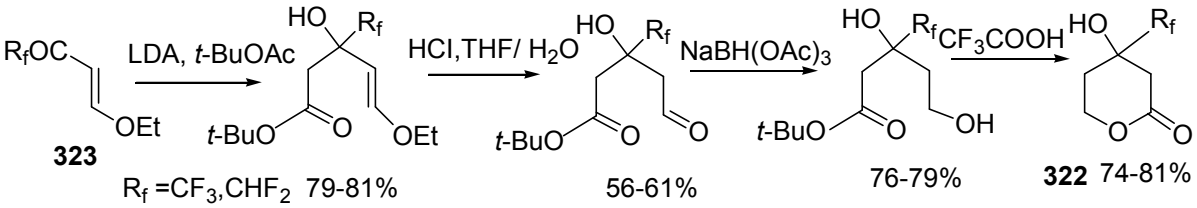
Scheme 96

Cycloaddition proceeded especially easily for β-alkoxy-substituted bis(trifluoromethyl) enones **318** due to the presence of the second strong electron-withdrawing group increasing the reactivity of trifluoromethylenones **318** as heterodienes. The reaction was carried out at room temperature to give 5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans **319** in high yields. Thioethers reacted similarly to give single diastereomers of pyranes **320**. Aryl vinyl ethers reacted with trifluoroacetic anhydride to give the corresponding bis(trifluoroacetyl) derivatives **318**. It was found that these compounds are unstable and can not be isolated in a pure form. However, they can be introduced without isolation in the reaction with a second equivalent of aryl vinyl ether to form **321** in good yields. In some cases, these products were formed directly in trifluoroacetylation of aryl vinyl ethers (Scheme 97).[106]



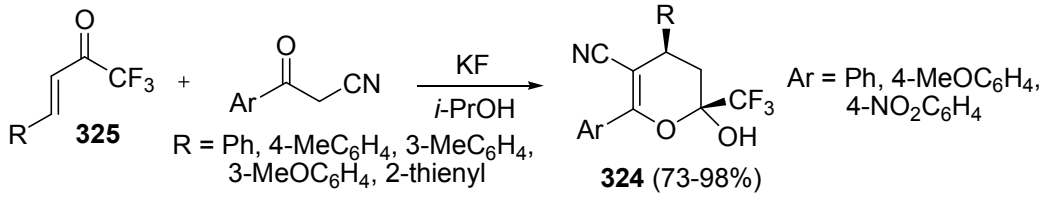
Scheme 97

A new multistep synthesis of tri- and difluoromevalonates **322** starting from alkoxy enones **323** has been developed. Enantiomers of fluoromevalonates can be obtained by chromatography separation (Scheme 98).[107]



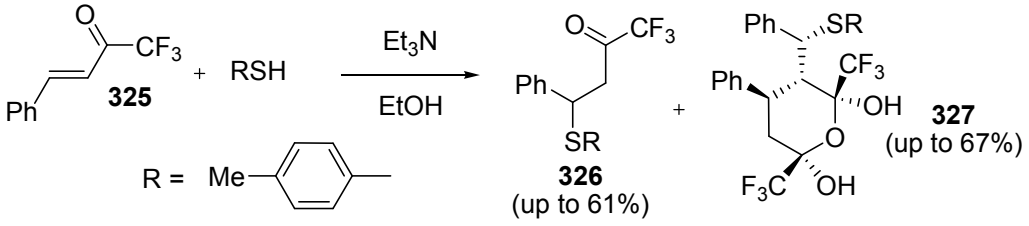
Scheme 98

Cyano substituted dihydropyrans **324** were obtained in the reaction of CF_3-enones **325** with α-cyanoketones. The reaction proceeds in the presence of calcinated KF as the base in good yields and 100% stereoselectively to form **324** with equatorial orientation of aryl substituent and CF_3-group (Scheme 99).[108]



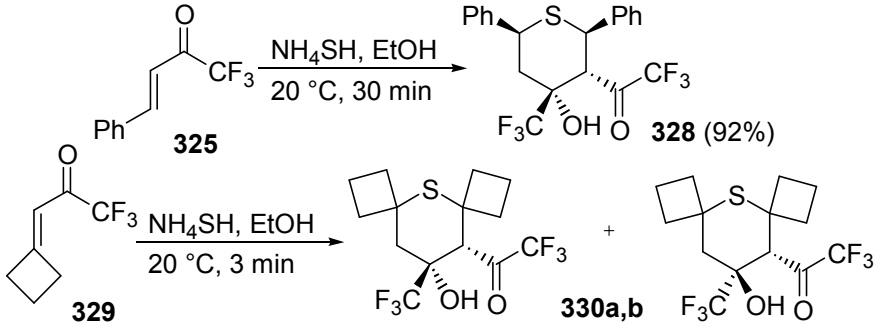
Scheme 99

Pyran derivatives were also obtained in the reaction of CF_3-enone **325** with 4-methylthiophenol. The mixture of Michael adduct **326** and the cyclic product of double ketone addition **327** was formed as the single diastereomer. Depending on the reaction conditions, each of the two products can be obtained selectively (Scheme 100).[109]



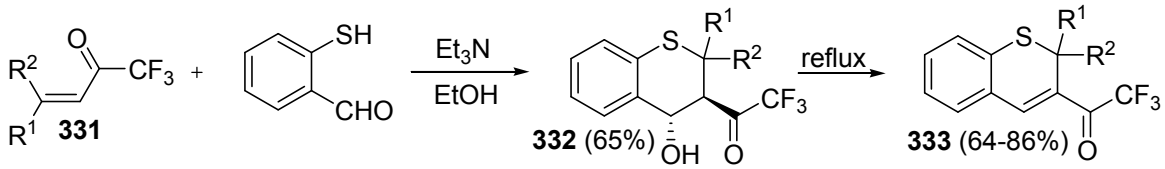
Scheme 100

The reactions of trifluoromethyl enones with ammonium hydrosulfide depends on the structure of the initial enone. For instance, enone **325** reacted stereospecifically yielding tetrahydrothiapyran **328** as one diastereoisomer of the eight possible isomers. The reaction with cyclobutylsubstituted enone **329** afforded a mixture of *cis*- and *trans*-diastereomers of tetrahydrothiopyran **330a,b** (total yield 90%) in 1:1 ratio (Scheme 101).[110]



Scheme 101

The reaction of ketones **331** with 2-mercaptobenzaldehyde led to thiochromanes **332** which can be easily transformed into 2*H*-thiochromenes **333** by heating of the reaction mixture. The intermediate thiochromanes **332** were isolated only in case of CF_3-enone having the phenyl substituent. It was established that all substituents in this compound have equatorial orientation (Scheme 102).[109]

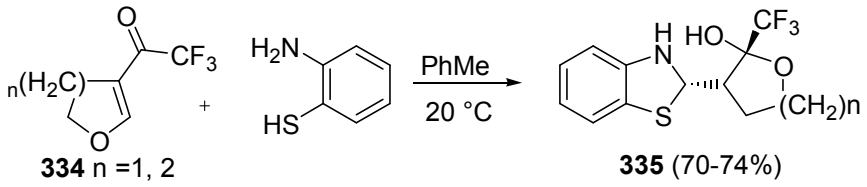


R^1 = Ph, R^2 = H; R^1 = 2-Th, R^2 = H; R^1 = N-methylpyrrolyl, R^2 = H; R^1,R^2 = -$(CH_2)_3$-

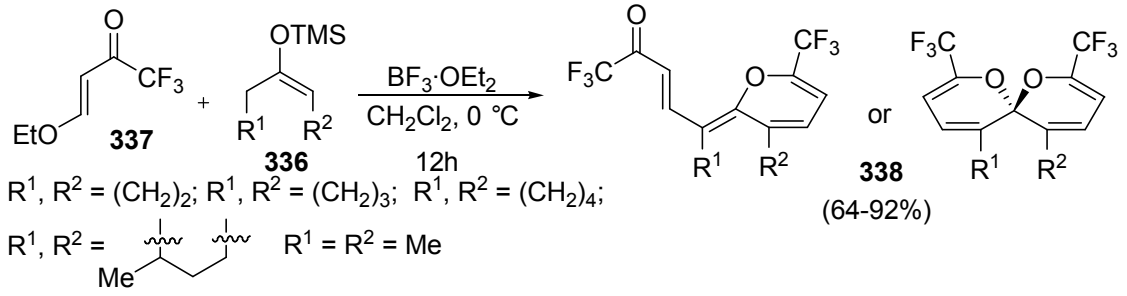
Scheme 102

The reaction of 2-aminothiopenol with two cyclic β-alkoxyenones **334** led to formation of benzothiazolines **335** binding with tetrahydrofuran and tetrahydropyran ring as the single diastereomer. Trifluoromethyl group and the benzothiazoline substituents are oriented equatorially (Scheme 103).[111]

Spiro-pyrane derivatives **338** were obtained in good yields in the reaction of trimethylsilyl ethers **336** with β-ethoxy ketone **337** catalyzed by boron trifluoride-diethyl ether complex (Scheme 104).[112]

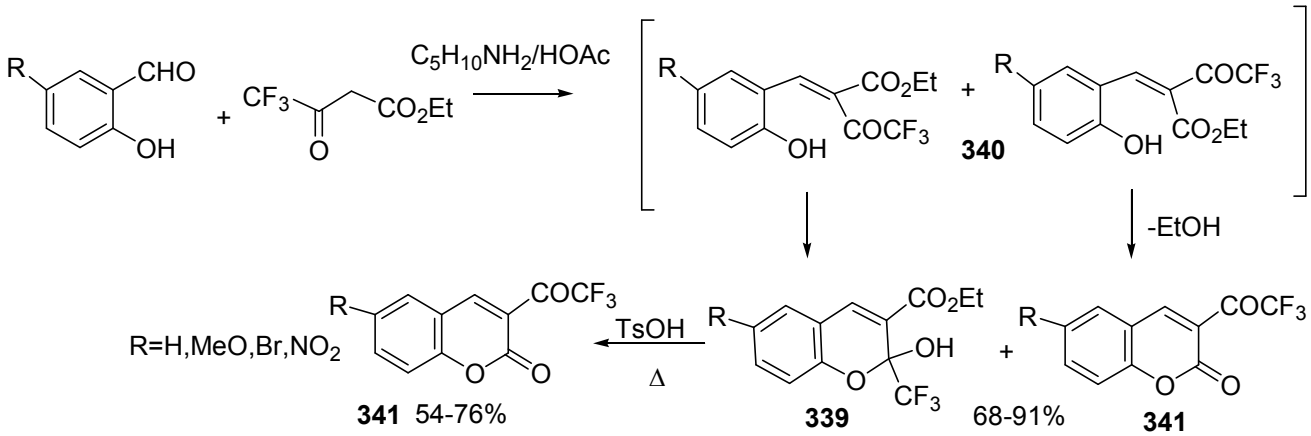


Scheme 103



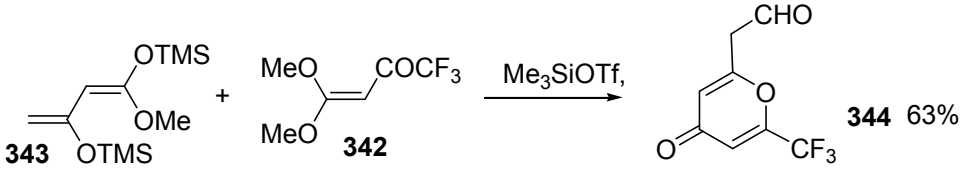
Scheme 104

The Knoevenagel condensation of ethyl trifluoroacetoacetate with salicylaldehydes provided a simple and convenient approach to substituted (trifluoromethyl)-2*H*-chromene **339** *via* intermediate formation of enones **340**. The subsequent recyclization of **339** proceeded smoothly in the presence of TsOH affording previously unknown 3-(trifluoroacetyl)coumarins **341** in moderate to good yields (Scheme 105).[113]



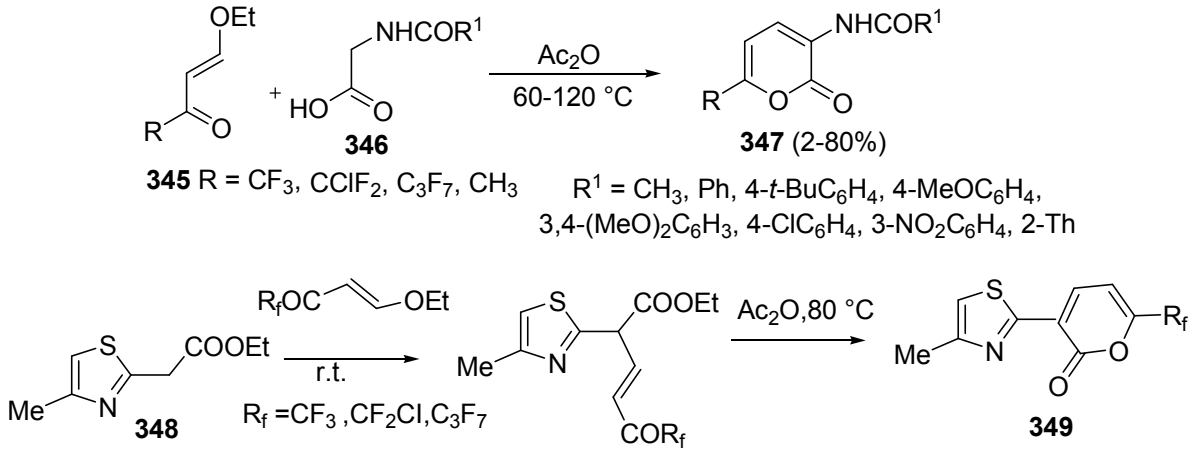
Scheme 105

The Me_3SiOTf-mediated reactions of dimethoxy-substituted CF_3-enones **342** with 1,3-bis(silyloxy)-1,3-butadienes **343** afforded pyran-4-ones **344** (Scheme 106).[114]



Scheme 106

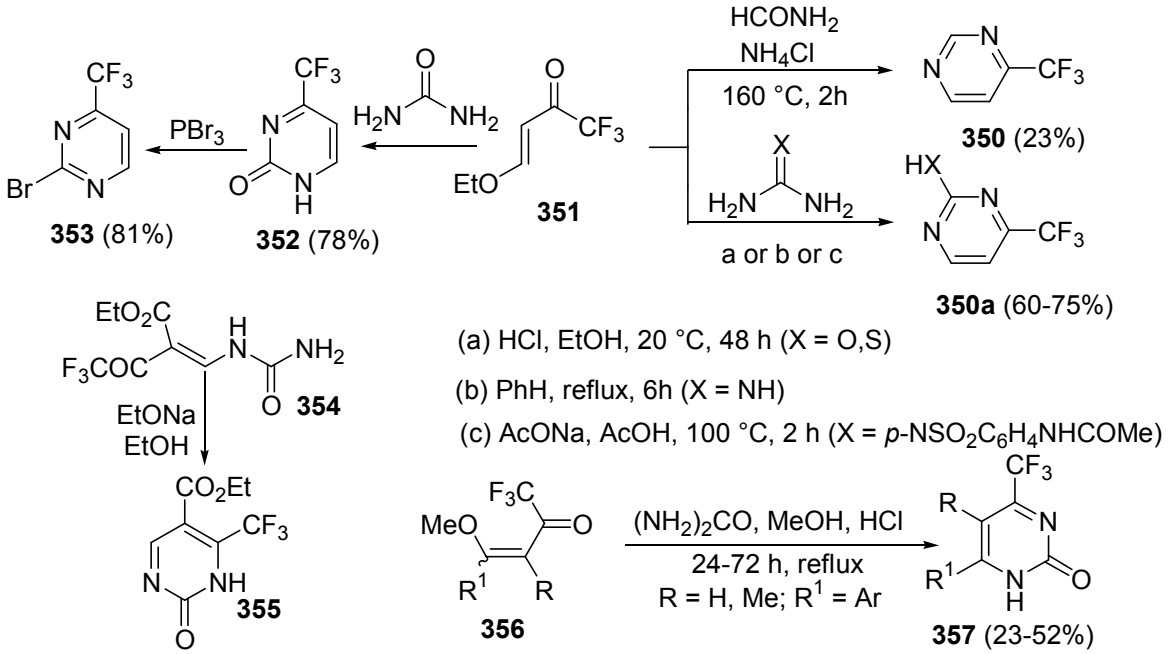
The reactions of β-ethoxyenones **345** with various *N*-aroyl glycines **346** in the presence of acetic anhydride led to 2*H*-pyran-2-ones derivatives **347**.[115] The reaction between fluorinated enones and thiazole **348** bearing a methylene group activated by an electron-withdrawing substituent led to the formation of pyrones **349** (Scheme 107).[116]



Scheme 107

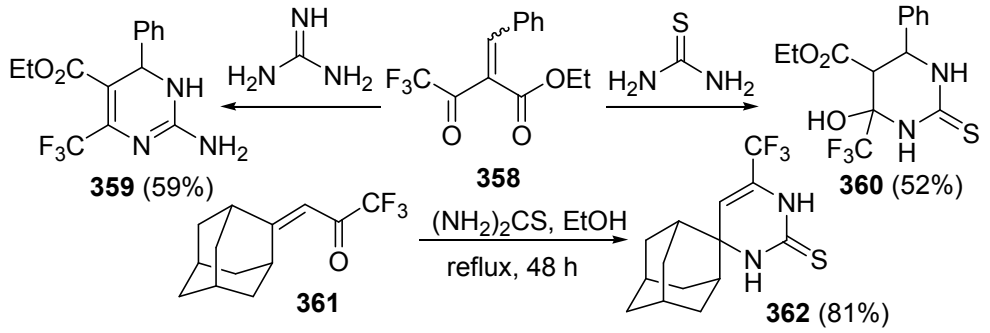
4.4. Synthesis of pyrimidines and their derivatives

Trifluoromethylpyrimidines **350** are formed when β-alkoxy-substituted enone **351** was allowed to react with formamide in the presence of ammonia chloride or with the compounds of the urea series.[117] Bonacorso *et. al.* reported the synthesis of pyrimidones **352** using the reaction of enones **351** with urea in the acidic conditions.[118] The condensation of urea with ketones **351** and **356** afforded **352** and **357** in good yields. 2-Bromo-4-(trifluoromethyl)pyrimidine **353** was prepared by reaction of **352** with phosphorus tribromide. The analogous condensation of urea with 3-bromo-4-ethoxy-1,1,1-trifluoro-3-buten-2-one produced tars rather than the expected 5-bromo-4-(trifluoromethyl)-2(1*H*)-pyrimidone.[119] Enamidoketone **354** was used for preparation of pyrimidine derivative **355**.[120] The heterocyclization was carried out under basic conditions (Scheme 108).



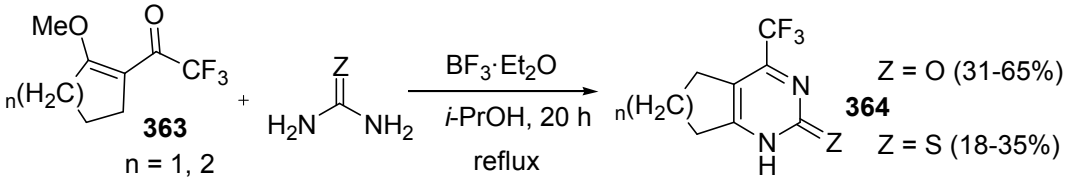
Scheme 108

The reactions of CF_3-enone **358** containing the ethoxycarbonyl group in the α-position with thiourea and guanidine sulfate gave the corresponding dihydro-**359** and tetrahydro-derivative **360** in moderate yields.[121] The stereochemistry of **360** was not studied. The reaction of a sterically hindered trifluoromethyl enone **361** having an adamantane fragment with thiourea afforded dihydropyrimidine **362** (Scheme 109).[122]



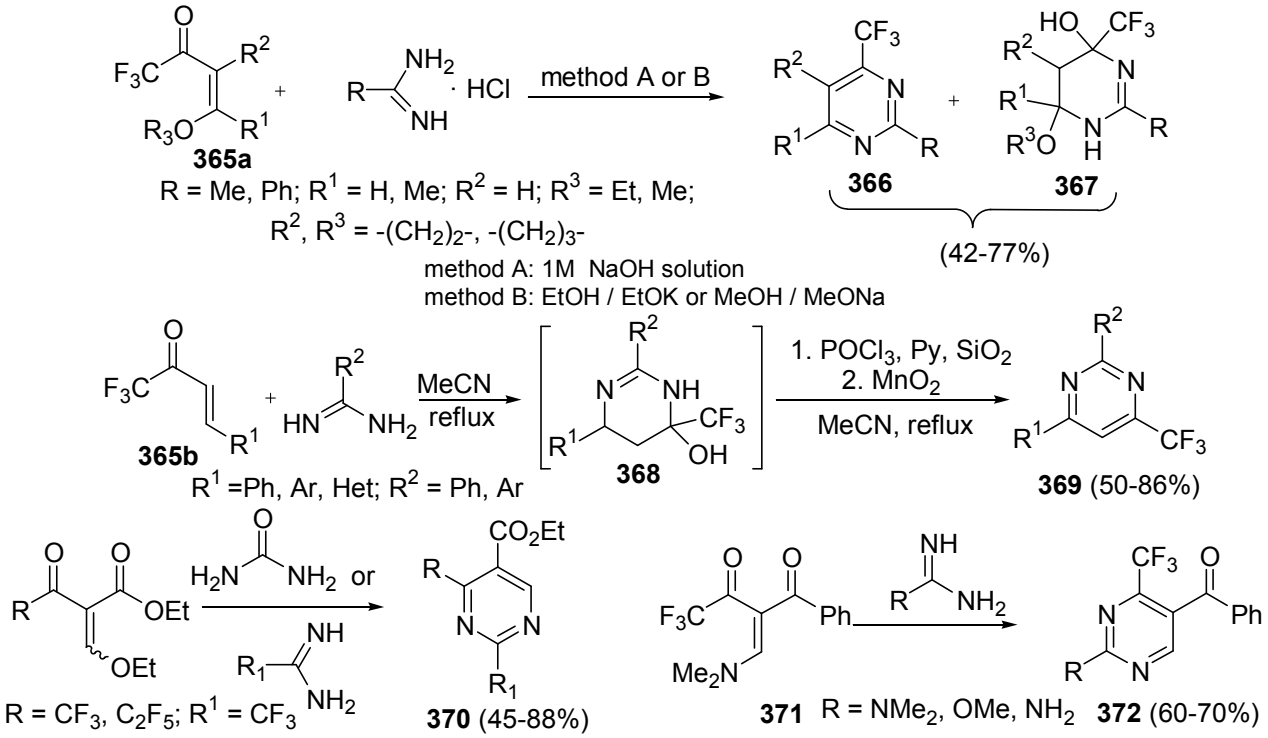
Scheme 109

Cyclic CF_3-enones **363** were used for the preparation of 2-pyrimidones **364** and their thio-analogous by the reaction with urea and thiourea. The target compounds were obtained in moderate yields (Scheme 110).[123]



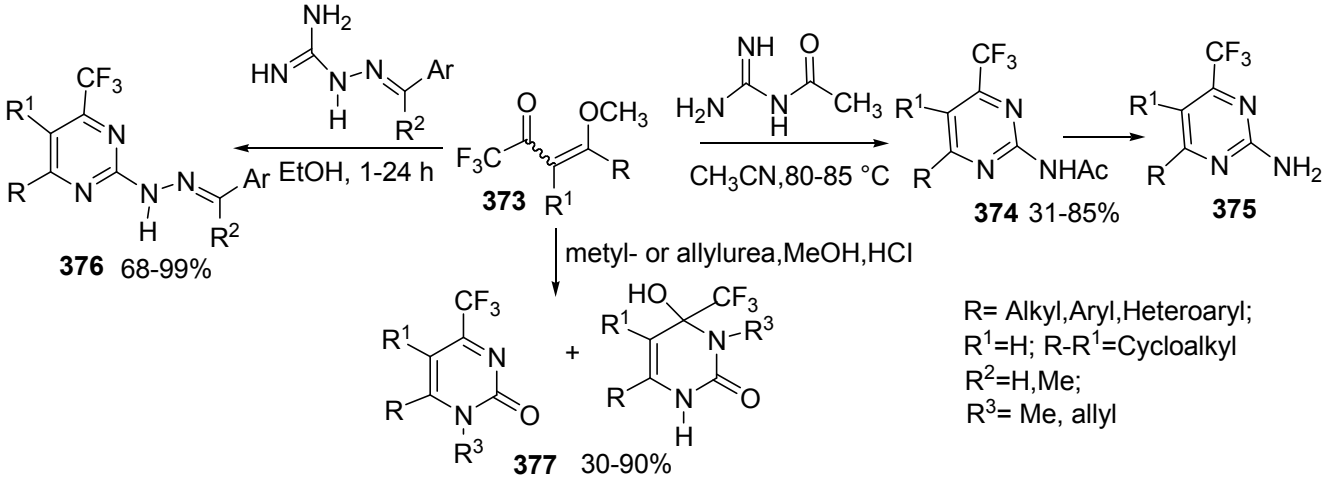
Scheme 110

The reaction of series of CF_3-enones **365a,b** with acet- and benzamidine was carried out.[124] The formation of pyrimidine **366** or the mixture of **366** and its tetrahydro-derivative **367** was observed. In the case of enones **365b**, subsequent dehydration and oxidation of intermediate adducts **368** without isolation permitted the preparation of **369** in high yields.[125] The library of pyrimidine derivatives **370** containing CF_3-group was synthesized for investigation of the physiological activity.[126] The possibility of application of β-enamino-CF_3-enones **371** for the synthesis of pyrimidine derivatives was shown. The corresponding pyrimidines **372** were obtained in good yields using the reaction with urea derivatives (Scheme 111).[127]



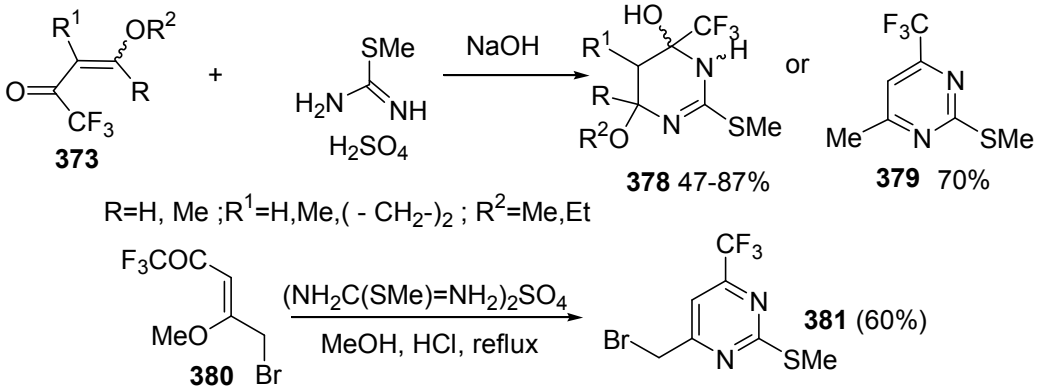
Scheme 111

The one-pot synthesis of substituted 2-acetylaminopyrimidines **374** using the reaction of β-methoxy CF_3-enones **373** with 1-acetylguanidine was elaborated. The acetylamino group of 2-acetylaminopyrimidines can be hydrolyzed to afford the corresponding 2-aminopyrimidines **375**.[128] The *N*'-benzylidenehydrazino-pyrimidines **376** were obtained through one-step cyclocondensation of *N*-guanidinobenzylimines and 4-alkoxyvinyl-CF_3-ketones in good yields. Most heterocycles were isolated as a single diastereoisomer (*E*-isomers).[129] *N*-Substituted pyrimidinones **377** were synthesized by condensation of 4-alkoxy-CF_3-enones **373** with excess *N*-methyl- and *N*-allylureas. It has been demonstrated that the reactions give better yields and furnish either N^1- or N^3-alkylated products depending on both the reaction conditions and the substituents on the enones, whereas the alkylation of pyrimidinones gave lower overall yields and either an N^1-alkylated product or a mixture of N^1- and *O*-alkylated products (Scheme 112).[130]



Scheme 112

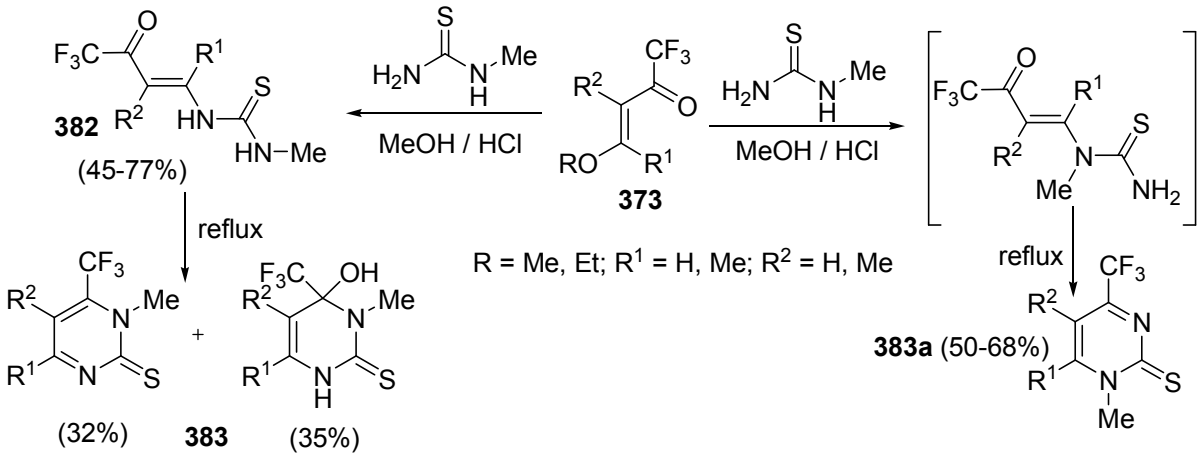
The reaction of β-alkoxyvinyl CF_3-ketones **373** with 2-methyl-2-thiopseudourea sulfate carried out in the presence of sodium hydroxide solution furnished substituted 4-CF_3-2-methylsulfanyl-tetrahydro-pyrimidines **378** in good yields, but the product was unstable and rapidly lost an alcohol and water molecule to give the parent aromatic pyrimidine **379**.[131] The compound **380** reacted with methylisothiouronium sulfate forming directly the corresponding pyrimidine **381** in moderate yield (Scheme 113).[132]



Scheme 113

The cyclocondensation of β-alkoxyvinyl CF_3-ketones **373** toward an nonsymmetric binucleophile, the *N*-methylthiourea, was choosen to study its regiochemistry. Depending on the temperature and the reaction time the open-chain products **382** or pyridinethiones **383** were obtained. In general, low temperature and

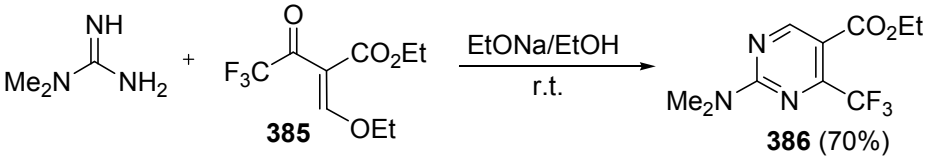
short reaction time promote the formation of open-chain products **382**. Higher temperature and longer reaction time results in the pyrimidinethiones **383** (Scheme 114).[133]



382 **373** **383**

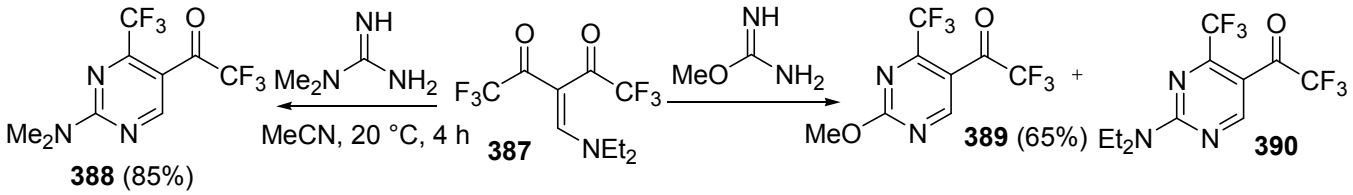
Scheme 114

Analogous reaction was used for the synthesis of 2-dimethylamino-derivative of 4-CF_3-pyrimidine-5-carboxylic acid **386** that showed cardiotonic activity.[134] The reaction of β-ethoxy-CF_3-enone **385** with 2,2-dimethylguanidine was performed. The target product **386** was obtained in high yield (Scheme 115).



Scheme 115

The enaminodione **387** has been introduced in reactions with compounds of the urea series. The reaction with guanidine afforded pyrimidine **388** in good yield. The reaction with *O*-methylisourea afforded two products: 1-methoxypyrimidine **389** and 1-diethylaminopyrimidine **390** because diethylamine formed in the reaction reacted with methoxypyrimidine **389**. Optimization of the reaction conditions has made it possible to prepare the target compound in 65% yield (Scheme 116).[135]

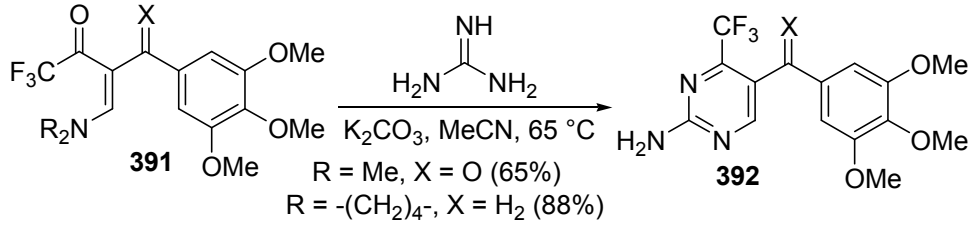


Scheme 116

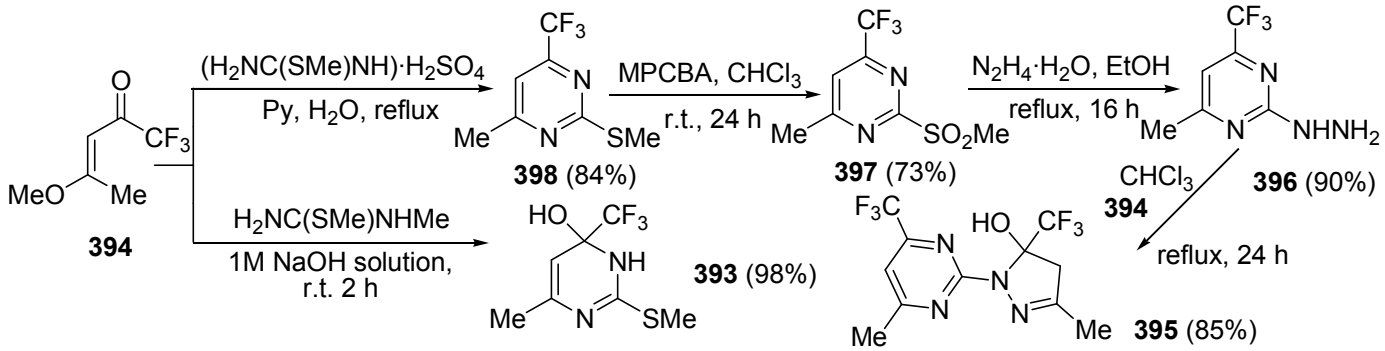
The work was undertaken to apply the methodology of the synthesis of fluorinated aminopyrimidines analogous to trimethoprim (TMP).[136] Trimethoprim (TMP) and pyrimethamine (PYR) have become the reference drugs for prophylaxis and treatment of opportunistic infections due to *Pneumocystis carinii* and *Toxoplasmagondii*. Enaminoketones **391** were reacted with guanidine to give **392** (Scheme 117).

Four novel pyrimidines were prepared to investigate the effects of on NTPDase activity in a synaptosomal fraction obtained from rat cerebral cortex.[137] The pyrimidine **393** was prepared by the cyclocondensation reaction of **394** with 1,2-dimethyl-isothiourea. The synthesis of **395** was achieved from

the cyclization of hydrazine **396** with the ketone **394**. The pyrimidine **397** was prepared by the oxidation of 2-methylsulfanyl-pyrimidine **398** with MCPBA which underwent nucleophilic displacement of the 2-methylsulfonyl group by hydrazine hydrate to furnish the 2-hydrazino-pyrimidine **396** in excellent yield (Scheme 118). The presence of pyrimidine core was essential for enzyme recognizing in both peripheral and active sites.

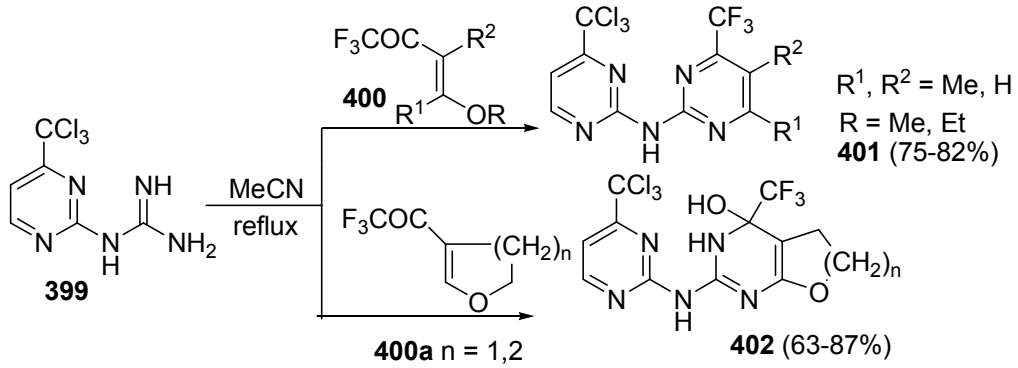


Scheme 117



Scheme 118

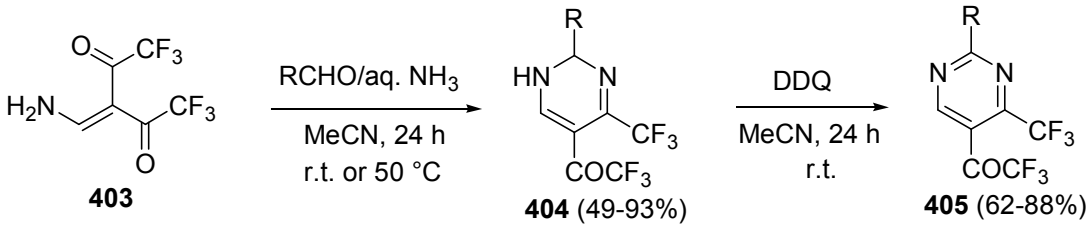
The reactions of 2-guanidinopyrimidine **399** with β-alkoxy-CF_3-enones **400** and cyclic enones **400a** led to dipyrimidylamines **401** or their condensed dihydrofuran and dihydropyran derivatives **402** (Scheme 119).[138]



Scheme 119

Enaminoketone **403** reacted with various aldehydes in the presence of ammonia to give dihydropyrimidine derivatives **404** in good yields. Oxidation of 1,2-dihydropyrimidines **404** with DDQ at room temperature for 24 hours in acetonitrile caused smooth dehydrogenation to give the desired pyrimidines **405** having both trifluoromethyl and trifluoroacetyl groups which are not easily obtained by other methods (Scheme 120).[139]

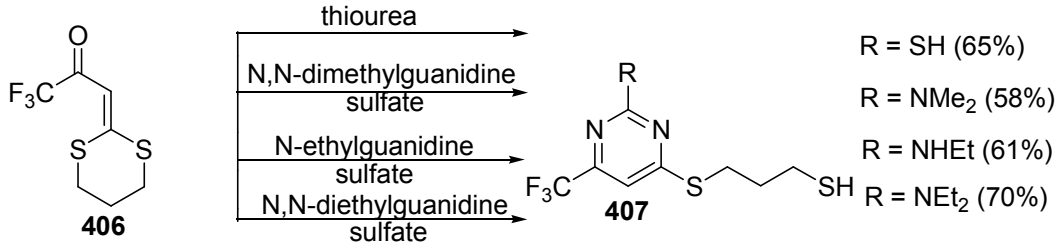
The reactions of CF_3-enone **406** with several *N*,*N*-binucleophiles were investigated. Various 2-substituted pyrimidines **407** containing 1,3-dithiopropyl substituent were prepared (Scheme 121).[40]



403 → **404** (49-93%) → **405** (62-88%)

R = H, Me, Et, *i*-Pr, 4-$MeOC_6H_4$, 4-MeC_6H_4, Ph, 4-ClC_6H_4

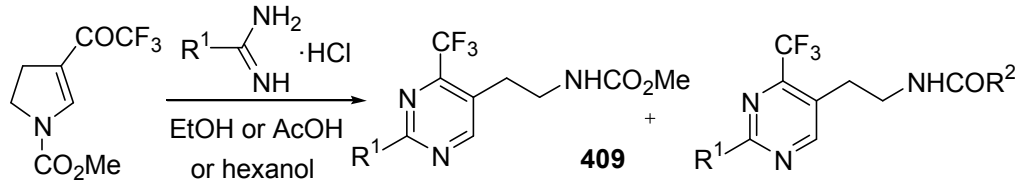
Scheme 120



406 → **407**

Scheme 121

The example of application of trifluoroacetyl pyrroline **408** for the preparation of pyrimidines **409** was also described.[37] In this case, the reaction is less selective. Nevertheless, the products **409** are very attractive objects for medicinal chemistry (Scheme 122).

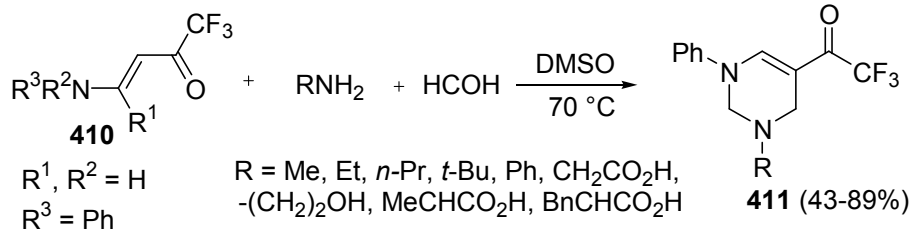


408 → **409**

R^1 = H, Me, Ph, NH_2; R^2 =Et, Pr (3-74%)

Scheme 122

The multicomponent reaction of β-phenylamino-CF_3-enone **410**, primary amine and formaldehyde was used for the synthesis of tetrahydropyrimidines **411**. The reaction proceeded in moderate to high yields (Scheme 123).[140]



410

R^1, R^2 = H

R^3 = Ph

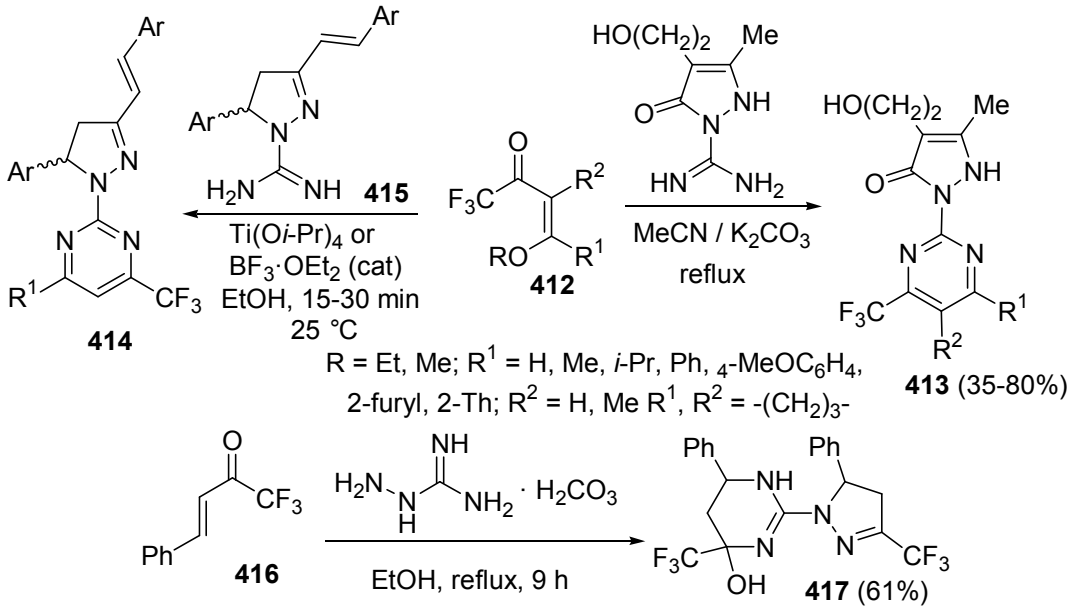
R = Me, Et, *n*-Pr, *t*-Bu, Ph, CH_2CO_2H, $-(CH_2)_2OH$, $MeCHCO_2H$, $BnCHCO_2H$

411 (43-89%)

Scheme 123

β-Alkoxy-CF_3-enones **412** were also used for preparation of various CF_3-pyrimidines **413** containing 3-oxo-2,3-dihydropyrazole substituent.[141] These compounds are of particular interest because of potential anti-inflammatory nonsteroid agents. Similarly, pyrimidines **414** were synthesized by reaction of **415** with **412**.[142] β-Trifluoroacetylstyrene **416** reacted with aminoguanidine to give compound **417**, resulting from addition of two enone molecules to an aminoguanidine molecule and containing two heterocyclic moieties (tetrahydropyrimidine and pyrazoline). In this case, water is eliminated only from the five-membered ring,

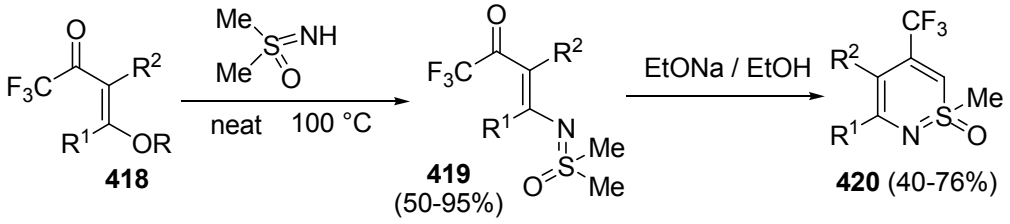
which is consistent with the general rule according to which trifluoro-substituted pyrazolidines are dehydrated more readily than tetrahydropyrimidines (Scheme 124).[122,143]



Scheme 124

4.5. Synthesis of 1,2-, 1,3- and 1,4-thiazines

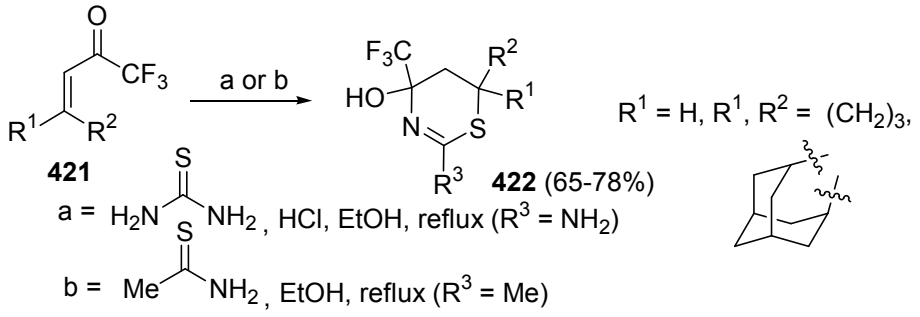
The reaction of β-alkoxy-CF_3-enones **418** with *S*,*S*-dimethylsulfoximine was studied. Initially formed products **419** can be cyclized into the derivatives of 1,2-thiazine-1-oxide **420** in high yields (Scheme 125).[144]



R = Et, Me; R^1 = H, Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, t-Bu, $-(CH_2)_2OMe$, Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$; R^2 = H, Me

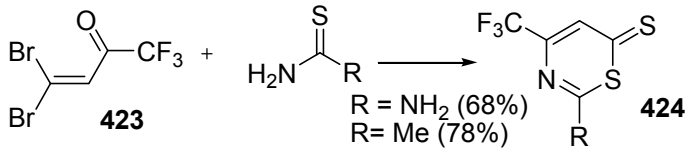
Scheme 125

The reactions of trifluoromethyl enones **421** with thiourea and thioacetamide in an acidic medium afforded dihydrothiazines **422**. Both reactions were regiospecific and give one isomer formed upon the addition of sulfur at the double bond and nitrogen of the carbonyl group. This reaction route was interpreted in terms of the principle of hard and soft acids and bases (Scheme 126).[145]



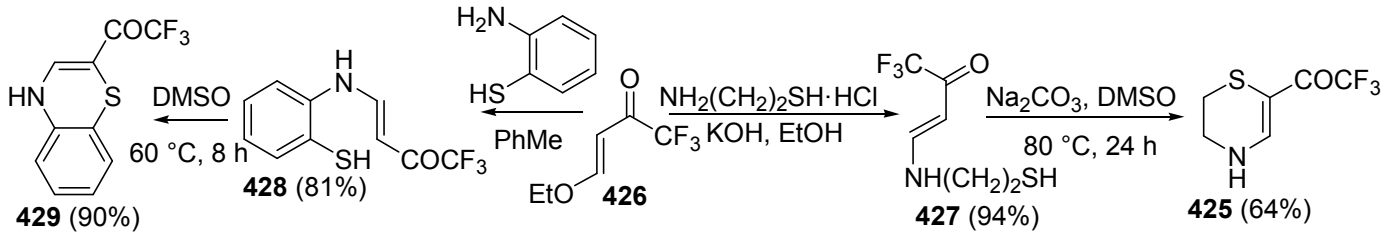
Scheme 126

The reaction of β,β-dibromo-CF_3-ketone **423** with thioacetamide and thiourea led regioselectively to the corresponding 1,3-thiazine derivatives **424** in good yields; nitrogen atom attacks carbonyl group of **423** (Scheme 127).[146]



Scheme 127

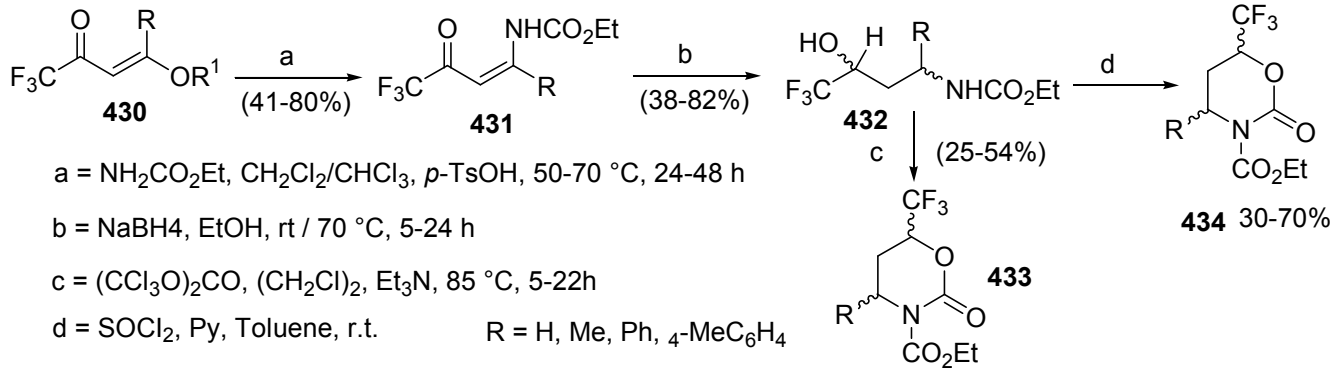
Dihydrothiazine **425** can be prepared using the reaction of ketone **426** with 2-aminoethanethiol with the subsequent oxidative cyclization of the adduct **427**.[111] The reaction with 2-aminothiophenol resulted in the formation of enaminoketone **428**. Heating of **428** in DMSO for 8 hours led to benzothiazine derivative **429** in high yield (Scheme 128).[111]



Scheme 128

4.6. Synthesis of 1,3-oxazines and 1,2,3-oxathiazines

The reaction of β-alkoxy-CF_3-enones **430** with ethyl carbamate leads to the formation of enamido-ketones **431**. Subsequent reduction into **432** and cyclization to oxazines **433** or **434** was performed. One of the evaluated compounds **433** exhibited significant activity against tested microorganism strains,[147] but no activity was observed for **434** (Scheme 129).[148]



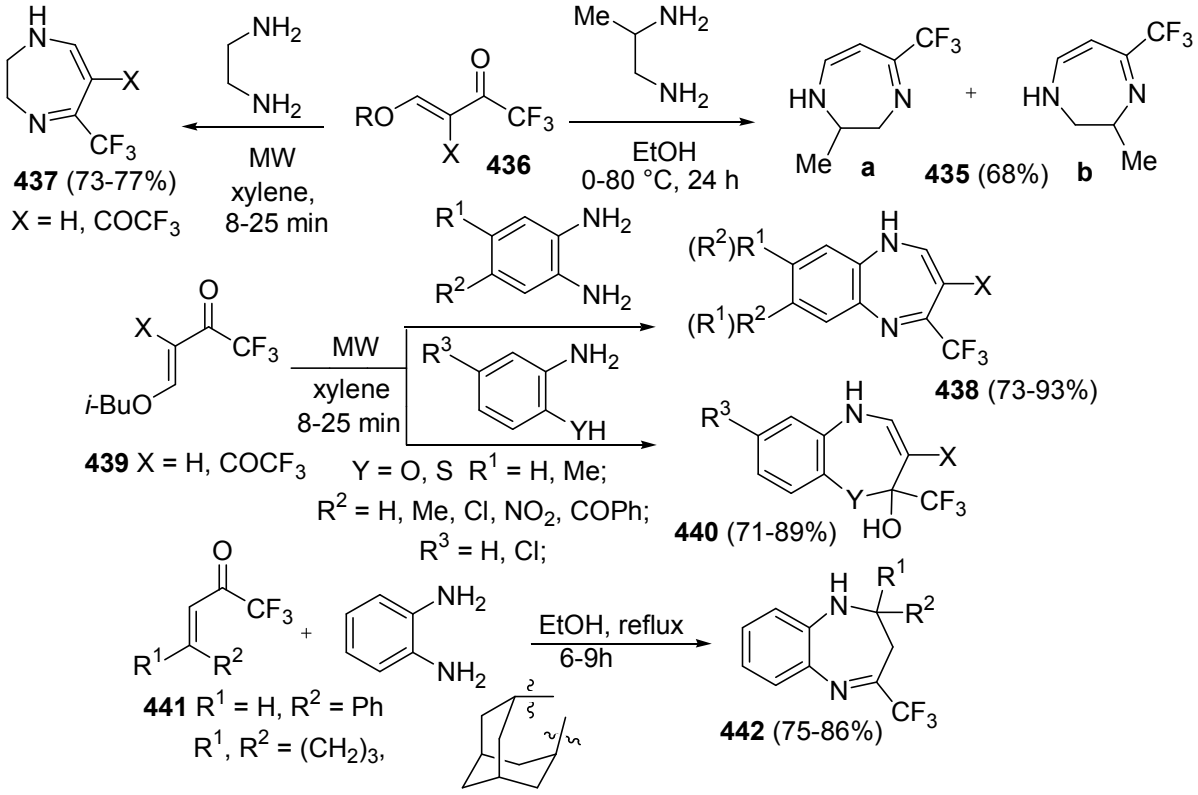
Scheme 129

5. Synthesis of seven-membered heterocycles

5.1. Synthesis of 1,4-diazepines (benzoanalogues) and 1,5-benzoxazepines

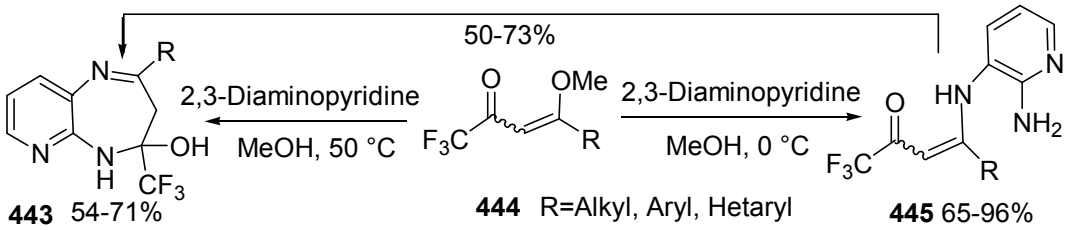
5-Trifluoromethyl-2,3-dihydro-1,4-diazepines **435** were prepared by the reaction of CF_3-enone **436** with 1,2-propylenediamine.[149] The reaction gave two isomeric products **435a,b** in a nearly 1:1 ratio. Similarly, 1,4-diazepines **437** were prepared in good yields with ethylenediamine using microwave irradiation, whereas carrying out the reaction in refluxing xylene resulted in a complicated mixture of

products.[150] Benzodiazepines have been considered the most extensively consumed psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity. The high yield preparation of benzodiazepines **438** by one-step reaction of **439** with *o*-phenylendiamines was shown.[151] The reactions with *o*-aminophenol or *o*-amino-thiophenol yielded 1,5-oxazepines or 1,5-thiazepines **440**, respectively. Good yields were attained by microwave (MW) radiation, whereas the reaction in xylene resulted in a complex mixture of products.[150] The reaction of trifluoromethyl enones **441** having no eliminating group in β-position with *o*-phenylenediamine afforded 2,3-dihydro-1,5-benzodiazepines **442** (Scheme 130).[152]



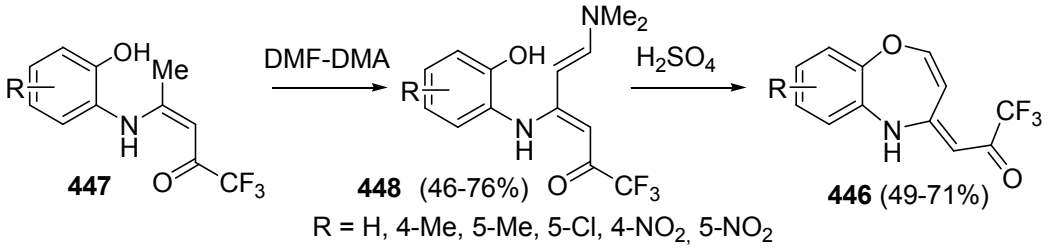
Scheme 130

The trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-b][1,4]diazepin-4-ols **443** were obtained by cyclo-condensation of 4-methoxy-CF_3-enones **444** with 2,3-diaminopyridine. The reactions proceeded regiospecifically in a moderate to good yields.[153] The compounds **443** were also obtained from intramolecular cyclization reaction of the respective trifluoroacetyl enamines **445** (Scheme 131).



Scheme 131

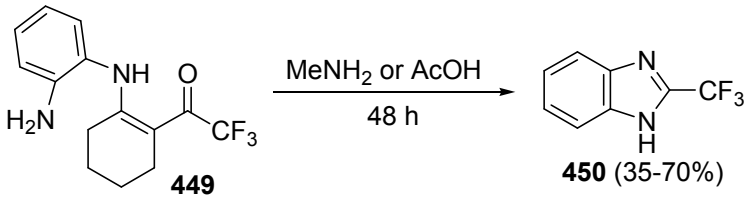
Useful approach to the preparation of new CF_3-containing 1,5-benzoxazepines **446** was presented. The reaction of enaminoketones **447** with DMF-DMA resulted in the corresponding dienamines **448**. Their cyclization with aqueous sulfuric acid occurred smoothly to give the fluorinated 1,5-benzoxazepines **446** (Scheme 132).[154]



Scheme 132

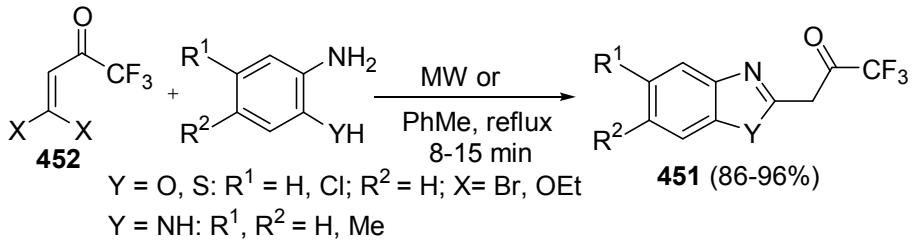
6. Synthesis of other condensed heterocycles

Treatment of enaminoketone **449** with methylamine or acetic acid led to the formation of 2-CF_3-benzimidazole **450**. It should be noted that destruction of skeleton of the starting ketone **449** took place (Scheme 133).[155]



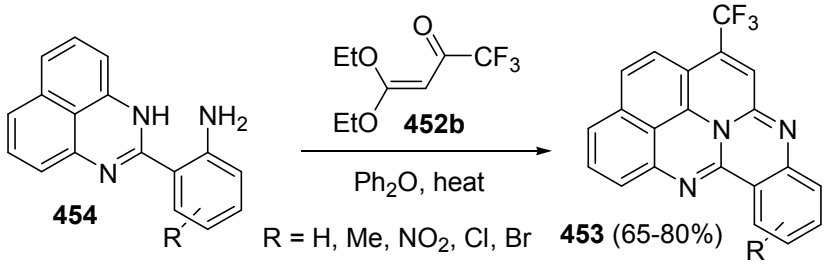
Scheme 133

The benzimidazolyl- and benzoxazolyl CF_3-ketones **451** were obtained in high yields in the reaction of *o*-phenylendiamine and *o*-aminophenol with β,β-dibromoketone **452a** and diethoxyketone **452b** (Scheme 134).[146,150]



Scheme 134

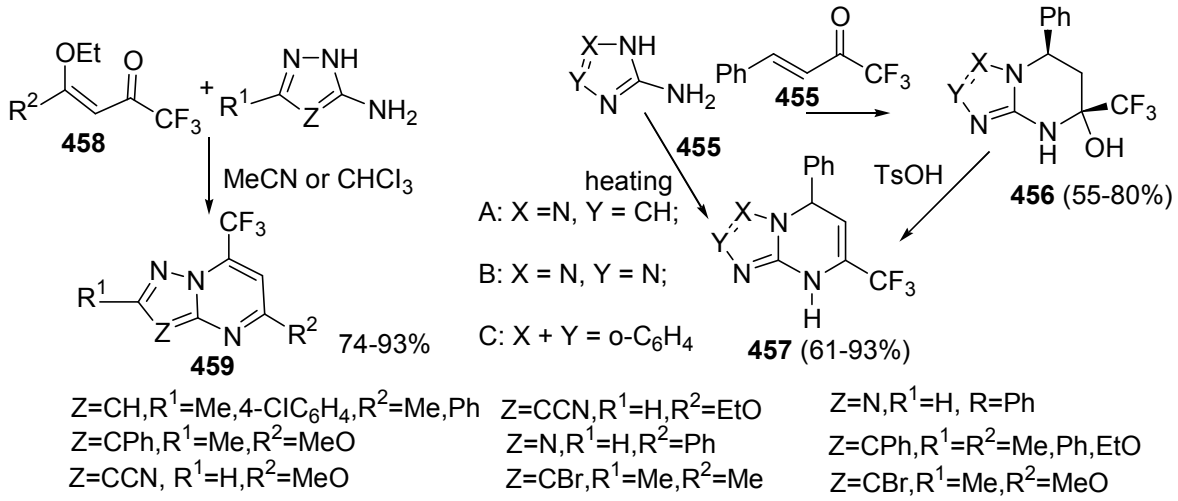
Ketone **452b** was applied for the synthesis of triazadibenzocrysenes **453**. These polycondensed heterocycles containing various substituents were prepared in good yields from 2-perimydinylamines **454** (Scheme 135).[156]



Scheme 135

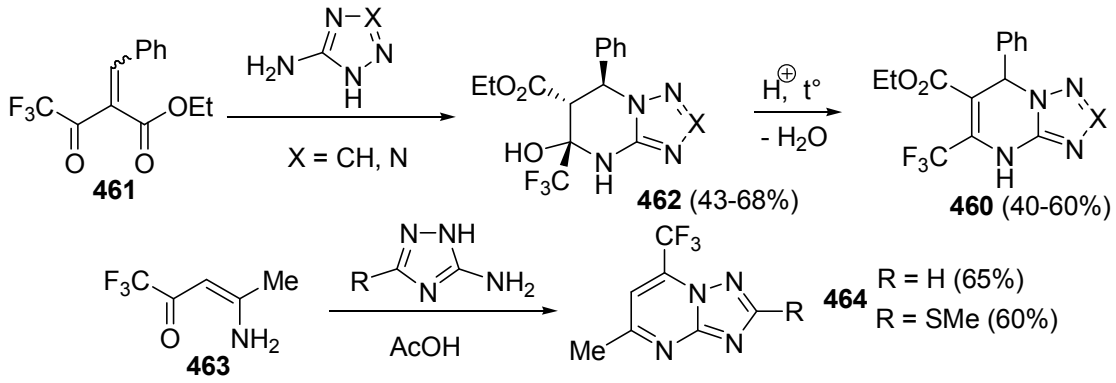
The reaction of CF_3-enone **455** with various aminoazoles was used for the preparation of dihydro-**457** and tetrahydroazolopyrimidines **456**. In the case of aminotriazole and aminotetrazole, the reaction proceeded 100% stereoselectively to form **457** having *cis*-orientation of CF_3- and Ph-groups. 2-Aminobenzimidazole

gave 3:1 mixture of **456** and **457**.[157] An effective and regioselective method for the synthesis of 7-CF_3-substituted azolopyrimidines **459** from CF_3-ketones **458** with 5(3)-aminoazoles was proposed (Scheme 136).[158]



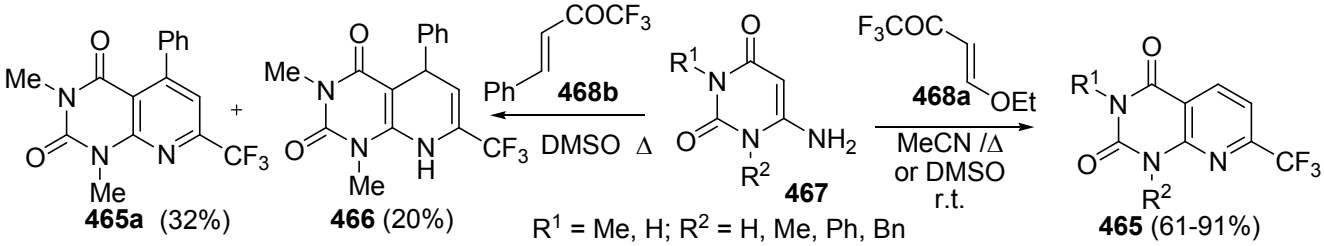
Scheme 136

The pyrimidine derivatives **460** have been prepared by using the reaction of **461** with aminotriazoles and aminotetrazoles. The intermediate tetrahydroderivatives **462** were obtained as single diastereomer. This fact was explained by high conformational energy of phenyl, ethoxycarbonyl and CF_3-groups.[159] The analogous reaction was investigated for β-enaminoketone **463**. The reaction led directly to condensed heterocyclic compounds **464**, bypassing the tetrahydro-intermediate. The reaction proceeded in 100% regioselective manner (Scheme 137).[160]



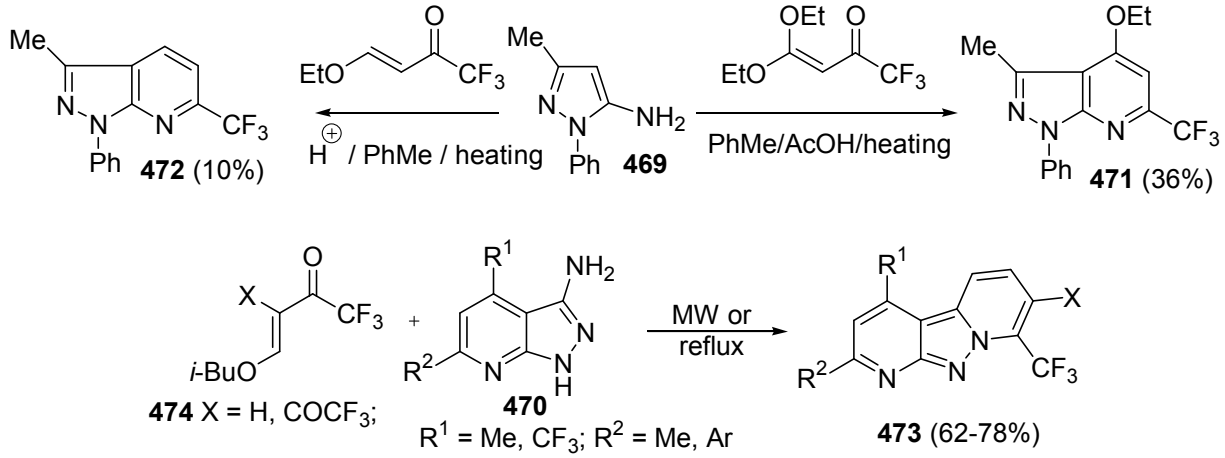
Scheme 137

The condensation of 6-aminouracil derivatives **467** and CF_3-enones **468** provided the preparation of CF_3-derivatives of pyrido[2,3-d]pyrimidine **465a,b** and dihydro-derivative **466** (Scheme 138).[161]



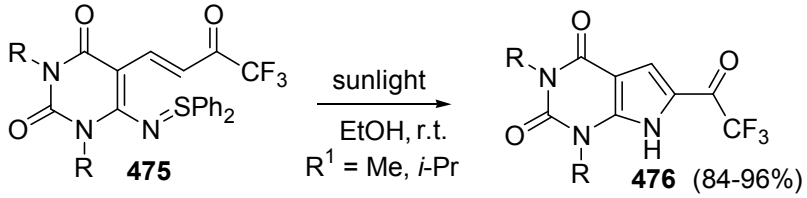
Scheme 138

In a similar manner, the reaction of 5-aminopyrazole **469** or aminopyrazolo[3,4-b]pyridine derivatives **470** gave rise to formation of condensed pyridine systems **471–473**. On exposure to microwave radiation, trifluoromethyl-substituted derivatives of pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine **473** were formed in good yields from ketones **474** (Scheme 139).[162]



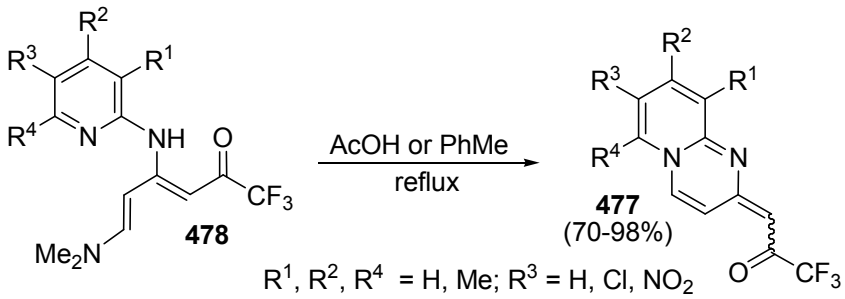
Scheme 139

Photoinduced cyclization of uracil-substituted ketones **475** having sulfimino-substituent was used for the preparation of pyrrolo[2,3-d]pyrimidine-2,4-diones **476** containing CF_3-group (Scheme 140).[163]



Scheme 140

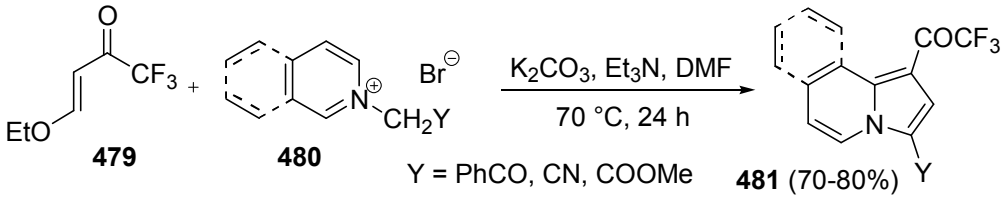
The corresponding pyrido[1,2-*a*]pyrimidine derivatives **477** were formed in good yields by heating the dienone **478** in toluene or acetic acid solution (Scheme 141).[77]



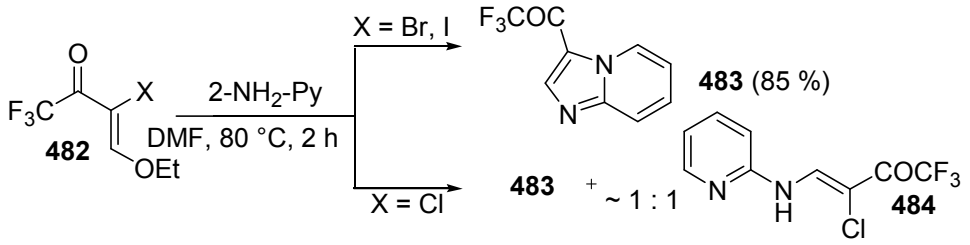
Scheme 141

It was shown that the reaction of ketone **479** with pyridinium (isoquinolinium) salts **480** in the presence of the base led to indolizines **481** due to the oxidation of intermediate dihydroderivatives with air oxygen. Noteworthy, the reaction proceeded with low yields or did not proceed at all for quinolinium salt (Scheme 142).[164]

The reaction of ketones **482** (X=Cl, Br, I) with 2-aminopyridine led to imidazopyridine **483**. In the case of the compound with X=Cl, the formation of mixture of two products was observed (Scheme 143).[165]

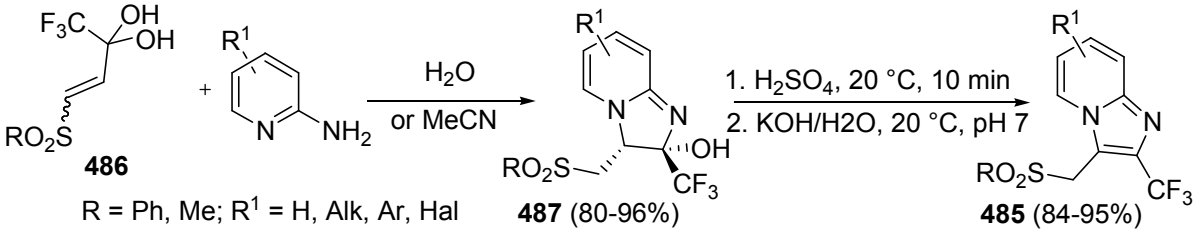


Scheme 142



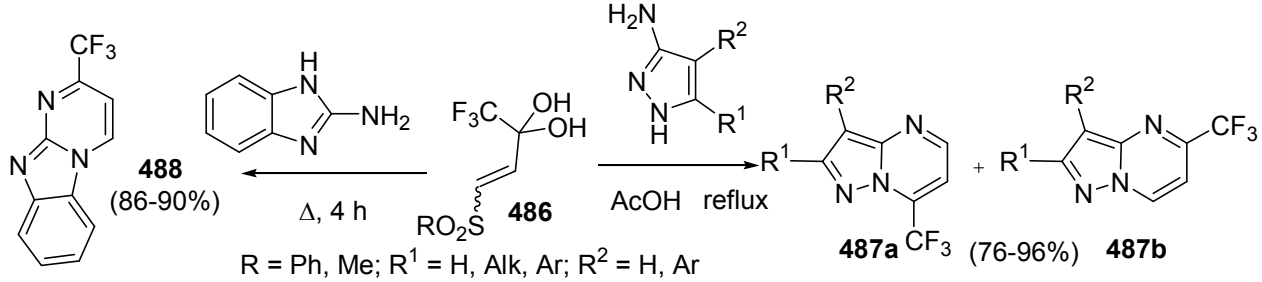
Scheme 143

The synthesis of imidazopyridines **485** using the reaction of β-sulfonyl-substituted trifluoromethyl ketones **486** with several 2-aminopyridines was described. The reaction proceeded regio- and stereoselectively (the intermediate dihydro-derivatives **487** were isolated as the single diastereomer). This reaction is the exception of the commonly observed direction for the reaction of **486** with amines because usually it leads to the products of sulfonyl-group substitution. It is noteworthy that the electrophilic attack is directed on C^3 carbon atom of **486**. Commonly C^4 carbon atom is the object of electrophilic attack for most of α,β-unsaturated trifluoromethylketones. Such regiochemistry was observed, probably due to the electron negative properties of sulfonyl group (Scheme 144).[166]



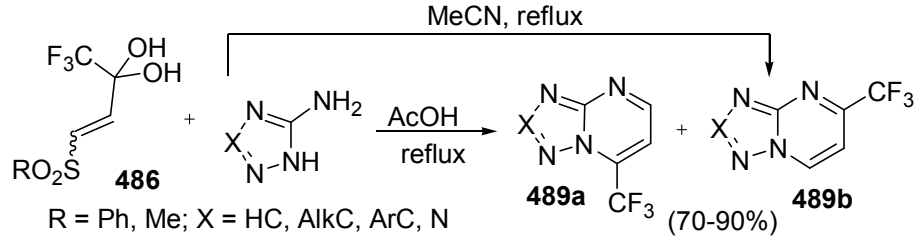
Scheme 144

The synthesis of various heterocyclic systems using the reaction of enones **486** with several diazoles was investigated. Reflux of **486** with 3-aminopyrazoles led to the formation of pyrazolopyrimidines **487a**. In several cases, the isomeric pyrazolopyrimidines **487b** were formed as the second product. Using aryl-substituted aminopyrazoles, the reaction proceeded stereoselectively forming **487a** as the only isomer. In the reaction of ketones **486** with 2-amino-1*H*-benzimidazole, the formation of imidazopyridines **488** was observed (Scheme 145).[167]



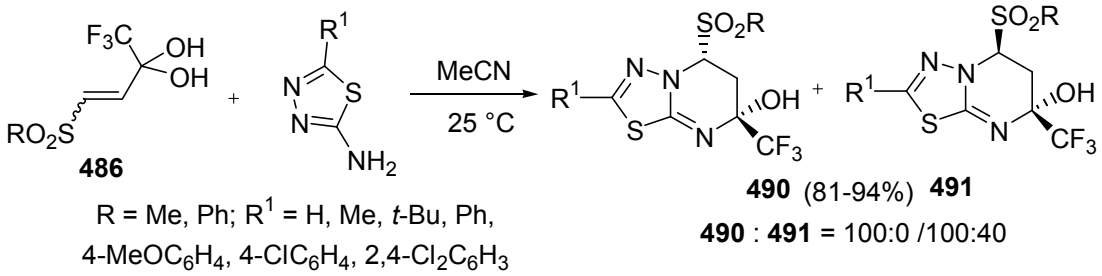
Scheme 145

The analogous regioselectivity was observed in the reaction of enones **486** with various 3-amino-1,2,4-triazoles and 5-aminotetrazoles. 7-Trifluoromethyl-substituted cycloadduct **489a** dominated in most cases. The method for the synthesis of triazolopyrimidines **489b** was elaborated. Such an inversion of selectivity was achieved by the reaction in acetonitrile (Scheme 146).[168]



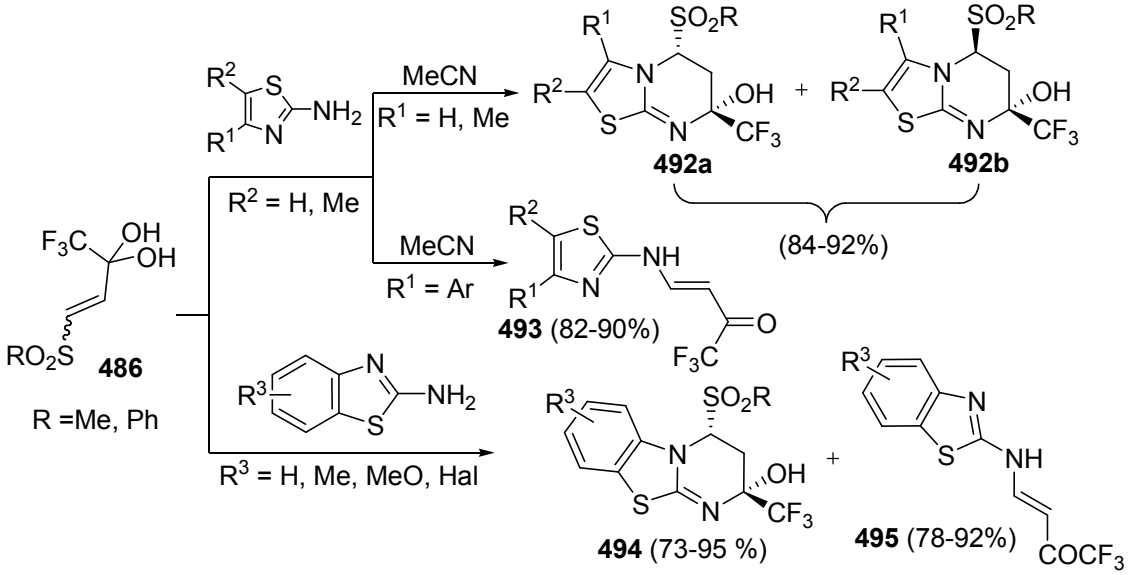
Scheme 146

The reaction of 2-amino-1,3,4-thiadiazoles with **486** closely related to the reaction described above was also investigated. The reaction proceeded in high yields and with high stereoselectivity although the products **490** and **491** contain two asymmetric centres. This is probably due to the formation of intra-molecular hydrogen bond between hydroxy- and the phenylsulfonyl group oxygen atom (Scheme 147).[169]



Scheme 147

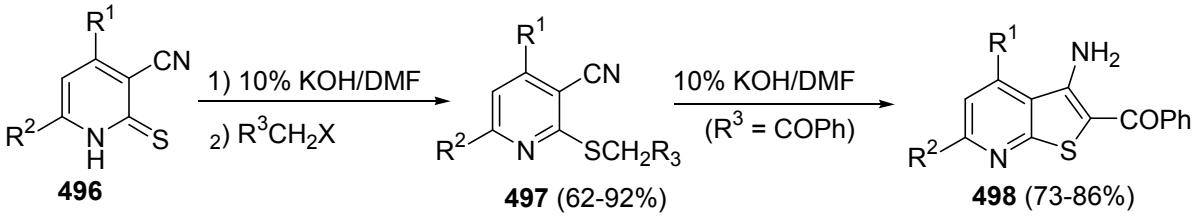
As the scaffold for the construction of condensed heterocyclic systems, several 2-aminothiazoles were used. The isomer **492a** dominated among the products of this reaction. The effort to use 2-amino-4-aryl-1,3-thiazoles failed because the reaction led to predominant formation of enaminoketones **493**, the products of sulfonyl-group nucleophilic substitution (Scheme 148).



Scheme 148

In the reaction of benzothiazoles, the heterocycles **494** were formed as single reaction product only in the case of compounds having no substituent in the position 4 otherwise the formation of enaminoketone **495** was observed. Furthermore, the cyclization with 2-aminobenzothiazoles proceeded regio- and stereoselectively (Scheme 148).[170]

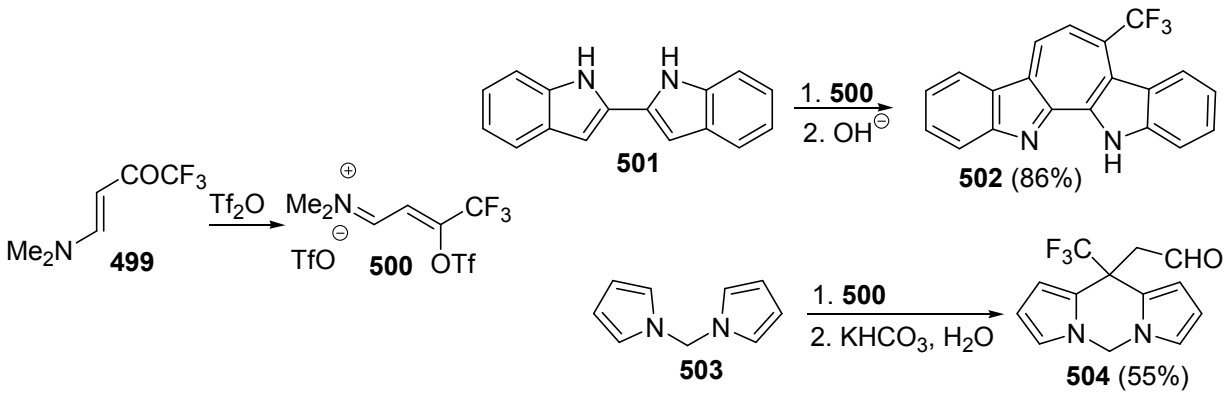
The alkylation of pyridinethiones **496** with methyl iodide and ω-bromoacetophenone was studied.[87] The corresponding methylthio- and phenacylthio-derivatives of nicotinonitrile **497** were obtained in good yields. These compounds **497** were also used for heterocyclization into the corresponding benzoylthieno [2,3-b]pyridines **498** treating **497** with potassium hydroxide in DMF solution (Scheme 149).[171]



R^1, R^2 = Me or CF_3 ; R^3 = H, X = I; R^3 = COPh, CONHPh, X = Cl, Br

Scheme 149

The trifluoromethyl enone **499** can be applied for the preparation of electrophilic reagent **500**, the vinylogous of Vilsmeier-type reagent. The complex **500** can be used for the different purposes. For example, the reaction of 2,2'-*bis*-indolyl **501** with **500** led to the formation of pentacyclic compound **502**. The reaction of *N,N'*-dipyrylmethane **503** with **500** leads to the formation of aldehyde **504** (Scheme 150).[172]



Scheme 150

7. Conclusion

Summarizing the facts given in the review, one might say that α,β-unsaturated trifluoromethylketones exhibit a very high synthetic potential as molecular building blocks containing trifluoromethyl group. α,β-Unsaturated trifluoromethylketones are widely used in modern organic synthesis, especially for the preparation of fluorinated heterocyclic compounds. However, the application of these very useful molecular building blocks is not restricted by this area.

The peculiarities of α,β-unsaturated trifluoromethylketones are their high reactivity towards nucleophiles, as well as high chemo, regio- and stereoselectivity in these reactions. The distinctive trait is the stability of *hem*-hydroxy-trifluoromethyl fragments, sometimes very resistant to the action of dehydrating agents.

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SYNTHESIS OF HETEROAROMATICS AND RELATED COMPOUNDS FROM β-LACTAMS

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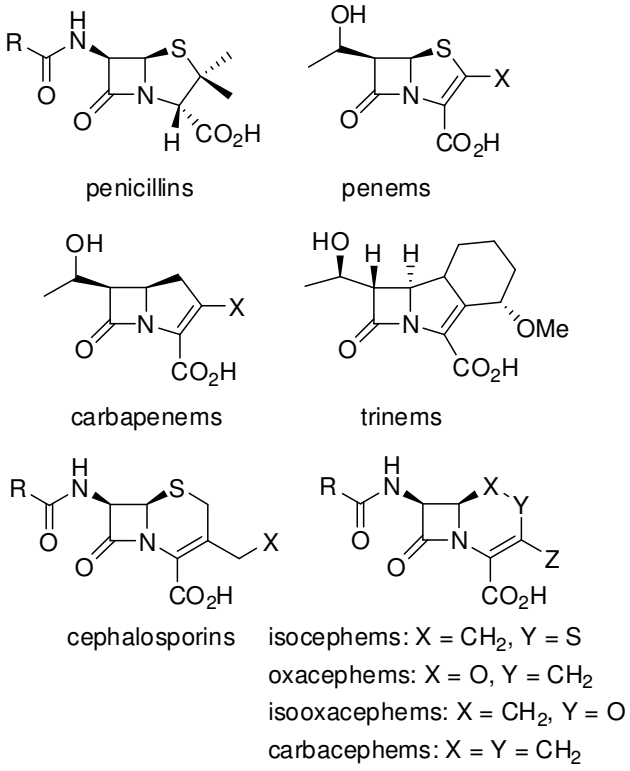
Abstract. *The β-lactam antibiotics have been the subject of much discussion and investigation, within both the scientific and public sectors. Recent discoveries focused other biological properties for these compounds apart from their antibacterial activity. In addition, research efforts on β-lactam chemistry have been provided by the introduction of the β-lactam synthon method, according to which 2-azetidinones can be employed as useful intermediates in organic synthesis. 2-Azetidinones possess potential as building blocks in the preparation of heteroaromatic compounds. Although the development of strategies for the synthesis of aromatic heterocyles utilizing β-lactam is still scarce, the diverse applications described so far emphasize their utility. In the present article, we focus on the current status of the application of β-lactams in the preparation of heteroaromatics and related compounds.*

Contents

1. Introduction

Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation, within both the scientific and public sectors.[1] The primary biological targets of the β-lactam antibacterial drugs are the penicillin binding proteins, a group of transpeptidases anchored within the bacterial cellular membrane which mediate the final step of cell wall biosynthesis. In a key biochemical step, the D-alanine-D-alanine terminus of a peptidoglycan strand is enzymatically cleaved by a transpeptidase and joined to another peptidoglycan residue within the bacterial cell wall. β-Lactam antibiotics possess the

unusual ability to interrupt this crucial cross-linking event by acylating the catalytic serine unit within the enzyme active site, resulting in bacteria having weakened or poorly formed cell walls. In this sense, ESI-MS and NMR studies have shown that the antibacterial properties of the β-lactam antibiotics arise from an acylation process in which the N1–C2 bond of the four-membered 2-azetidinone ring is opened.[2] Over the years, numerous penicillin derivatives have been prepared and examined for antibacterial activity.[3] Aditionally, a variety of new β-lactam-containing ring systems isolated from natural sources or from synthetic laboratories have been reported, including the penems, carbapenems, trinems, cephalosporins, isocephems, oxacephems, isooxacephems and carbacephems (Scheme 1).



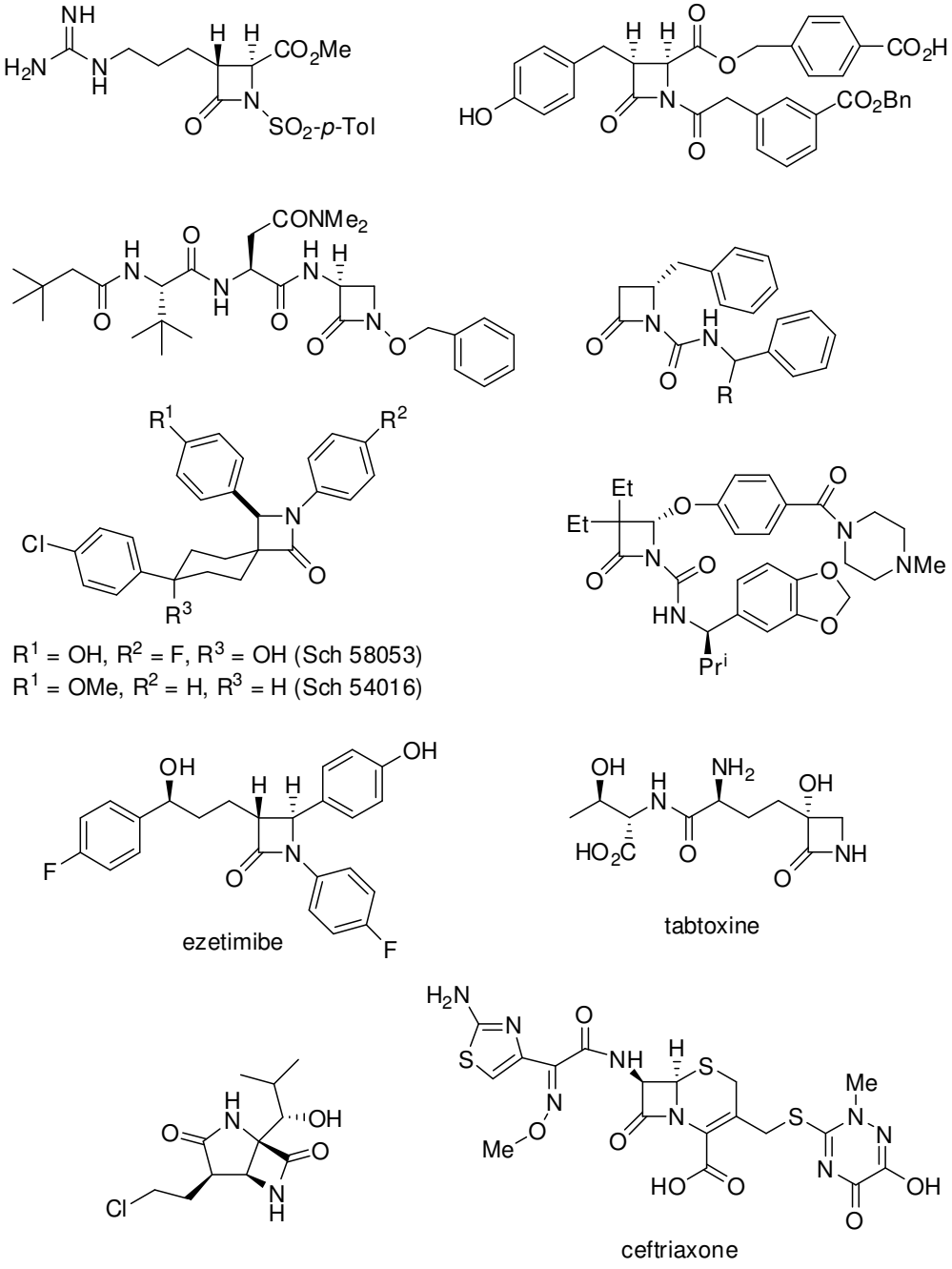
Scheme 1

Nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition[4] to gene activation are reported.[5] Some of the more notable advances in enzyme inhibition concern the development of mechanism-based serine protease inhibitors of elastase, cytomegalovirus protease, thrombin, prostate specific antigen and cell metastasis and as inhibitors of acyl-CoA cholesterol acyl transferase (Scheme 2). For example, in addition of its antibiotic activity, it has been reported that ceftriaxone acts to modulate the expression of glutamate neurotransmitter transporters *via* gene activation (Scheme 2).

In addition of previously described properties, the 2-azetidinone skeleton has been recognized as a useful building block in the synthesis of pharmaceutically useful products.[6] β-Lactams are versatile and powerful building blocks in organic synthesis due to their high reactivity as well as stereo- and regio-selectivity in the ring-opening reactions with nucleophiles. Opening of the β-lactam nucleus can occur through cleavage of any of the single bonds of the four-membered ring (Scheme 3).

This ring cleavage is enhanced by ring strain of the β-lactam system, leading to the construction of functionalized chiral cyclic and acyclic building blocks. Thus, 2-azetidinones possess potential as building

blocks in the preparation of heteroaromatic compounds. Although the development of strategies for the synthesis of aromatic heterocycles utilizing β-lactam is still scarce, the diverse applications described so far emphasize their utility. In the present article, we focus on the current status of the application of β-lactams in the preparation of heteroaromatics and related compounds.



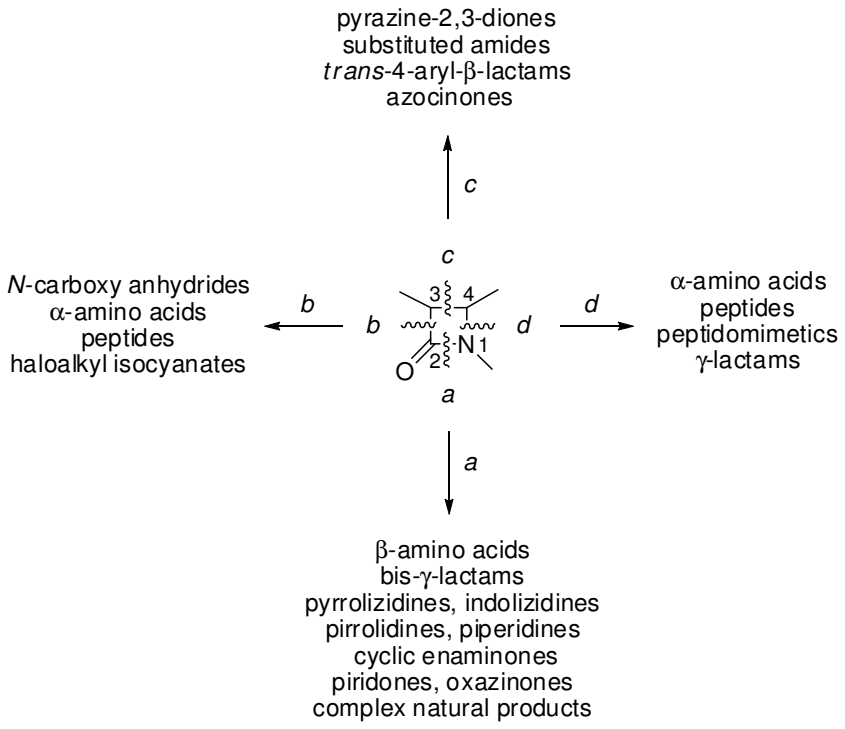
Scheme 2

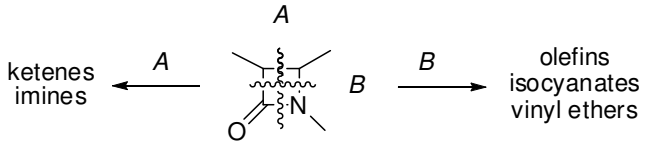
2. Preparation of heteroaromatics and related compounds

2.1. Preparation of quinazoline derivatives

The reaction of λ^5-phosphazenes (iminophosphoranes, phosphine imines) with carbonyl compounds affording the corresponding imination products is known as the aza-Wittig reaction. The intramolecular version of this reaction received considerable attention because of its high potential in heterocyclic synthesis.

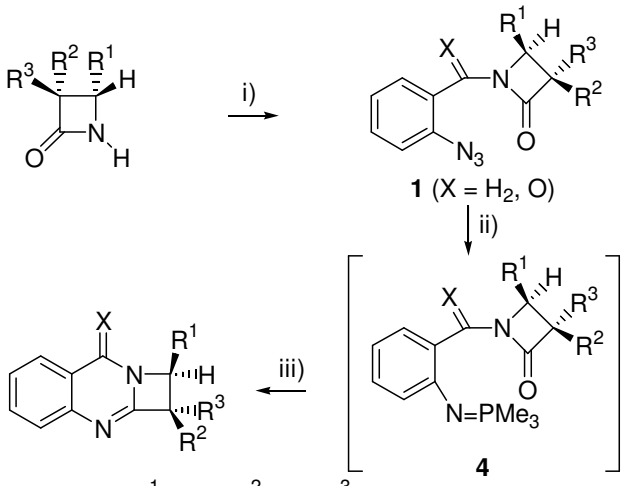
However, until recently there were no examples of successful aza-Wittig reactions involving the carbonyl group of a β-lactam ring. It has been described that the imination of the β-lactam carbonyl group by the aza-Wittig reaction is synthetically operative when carried out intramolecularly, by using *P,P,P*-tri-methyl-λ^5-phosphazenes as the imination reagents.[7]





Scheme 3

The conversion of compounds **1** to the corresponding azeto[2,1-b]quinazolines **2** (X=H_2) or quinazolin-8-ones **3** (X=O) was accomplished when a 1.0 M toluene solution of PMe_3 was used. The conversion of the azido group in **1** to the non isolable *N*-aryl-*P,P,P*-trimethyl-λ^5-phosphazenes **4** (nitrogen evolution was observed), followed by refluxing of the resulting toluene solution under nitrogen for 12–24 hours, yielded the fused four-membered heterocycles **2** and **3** (Scheme 4). Due to the extreme hydrolytic susceptibility of the trimethylphosphazene group, strict anhydrous conditions were required for the success of these reactions, the corresponding benzo-fused bicyclic amidines **2** and **3** being obtained in variable yields (40–90%). In some cases, the chromatographic purification of the reaction products caused the oxidation of azeto[2,1-b]quinazolines **2** (X=H_2) to quinazolin-8-ones **3** (X=O), which occasionally renders difficult the isolation of pure tricycles **2**. Attempts to carry out reactions similar to that summarized in Scheme 4, in an intermolecular way, required by the employment of several *N*-substituted (alkyl, acyl) β-lactam and the phosphazenes $PhCH_2N{=}PMe_3$ and $PhCON{=}PMe_3$ (generated *in situ* from the azides and PMe_3) failed. Other intramolecular attempts, starting from alkyl or aryl azides and leading to five-membered aza-rings resulted in a failure.



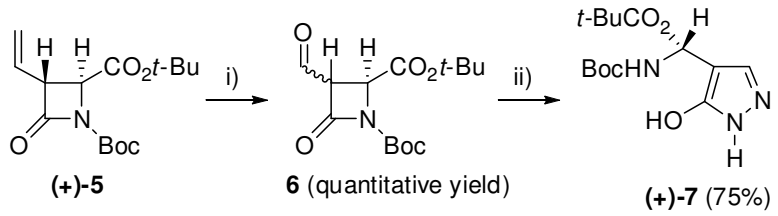
2a X = H_2, R^1 = Ph, R^2 = H, R^3 = H (60%)
2b X = H_2, R^1 = 4-$NO_2C_6H_4$, R^2 = Ph, R^3 = Ph (84%)
2c X = H_2, R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = Me (40%)
3a X = O, R^1 = H, R^2 = H, R^3 = H (90%)
3b X = O, R^1 = Ph, R^2 = H, R^3 = H (88%)
3c X = O, R^1 = AcO, R^2 = H, R^3 = H (50%)

Key: i) 2-$N_3C_6H_4CH_2I$, K_2CO_3, MeCN, reflux, 20 h or 2-$N_3C_6H_4COCl$, Et_3N, CH_2Cl_2, 0 ^oC, 1 h. ii) PMe_3, toluene, RT, 10 min. iii) Toluene, reflux, 12–24 h.

Scheme 4

2.2. Preparation of of pyrazoles

The vinyl-β-lactam urethane **5** by ozonolysis afforded aldehyde **6** in a *cis:trans* ratio 1:9, irrespective of the *cis:trans* ratio of the olefinic starting material. The aldehyde **6** was used directly in the next step without further purification due to its instability. When the aldehyde **6** was treated with hydrazine in methanol at room temperature (Scheme 5), the pyrazolylglycine **7** was obtained as a white solid in 75% yield.[8] The pyrazole formation can be explained by initial hydrazone generation followed by rearrangement to the five-membered ring. Reaction of the aldehyde **6** with hydroxylamine gave however no recognizable products.



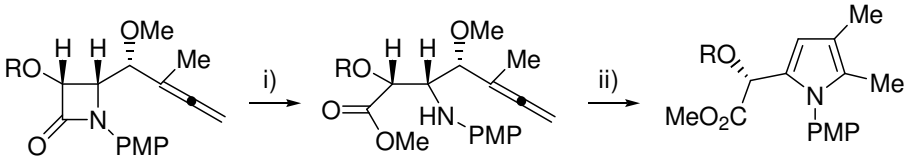
Key: i) O_3, CH_2Cl_2, –78 ^oC, 20 min, then Me_2S. ii) NH_2NH_2, methanol, RT, 11 h.

Scheme 5

2.3. Preparation of of pyrroles

Among the synthetic and naturally occurring heterocyclic structures, the pyrrole nucleus is the most prevalent, because of its remarkable pharmacological activities. Recently, it has been discovered the formation of highly functionalized pyrrole derivatives from allene-β-lactams.[9] Treatment of allene-β-lactams **8a** and **8b** with sodium methoxide at room temperature afforded β-allenamines **9a** and **9b** in excellent yields. After an extensive screening, $AgNO_3$ in the presence of K_2CO_3 was found to be effective in promoting this

aminocyclization in MeCN at room temperature, providing pyrroles **10a** and **10b** bearing a stereogenic centre in the side chain (Scheme 6). Compounds **10** can be considered as hybrid scaffolds due to the combination of the biological and synthetically relevant pyrrole and α-hydroxy acid cores. Although complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures, some decomposition was observed on sensitive pyrroles **10** during purification by flash chromatography, which may be responsible for the moderate isolated yields.



(+)-**8a** (+)-**8b**

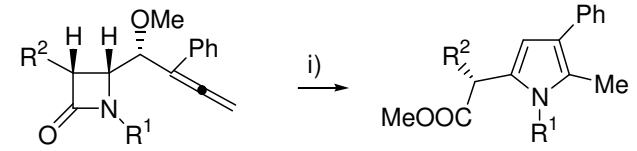
(–)-**9a** R = Me (93%) (–)-**9b** R = Ph (89%)

(–)-**10a** R = Me (47%) (–)-**10b** R = Ph (70%)

Key: i) NaOMe, MeOH, RT, 8 h. ii) 20 mol% $AgNO_3$, K_2CO_3, MeCN, RT, 12 h. PMP=4-$MeOC_6H_4$.

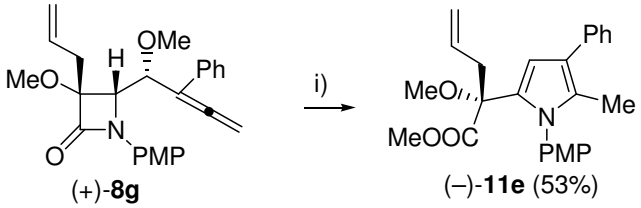
Scheme 6

The reaction of phenyl allenes **8c–h** with sodium methoxide at room temperature did not give the expected β-allenamines, yielding the corresponding 1,2,3,5-tetrasubstituted pyrroles **11** (Scheme 7).

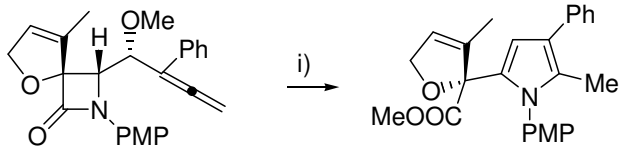


(+)-**8c** R^1 = PMP, R^2 = MeO
(+)-**8d** R^1 = PMP, R^2 = PhO
(–)-**8e** R^1 = allyl, R^2 = MeO
(±)-**8f** R^1 = PMP, R^2 = Me

(–)-**11a** (77%)
(–)-**11b** (50%)
(–)-**11c** (50%)
(±)-**11d** (54%)



(+)-**8g** (–)-**11e** (53%)

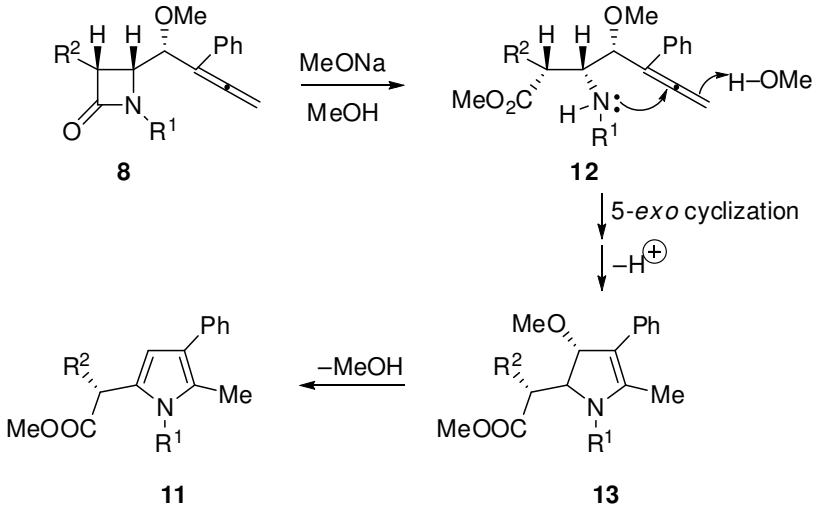


(–)-**8h** (–)-**11f** (57%)

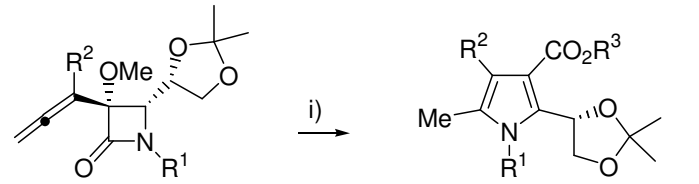
Key: i) MeONa, MeOH, RT, 8–96 h. PMP=4-$MeOC_6H_4$.

Scheme 7

From a mechanistic point of view, the preparation of heteroaromatic compounds **11** could be explained through a bond cleavage process at the four-membered lactam followed by allene cyclization, with concomitant aromatization.

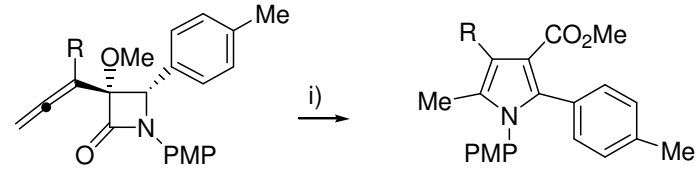


Scheme 8



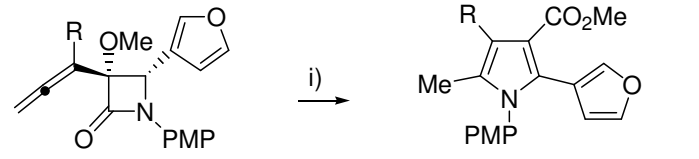
(+)-**14a** R^1 = PMP, R^2 = Me
(–)-**14b** R^1 = allyl, R^2 = Me
(+)-**14e** R^1 = PMP, R^2 = Ph
(+)-**14f** R^1 = allyl, R^2 = Ph

(+)-**15a** R^3 = Me (60%)
(–)-**15b** R^3 = H (54%)
(+)-**15c** R^3 = Me (49%)
(–)-**15d** R^3 = Me (53%)



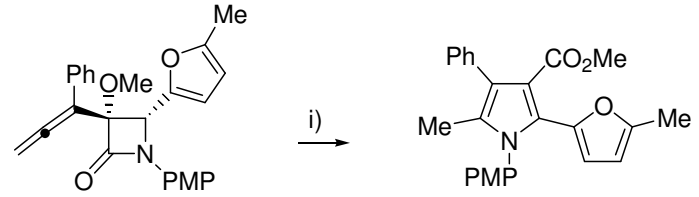
(±)-**14c** R = Me
(±)-**14g** R = Ph

15e R = Me (54%)
15f R = Ph (52%)



(±)-**14d** R = Me
(±)-**14h** R = Ph

15g R = Me (49%)
15h R = Ph (65%)



(±)-**14i**

15i (68%)

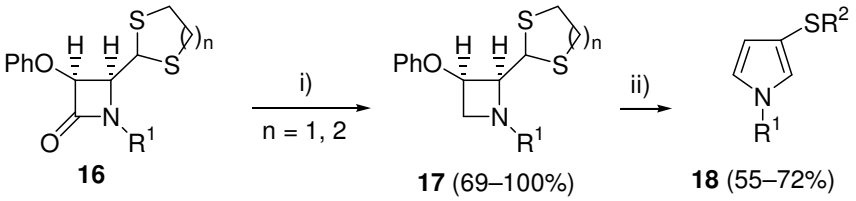
Key: i) NaOMe, MeOH, reflux, 2–54 h. PMP=4-$MeOC_6H_4$.

Scheme 9

The selective N1–C2 bond cleavage of the β-lactam nucleus in 2-azetidinone-tethered allenes **8** gave the non-isolable allenic-β-amino esters **12**, which, after a totally regioselective cyclization onto the central carbon atom of the neighbouring allene, under the reaction conditions followed by aromatization of the pyrrolines **13**, yielded the pyrroles **11** (Scheme 8). The pyrrole formation must be driven by relief of the strain associated with the four-membered ring, on forming a more stable five-membered ring.

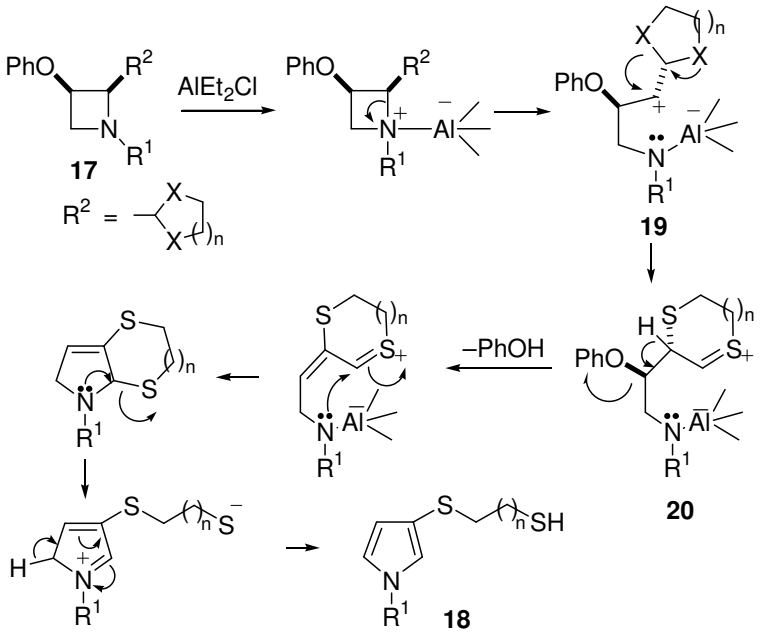
The influence of the position of the allene moiety at the β-lactam ring for the one-pot synthesis of the pyrrole nucleus was investigated by stirring methyl and phenyl quaternary α-allenol derivatives **14** for 48 hours in a mixture of NaOMe in MeOH at room temperature. After workup, the starting materials were recovered. Only after heating at reflux temperature the β-lactam α-allenic ethers **14a–i** reacted to form the corresponding heterocycles. New pentasubstituted pyrroles **15a–i** were obtained in fair yields by means of our one-pot procedure, without the concomitant formation of any regioisomer (Scheme 9). Structural features, which are often associated with pronounced physiological activities of pyrroles, are the presence of hydroxymethyl functionalities or aryl moieties at the 2-position.[10,11] Interestingly, compounds **15a–d** are derivatives of 2-(hydroxyalkyl)pyrroles, while compounds **15e–i** are 2-arylpyrroles.

A three-step preparation of pyrroles from 4-oxoazetidine-2-carbaldehydes has been achieved.[12] The starting 4-formyl-β-lactams were converted by standard chemistry to acetal-β-lactams **16**, which were reduced to the corresponding azetidines **17**. Saturated azaheterocycles **17** underwent rearrangement reactions promoted by diethylaluminum chloride to yield pyrroles **18** (Scheme 10).



Key: i) AlH_2Cl, Et_2O, reflux. ii) $AlEt_2Cl$, CH_2Cl_2, RT.

Scheme 10

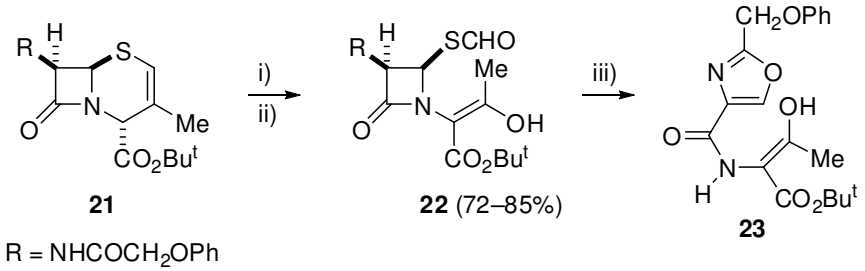


Scheme 11

Formation of pyrroles **18** can be rationalized through initial coordination of the electron lone pair at nitrogen to $AlEt_2Cl$. This coordination should promote the C2–N1 bond cleavage of the azetidine nucleus to form a zwitterion **19**. The acetal moiety promotes the conversion of this intermediate to a new zwitterion **20**, which, after phenol elimination, is trapped intramolecularly by the nitrogen atom, evolving to yield pyrroles **18** (Scheme 11).

2.4. Preparation of of oxazoles

The ozonolysis of Δ^2-cephem derivative **21** to yield functionalized 4-(formyl)thio-β-lactam **22** has been described.[13] However, compound **22** was stable for only a few days when stored at 5 °C under a nitrogen atmosphere and the oxazole derivative **23** was the only detectable degradation product (Scheme 12). An unusual nucleophilic ring opening of the 2-azetidinone nucleus and the displacement of the whole (formyl)thio moiety may be important steps in the formation of **23**.

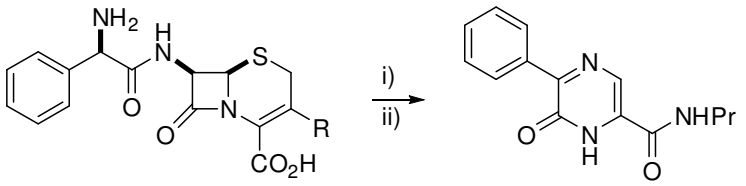


Key: i) O_3, CH_2Cl_2. ii) Me_2S. iii) 5 °C.

Scheme 12

2.5. Preparation of pyrazinone, pyridazinone and pyrimidinone derivatives

Cephalosporins with an α-amino group on the 7-β-acyl substituent, cefaclor **24** and cephalexine **25** have been aminolyzed and the initial, unstable intermediates have been shown to degrade finally affording a substituted pyrazinone derivative **26**, albeit in low isolated yields (Scheme 13).[14]

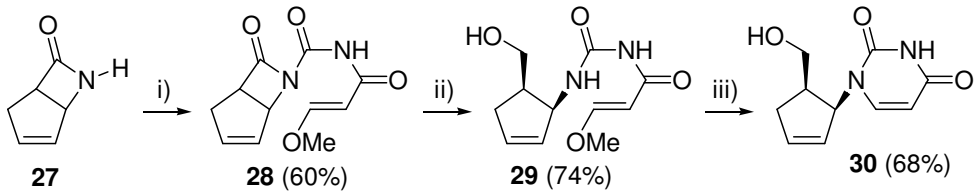


Key: i) $PrNH_2$. ii) pH=7.4.

Scheme 13

The synthesis of a 1,2-disubstituted carbonucleoside analogue containing a pyrimidine ring has been accomplished starting from the bicyclic β-lactam **27**, which was obtained in 46% yield by a [2+2] cycloaddition between cyclopentadiene and chlorosulfonyl isocyanate. The uracil derivative was prepared following the synthetic route outlined in Scheme 14, which involves the reductive C–N bond cleavage of the four-membered ring as the key step.[15] Initial reaction of 2-azetidinone **27** with 3-methoxy-acryloyl isocyanate in anhydrous benzene afforded the corresponding carbamoyl derivative **28**. Reduction of

compound **28** with an excess of $NaBH_4$ in methanol gave the corresponding acyclic ureide **29** with *cis* stereochemistry and subsequent acidic ring closure afforded the desired uracil derivative **30**.

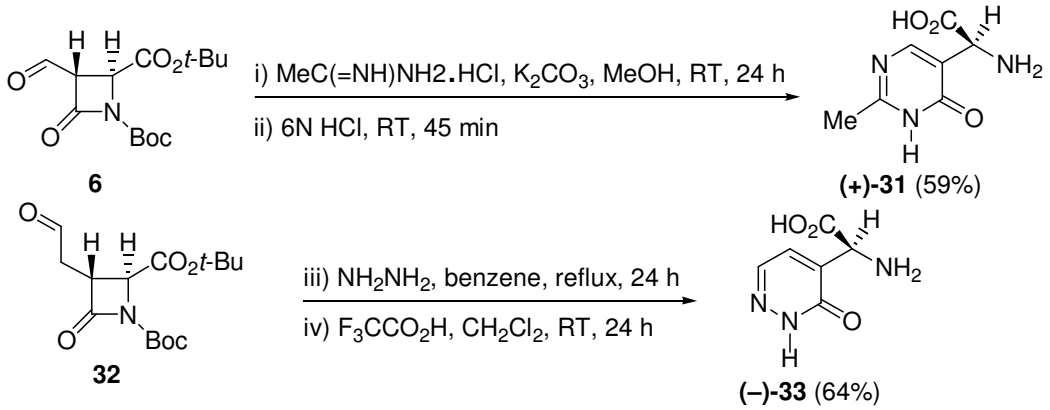


27 **28** (60%) **29** (74%) **30** (68%)

Key: i) MeOCH=CHCONCO, benzene, 60 °C, 3 h. ii) $NaBH_4$, MeOH, RT, 20 min. iii) aq. H_2SO_4 (2M), reflux.

Scheme 14

When the aldehyde **6** was reacted at room temperature with acetamidine hydrochloride in methanol containing potassium carbonate, the corresponding pyrimidinone was obtained in 61% yield. Further hydrolysis in 6N aq. HCl gave the hydrochloride of the amino acid **31** in 97% yield (Scheme 15).[8] The homologous aldehyde **32**, after treatment with four equivalents of hydrazine hydrate in refluxing benzene, gave as the sole product in 64% yield the Boc-protected pyridazine, which, after hydrolysis with trifluoroacetic acid in dichloromethane, afforded the trifluoroacetate of the amino acid **33** in nearly quantitative yield (Scheme 15).[8]



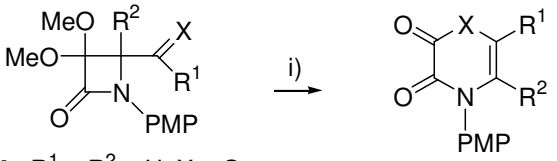
6 **(+)-31** (59%)

32 **(–)-33** (64%)

Scheme 15

The tandem C3–C4 bond cleavage-carbocationic rearrangement of 4-acyl- or 4-imidoyl-3,3-dimethoxy-2-azetidinones **34** and **35** promoted by tin(II) chloride has been documented as an entry to dihydro-1,4-oxazines or pyrazine-2,3-diones derivatives **36** and **37** (Scheme 16).[16] 4-Acyl-β-lactams **34** were reacted with different protic and Lewis acids. The best results were obtained by working with an equimolecular amount of $SnCl_2 \cdot 2H_2O$ in dichloromethane at room temperature. Disappearance of the starting material occurred after a few hours. Standard workup gave **36** which was then purified by either crystallization or column chromatography. A control experiment demonstrated that rearrangement to the six-membered ring occurs prior to hydrolysis of the ketal group. When 4-imidoyl-3,3-dimethoxy-2-azetidinones **35** were reacted with $SnCl_2 \cdot 2H_2O$, a clean almost quantitative conversion to reaction products **37** was obtained. These results confirm that imidoyl groups attached to the C4 position of the β-lactam ring are also suitable to give the C3–C4 fragmentation-rearrangement process. Clearly, in these cases, the rearrangement competes favourably with the hydrolysis of the C=N group, which is not the case when aqueous hydrochloric acid is used. The

above rearrangements also took place in the presence of protic acids (H_2SO_4 or HCl). However, yields were erratic and mixtures of the different reaction products were usually obtained.

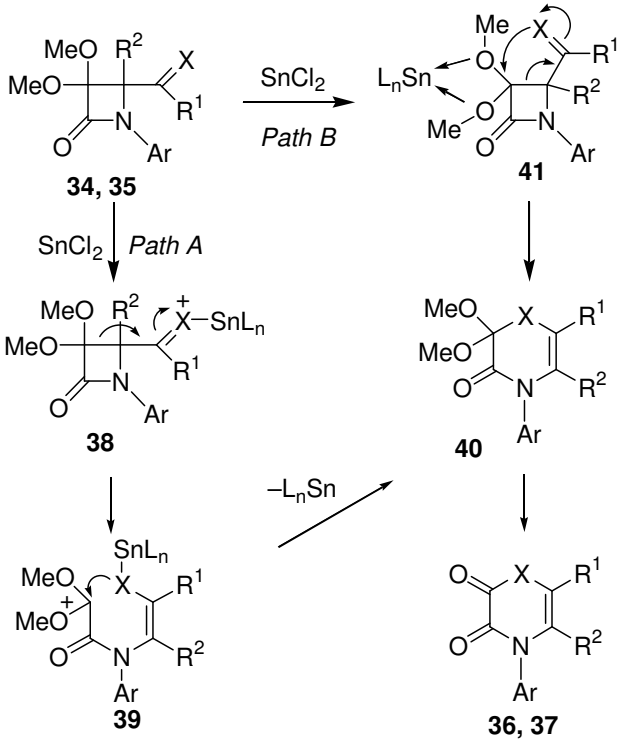


34a $R^1 = R^2$ = H, X = O — **36a** (75%)
34b $R^1 = R^2$ = Me, X = O — **36b** (88%)
34c R^1 = Ph, R^2 = H, X = O — **36c** (95%)
35a $R^1 = R^2$ = H, X = NPMP — **37a** (95%)
35b $R^1 = R^2$ = Me, X = NPMP — **37b** (99%)

Key: i) $SnCl_2 \cdot 2H_2O$, CH_2Cl_2, RT, 15 min–20 h.

Scheme 16

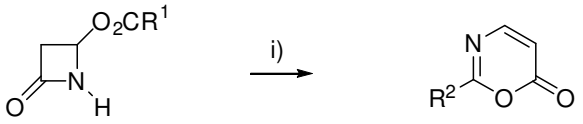
It seems clear that both imidoyl and carbonyl groups in compounds **34** and **35** are prone to promote the rearrangement to **36** and **37**. Reaction pathways in Scheme 17 may account for the observed reaction products. Both mechanistic rationalizations rest in the coordination of the tin with the starting material as the promoter of the rearrangement. Path A involves coordination of tin to the group at C4 to yield intermediate **38** which evolves by C3–C4 bond breakage, due to the enhanced reactivity of the double bond and the ability of the ketal to stabilize the emerging carbocation at C3 to give **39**. Annelation of intermediate **39** renders compounds **40**, which are further hydrolyzed giving the final products **36** and **37** upon treatment with tin(II) chloride. Alternatively, compounds **34** and **35** upon dicoordination at the ketal functionality to yield **41**, may transform into compounds **40** through a concerted or stepwise six electron rearrangement.



Scheme 17

2.6. Preparation of oxazine derivatives

A new route to 1,3-oxazin-6-ones involving a N1–C2 bond β-lactam cleavage and an electrocyclic ring opening has been described.[17] *N*-Unsubstituted-4-acyloxy-β-lactams **42** were converted into 2-substituted-1,3-oxazin-6-ones **43** in the presence of acid chlorides by the action of bases. A careful exploration of the reaction conditions (organic base, solvent, temperature) for the conversion of **42** to **43** revealed DBU (5 equivalents) as the base of choice and CH_2Cl_2, 25 °C as the optimal reaction conditions for obtaining the best yields of **43** (Scheme 18).

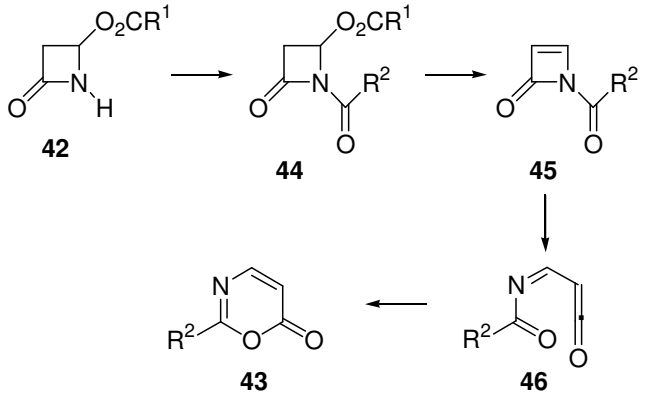


42a R^1 = Me, R^2 = Ph	**43a** (69%)
42b R^1 = Me, R^2 = 4-ClC_6H_4	**43b** (58%)
42c R^1 = Ph, R^2 = 2-furyl	**43c** (44%)
42d R^1 = Ph, R^2 = (E)-C_6H_5-CH=CH	**43d** (50%)
42e R^1 = Ph, R^2 = *t*-Bu	**43e** (76%)
42f R^1 = Ph, R^2 = Et	**43f** (40%)
42g R^1 = Ph, R^2 = 4-BrC_6H_4	**43g** (53%)

Key: i) R^2COCl (2 equiv.), DBU (5 equiv.), CH_2Cl_2, 25 °C, 2–5 h.

Scheme 18

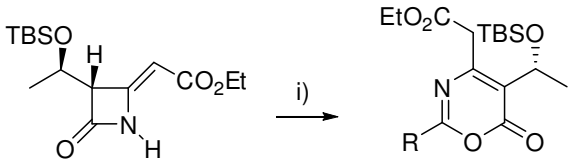
A reasonable mechanistic explanation is the following: the formation of the corresponding *N*-acyl-4-acyloxy-β-lactams **44** first takes place, next the organic base promotes the β-elimination of 1 equivalent of carboxylic acid R^1CO_2H across the C3–C4 bond of the β-lactam ring, giving rise to the highly strained *N*-acylazetinone **45**, which was not stable enough to survive in the reaction conditions and rapidly experienced a retro-[*4-exo-dig*] cyclization to the *N*-acylimidoylketene **46**, instead of a thermal conrotatory electrocyclic ring opening. The fourth step, which in turn is the transformation into the final 1,3-oxazin-6-one **43**, corresponds to another pseudopericyclic reaction instead of a six-electron disrotatory electrocyclization (Scheme 19).[18]



Scheme 19

In a tentative acylation reaction of the β-lactam nitrogen of 4-alkylidene-β-lactams **47**, it was found a completely different behaviour of *E* and *Z* isomers.[19] *N*-Acetylation of the *E*-isomer with acetic anhydride

and solid K_2CO_3 in acetone was rapid, whereas the *Z* isomer reacted sluggishly rearranging to the corresponding 1,3-oxazin-6-one **48** (Scheme 20). Compound *Z*-**47**, in fact, requires at least 2 equivalents of K_2CO_3 for satisfactory yields of 1,3-oxazin-6-ones **48**.

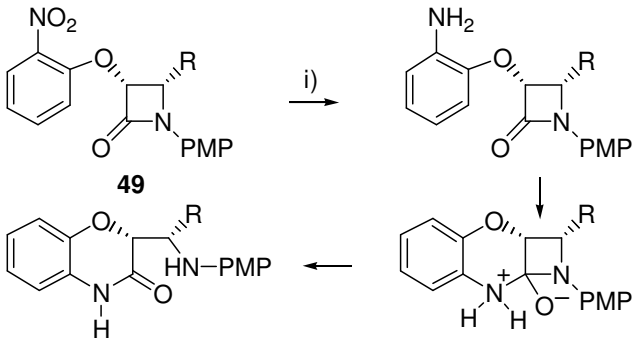


Z-**47a** R = Me — **48a** (77%)
Z-**47b** R = OBn — **48b** (54%)
Z-**47c** R = NHBn — **48c** (60%)
Z-**47d** R = Ph — **48d** (47%)

Key: i) Acylating reagent (1 equiv.), K_2CO_3 (2 equiv.), acetone, 16 h.

Scheme 20

An indium-induced reduction-rearrangement reaction of nitro-substituted β-lactams has been used for a facile synthesis of oxazines in aqueous ethanol.[20] Treatment of the nitro-β-lactams **49** with indium-ammonium chloride in aqueous ethanol under reflux produced oxazines **50** in an excellent yield (Scheme 21). The reaction did not proceed in the absence of water. A mixture of alcohol and water was necessary for the success of the rearrangement reaction. Other metals, such as zinc and tin did not promote the ring cleavage reaction effectively, the oxazines being obtained in poor yields. The reduction of the aromatic nitro group to the amino group and its nucleophilic attack to the β-lactam carbonyl presumably are the steps involved in the rearrangement toward oxazines (Scheme 21). Because of the oxophilic nature of indium, coordination to the β-lactam carbonyl is possible and this may increase the vulnerability of a nucleophilic attack by the amino group.



50a R = Ph (80%)
(+)-50b R = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl (85%)

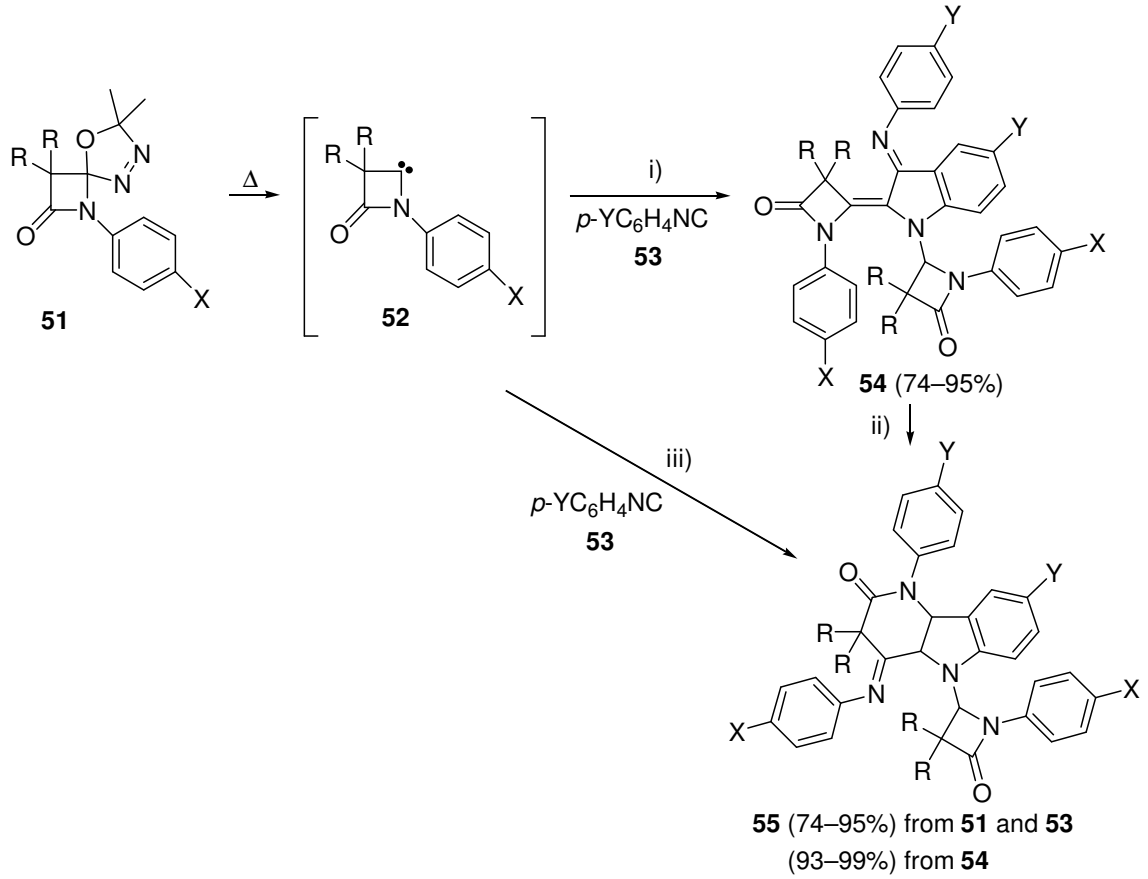
Key: i) In, EtOH-H_2O, NH_4Cl, reflux, 10 h.

Scheme 21

2.7. Preparation of δ-carboline derivatives

Carbolines and their derivatives comprise an important family of heterocyclic compounds owing to their unique biological properties. Some δ-carboline derivatives, for example, have shown antiplasmodial, antitrypanosomal, antimalarial and antineoplastic activities. It has been recently described that the reaction of

β-lactam carbenes with aryl isonitriles proceeded in a novel [2+2] fashion to give high yields of 2-azeti-dinonylidene indoles, which underwent an unprecedented rearrangement to furnish 4-arylimino-δ-carbolin-2-ones in almost quantitative yields.[21,22] β-Lactam carbenes **52** are generated *in situ* by thermolysis of spiro[β-lactam-4,2'-oxadiazolines] **51** following Warkentin and Zoghbi's method. Since the optimal temperature for the generation of carbene **52** was around 100–110 °C, the reaction of **52a** (R=Me, X=H) with *p*-chlorophenyl isonitrile **53c** (Y=Cl) was initially carried out in refluxing 1,1,2-trichloroethane (bp 110–115 °C) for 6 hours. Surprisingly, the reaction gave a totally unexpected product, 4-arylimino-δ-carbolin-2-one **55a**, in 80% yield. Compound **55a** was apparently derived from a [2+2] addition reaction between **52a** and **53c**, although the construction of a δ-carboline ring from β-lactam species and aryl isonitriles remained a mystery. During the process of the reaction, it was noted that an orange compound was initially formed and then disappeared later. To isolate the intermediate, the reaction of **52a** with **53c** in trichloroethane was repeated but at a lower temperature (100 °C). After 12 hours, an orange product, 2-azeti-dinonylidene indole **54a**, was isolated in addition to the yellow δ-carbolin-2-one **55a**. The reaction was then optimized using different solvents. Interestingly, in all reactions carried out in toluene, 1,4-dioxane and propionitrile, indole **54a** was obtained as the sole product. However, in refluxing 1,1,2-trichloroethane, **54a** was converted completely into **55a** (Scheme 22). Both solvent and reaction temperatures governed the transformation of **54** to **55**. For example, although toluene and 1,1,2-trichloroethane have very similar boiling points, almost no product **55a** was observed in refluxing toluene, while **54a** was efficiently converted into **55a** in refluxing trichloroethane.



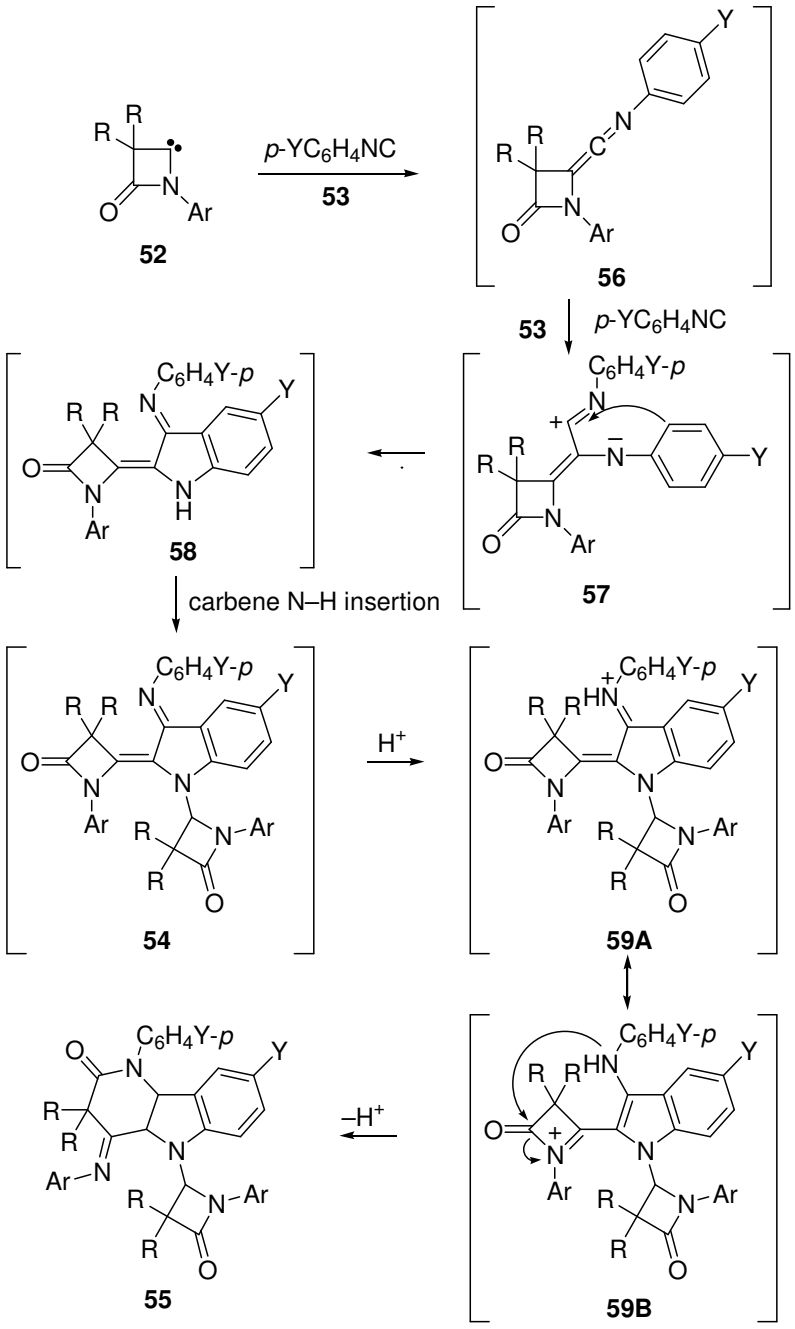
Key: i) Dioxane, reflux, 9–12 h. ii) $CHCl_2CH_2Cl$, reflux, 2–6 h; or dioxane, RT, 0.5 h.
iii) $CHCl_2CH_2Cl$, reflux, 6–8 h.

Scheme 22

On the other hand, in trichloroethane, the complete transformation of **54a** finished in 6 hours at 110–115 °C, while only half the amount of **54a** was transformed into **55a** within 12 hours at 100 °C. It is worth noting that, although arenes were not good solvents for the formation of product **55**, **54a** could also be converted into **55a** in xylene at elevated temperatures (140 °C) and in a prolonged reaction time (40 hours), indicating that high reaction temperatures can promote the conversion of **54** to **55**. The smooth and ready transformation of **54** into **55** in refluxing trichloroethane led the authors to propose that a trace amount of hydrogen chloride released from the solvent might accelerate the reaction. To validate this hypothesis, dry HCl gas was bubbled into the solution of 2-azetidinonylidene indole **54a** in 1,4-dioxane. Compound **54a** was forced to undergo transformation into δ-carbolinone **55a** in 93% yield in 30 minutes at room temperature. Taking all results aforementioned into consideration, it was concluded that the transformation of **54** to **55** was an acid catalyzed thermal rearrangement. To examine the scope of the reaction, β-lactam carbenes **52** bearing different substituents were employed to react with different aryl isonitriles **53** (Scheme 22). In refluxing 1,4-dioxane, all reactions produced indoles **54** in 74–95% yields, while 71–85% yields of δ-carbolinones **55** were obtained from the reaction in refluxing trichloroethane. The substituents on both starting materials have a negligible effect on the outcome of the reaction. δ-Carbolinones **5** were also prepared in almost quantitative yield by refluxing indoles **54** in trichloroethane.

The formation of 2-azetidinonylidene indole **54** can be best explained by the reaction pathway depicted in Scheme 23. The reaction was initiated by coupling of the carbene with isonitrile to form a ketenimine intermediate **56**. Nucleophilic addition of a second molecule of isonitrile to **56**, followed by intramolecular cyclization, led to the indole derivative **58**. Finally, N–H insertion of β-lactam carbene to **58** afforded product **54**. The rearrangement of indole **54** to δ-carbolinone **55** proceeded most probably through a novel acid catalyzed *N*-to-*N′* [1,5]-acyl migration. In the presence of an acid catalyst, indole **54** was protonated to **59A**, with its *N*-acyliminium resonance form **59B**. Intramolecular nucleophilic attack led to [1,5]-acyl migration of **59B** to form δ-carbolinone **55** (Scheme 23). Theoretically, nucleophilic attack of isonitrile to ketenimine **56** might take place at either face of the imine carbon and lead to the formation of both *Z*- and *E*-isomers of **54**. However, only the *Z*-isomer was detected. The structure of ketenimine intermediate **56a** optimized with the B3LYP/6-31G method (Gaussian 98) clearly shows that isonitrile can only attack on one face of the imine double bond of **56** and form the *Z*-configuration of the carbon-carbon double bond since the other face of the imine is hindered by the *N*-aryl group of the carbene moiety.

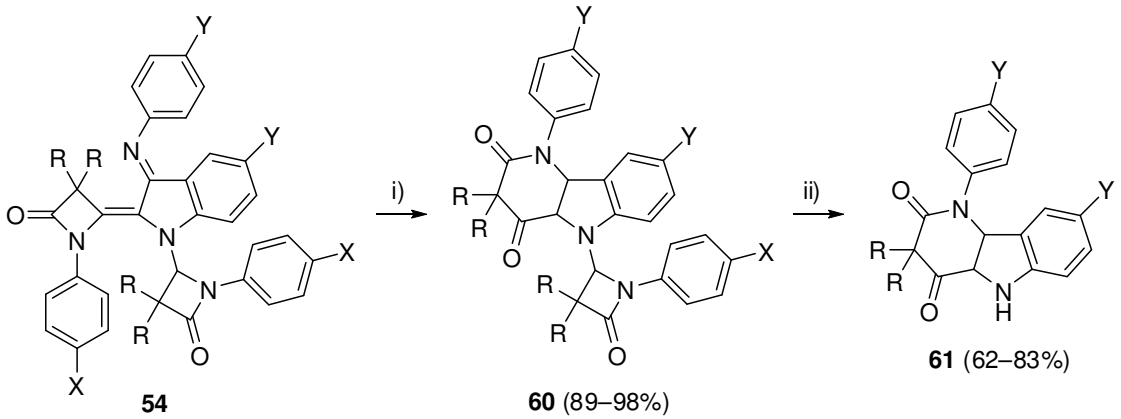
Upon the treatment of indole **54** with different acids including *p*-toluenesulfonic acid monohydrate, boron trifluoride and aqueous hydrochloride, two novel δ-carbolin-2,4-diones were obtained under different reaction conditions. When compound **54** was warmed with hydrated *p*-toluenesulfonic acid, boron trifluoride, or aqueous hydrochloride in trichloroethane or in dioxane for 0.5–1 hours, *N*-β-lactam-δ-carbolin-2,4-dione **60** was obtained in excellent yield. On the other hand, in the presence of 10 equivalents of hydrated *p*-toluenesulfonic acid, the *N*-unsubstituted δ-carbolin-2,4-dione **61** was obtained generally in good yield after a prolonged time (2–4 hours) (Scheme 24). Hydrochloric acid was not an efficient catalyst for the preparation of δ-carbolin-2,4-dione **61** because compound **60** did not undergo further hydrolysis to **61**, even in the presence of a large excess of hydrochloric acid (about 100 equivalents) for 6 hours. Transformation of indole **54** to δ-carbolin-2,4-diones **60** and **61** can be easily explained by isomerization of **54** to δ-carbolinone **55** followed by hydrolysis of **55** into **60** and then to **61**. Both δ-carbolin-2,4-diones **60** and **61** were found to be fluorescent.



Scheme 23

3. Conclusions

In addition of being the key structural motif of the β-lactam antibiotics and different compounds of medicinal interest, the 2-azetidinone skeleton has been recognized as a useful building block in the synthesis of pharmaceutically useful products. Opening of the β-lactam nucleus can occur through cleavage of any of the single bonds of the four-membered ring. This ring cleavage is enhanced by ring strain of the β-lactam system, leading to the construction of functionalized chiral cyclic and acyclic building blocks. Thus, 2-azetidinones possess potential as building blocks in the preparation of heteroaromatics compounds. Although the development of strategies for the synthesis of aromatic heterocyles utilizing β-lactam is still scarce, the diverse applications described so far emphasize their utility.



Key: i) TsOH, $CHCl_2CH_2Cl$, reflux, 0.5 h; or HCl (aq.), dioxane, reflux, 0.5–1 h.
ii) TsOH, $CHCl_2CH_2Cl$, reflux, 2 h.

Scheme 24

Acknowledgments

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STEREOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE PYRIDYL ALCOHOLS. PART II: PYRIDYL *TERT*-ALCOHOLS AND OTHER PYRIDINE ALCOHOLS

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Abstract. *The stereoselective synthesis of optically active pyridyl alcohols with a tert-carbinol chiral centre bound to a pyridine ring and the synthesis of some examples of pyridyl tert-alcohols without this topological element are described. Other kinds of these chiral non-racemic compounds such as pyridyl β-carbinols and pyridines bound to a phenolic ring are illustrated too.*

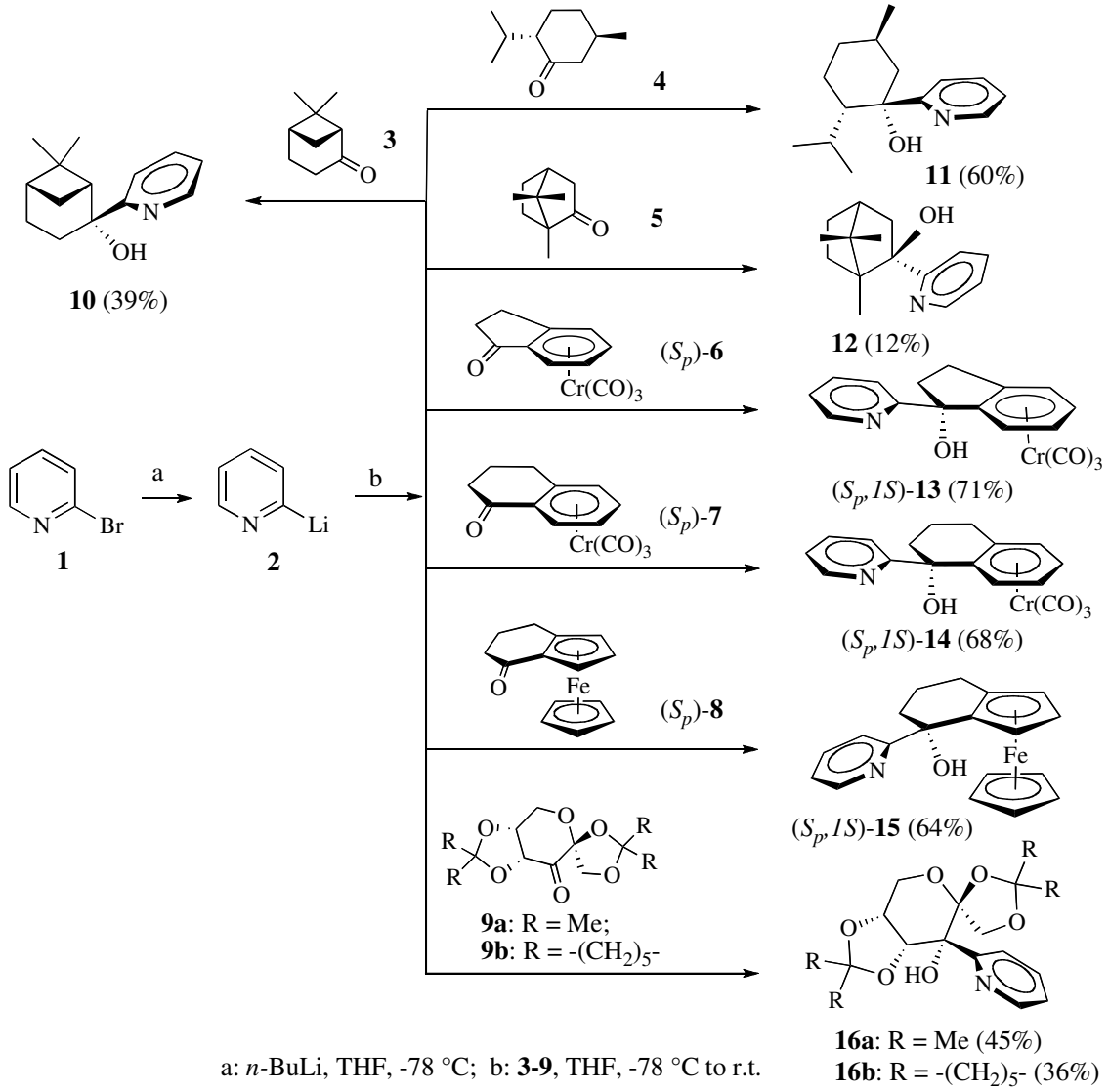
Contents

1. Introduction

Chiral pyridyl alcohols have seen a number of applications as privileged catalysts and ligands for enantioselective synthesis and catalysis.[1] Examples amenable to catalysis with pyridyl alcohols include the

epoxidation of allylic alcohols,[1a] the conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones,[1b–d] the nucleophilic addition of dialkylzinc reagents to aldehydes,[1e–h] Strecker-type reaction,[1i] ring-opening reaction[1j–l] and so on. Moreover, phosphorus ligands derived from pyridyl alcohols have been applied with success to iridium-catalyzed asymmetric hydrogenation.[1m–p] Many enantiomerically pure pyridyl alcohols are also biologically relevant compounds and key intermediates for commercial drugs such as ceramide,[2a–e] (*S*)-carbinoxamine,[2f,g] *allo*-heteroyohimbine,[2h] (*S*)-naproxen,[2i,j] (*R*,*S*)-mefloquine,[2k] thiostrepton,[2l] etc. Moreover, this skeleton is present in a number of compounds that have been described in recent patents reporting their herbicide and fungicide properties.[2m,n]

We discuss the subject of the synthesis optically active pyridyl alcohols in three accounts: the first two deal with chemical syntheses, whereas the third one talks about bioorganic methods. The first part[3] is dedicated only to the stereoselective synthesis of optically active pyridyl *sec*-alcohols, through the description of a variety of methods allowing to generate a *sec*-carbinol chiral centre bound to a pyridine ring. The second one, namely this account, is devoted principally to stereoselective methods to obtain the related *tert*-alcohols, but other kinds of these chiral non-racemic compounds such as pyridyl β-carbinols and pyridines bound to a phenolic ring are illustrated too.



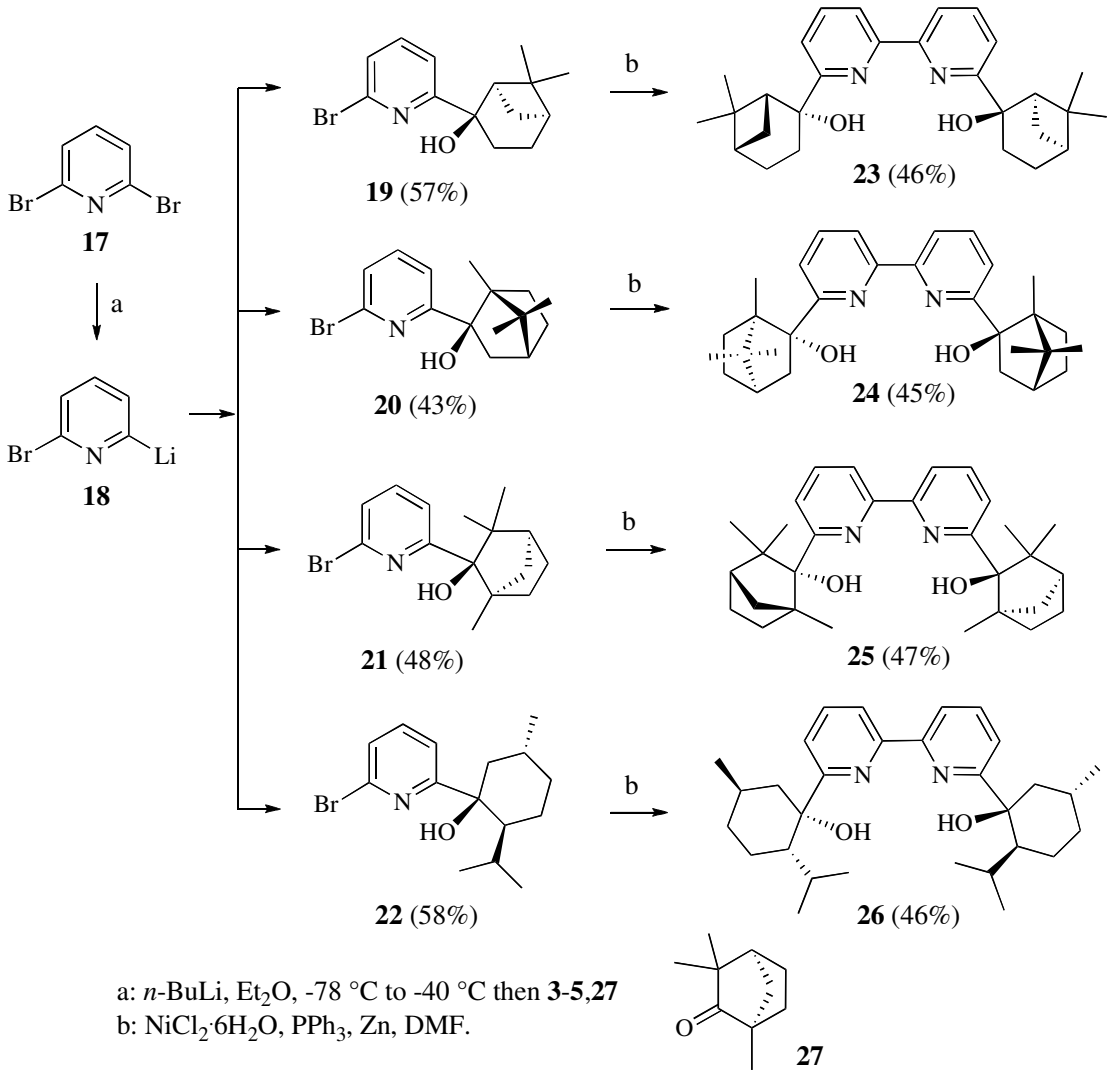
Scheme 1

2. α-(2-Pyridyl) *tert*-alcohols

2.1. Addition of 2-pyridyllithium to chiral ketones

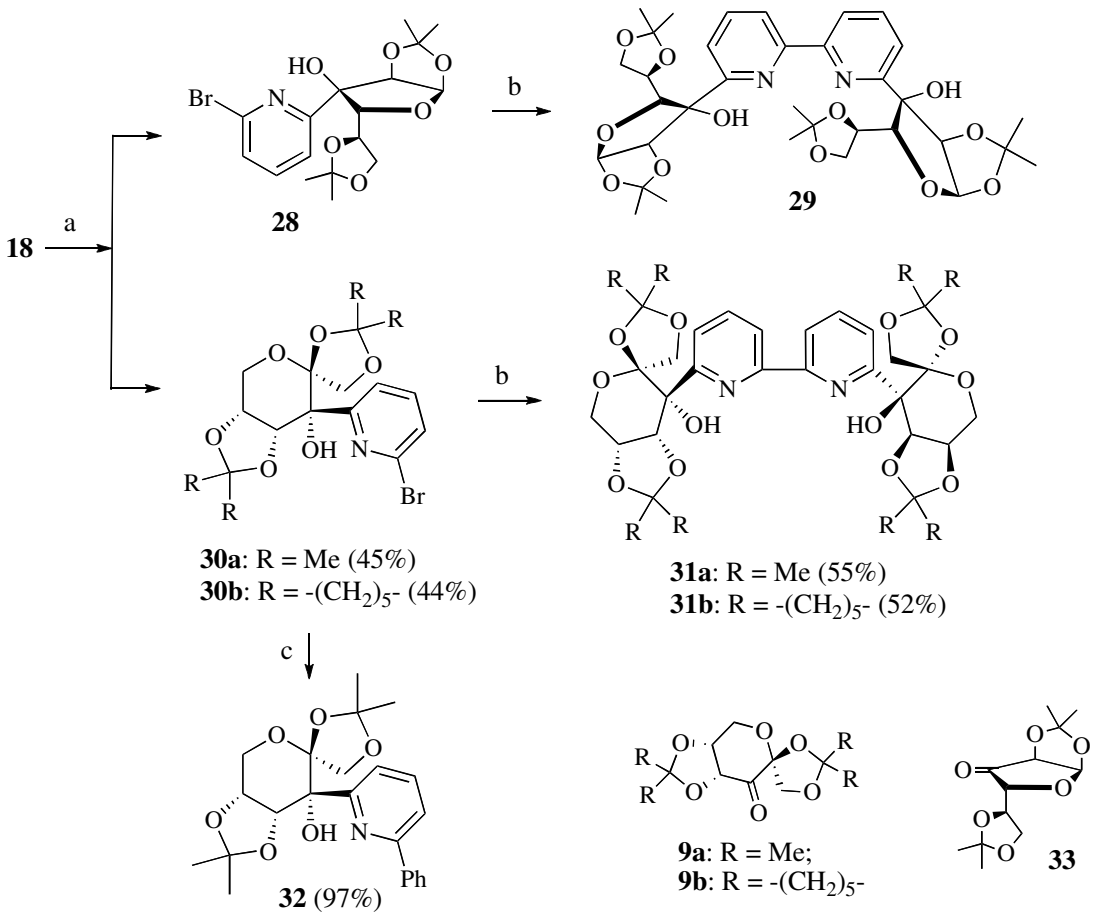
The easiest entry to pyridyl *tert*-alcohols involves the trapping of pyridyllithium derivatives with optically active carbonyl compounds. The first example of this approach was reported by Chelucci and co-workers, who prepared the pyridyl carbinols **10–12** by addition of 2-pyridyllithium, obtained by lithiation of 2-bromopyridine with *n*-BuLi at −78 °C, to ketones **3–5**, derived from the chiral pool (Scheme 1).[4] The reactions, carried out at −78 °C, because of the low thermal stability of this organolithium reagent, afforded pyridines **10–12** as single diastereomers. The yields (12–60%) greatly depend upon the nature of the ketone, dropping on passing from the moderately sterically-crowed menthone **4** (60% yield) to the very sterically-crowded camphor **5** (12% yield), an intermediate situation being found in the case of nopinone **3** (39% yield). Interestingly, the efficiency of the addition to obtain **12** was greatly improved to 53% yield when highly active anhydrous $CeCl_3$ was used to activate the carbonyl group of camphor.[5]

The addition of **2** to planar chiral ketones (S_p)-**6–8**[6] afforded (S_p,1*S*)-**13–15** in good yields (68–71%).[6] Also ketones **9a** and **9b**, obtained from D-fructose,[7] were converted to the alcohols **16a** and **16b** in 45 and 36% yields, respectively (Scheme 1).[8]



Scheme 2

When (6-bromopyridin-2-yl)lithium **18**, obtained by monolithiation of 2,6-dibromopyridine **17** with *n*-BuLi at −78 °C, was trapped with chiral carbonyl compounds, 6-bromopyridin-2-yl alkanols were obtained. The 6-bromo group of these pyridines can be then substituted by other groups opening the access to more complex pyridyl alcohols. A variety of chiral bipyridines were prepared using this strategy (Schemes 2, 3 and 4).

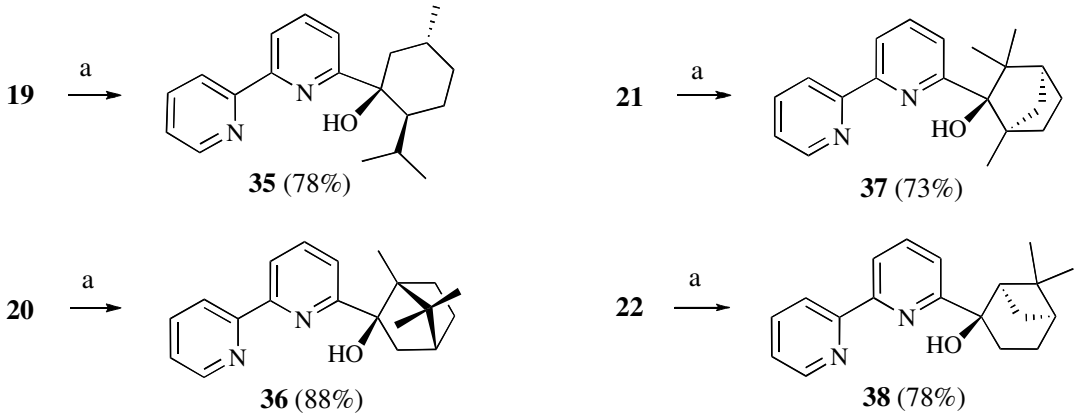


a: **9**,**33**; b: $NiCl_2 \cdot 6H_2O$, PPh_3, Zn, DMF; c: $PhB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, MePh/H_2O, 85 °C.

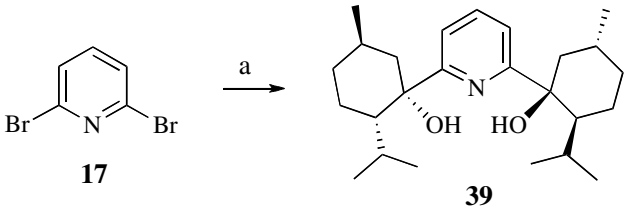
Scheme 3

The reaction of **18** with optically active ketones **3–5,27** (Scheme 2) and **9,33** (Scheme 3), all derived from naturally occurring compounds, afforded the bromopyridine alcohols **19–22**[9] (43–58% yields) (Scheme 2) and **30**[10] (44–45% yields) and **28**[11] (50% yield) (Scheme 3). These compounds were homocoupled in the presence of nickel(0) to give the C_2-symmetric bipyridines **23–26**[9] (45–47% yields) (Scheme 2), **31a,b**[10] (52–55% yields) and **29**[11] (Scheme 3) as single diastereomers in moderate yields, depending only slightly on the nature of the ketone. Suzuki heterocoupling of the bromopyridine **30a** with phenylboronic acid afforded the ligand **32** in nearly quantitative yield (Scheme 3).[10] Furthermore, the C_1-symmetric bipyridines **35,36**[9] (77–88% yields) and **37,38**[12] (73–75% yields) were prepared by palladium(0)-catalyzed cross coupling of **19,20** and **21,22** with 2-pyridylzinc chloride (Scheme 4).

The tridentate chiral ligand 2,6-bis-[(−)-menthyl]pyridine **39** was readily prepared in 40% yield by reaction of the 2,6-dilithium derivative of 2,6-dibromopyridine **17** with (−)-menthone (Scheme 5).[13]



Scheme 4

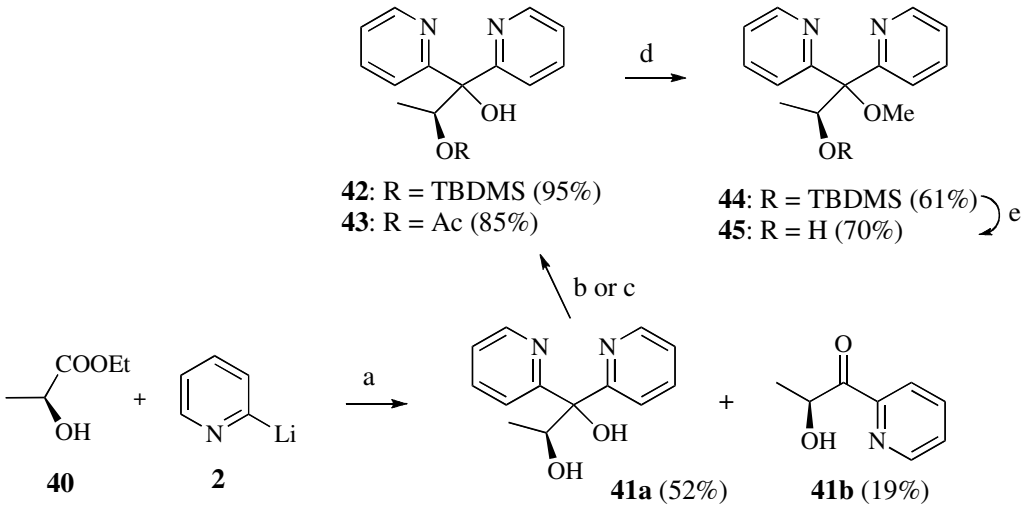


a: *n*-BuLi, THF, -78 °C, 3 h, then **4**, 40%.

Scheme 5

2.2. Addition of 2-pyridyllithium and organometallic reagents to chiral esters

Optically active pyridyl *tert*-carbinols were prepared from chiral esters *via* a dialkylation strategy using organometallic reagents (Schemes 6, 7 and 8).[14] Accordingly, treating ethyl L-lactate **40** with 2-pyridyllithium produced the dipyridine **41a** along with the pyridyl ketone **41b** in 52 and 19% yields, respectively (Scheme 6).

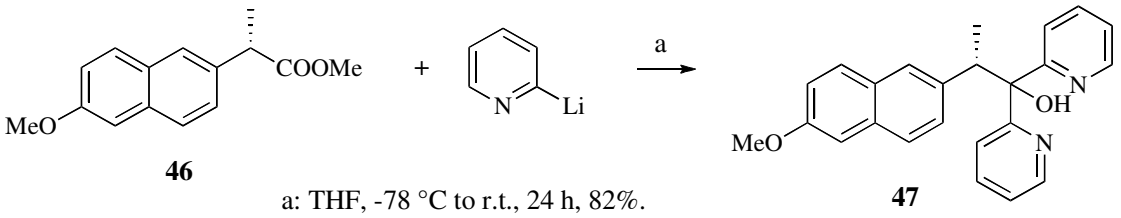


a: **2** (3.6 equiv), THF, r.t.; b: TBDMSCl, imidazole, DMF, r.t.; c: Ac_2O, 4-dimethylamino-pyridine, pyridine, r.t.; d: NaH, THF, then MeI, r.t.; e: 40% HF, MeCN, r.t..

Scheme 6

Selective protection of the secondary alcohol group of **41a** by reaction with *tert*-butyldimethylchlorosilane or acetic anhydride gave both corresponding dipyridyl silyl ester **42** and pyridyl monoacetate **43** in high yields. Furthermore, methylation of the free tertiary alcohol group in **42** followed by desilylation produced the dipyridyl secondary alcohol **45**.

Following the above strategy, dipyridyl carbinol **47** was obtained in 82% yield by treatment of naproxene methyl ester **46** with 2-pyridyllithium (Scheme 7).

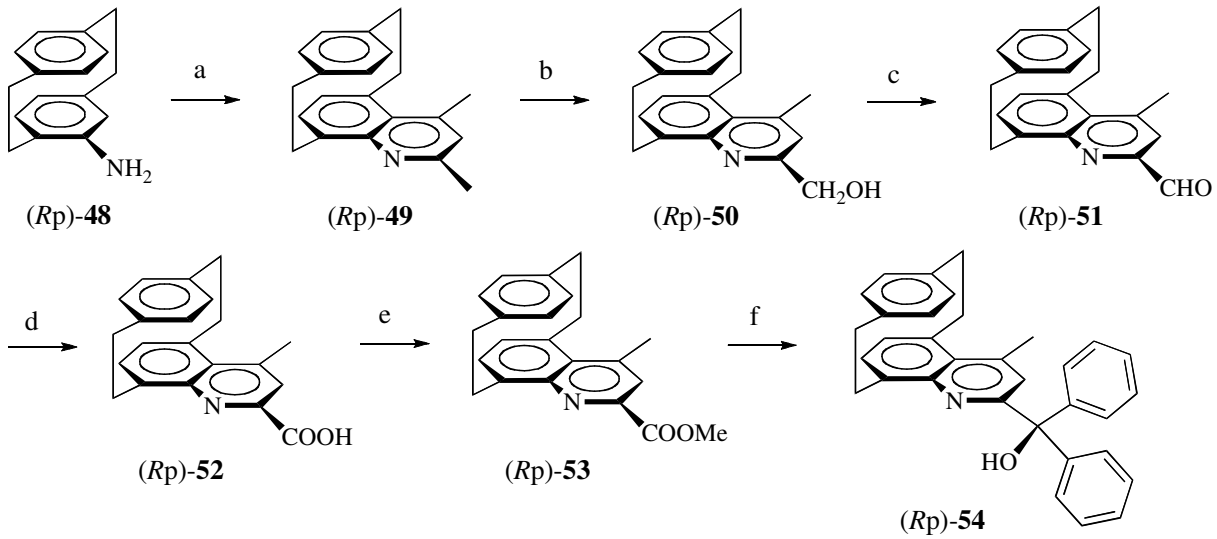


46 **47**

a: THF, -78 °C to r.t., 24 h, 82%.

Scheme 7

Ruzziconi and co-workers prepared quinolinophanyl carbinols (R_p)-**50** and (R_p)-**54** with planar chirality (Scheme 8).[15] Alcohol (R_p)-**50** was obtained in a three step sequence and 52% overall yield from (*R*)-(−)-4-amino[2.2]paracyclophene **48**. Cyclization of this amine with 2,4-pentanedione gave quinolinephane (R_p)-**49**, whose 2-methyl substituent was selectively metallated with *n*-BuLi and then treated with bis(trimethylsilyl)peroxide to afford the primary alcohol (R_p)-**50**. Alcohol (R_p)-**54** was obtained from (R_p)-**50** in four steps. Oxidation with pyridinium dichromate gave the quinolinophane-2-carboxyaldehyde (R_p)-**51**, which was further oxidized with H_2O_2 to furnish the acid (R_p)-**52**. This acid was quantitatively converted by reaction with diazomethane into the methyl ester (R_p)-**53**, which was finally reacted with 2 equivalents of phenylmagnesium bromide to give the diphenyl *tert*-carbinol (R_p)-**54** in 84% yield.



(*R*p)-**48** (*R*p)-**49** (*R*p)-**50** (*R*p)-**51**

(*R*p)-**52** (*R*p)-**53** (*R*p)-**54**

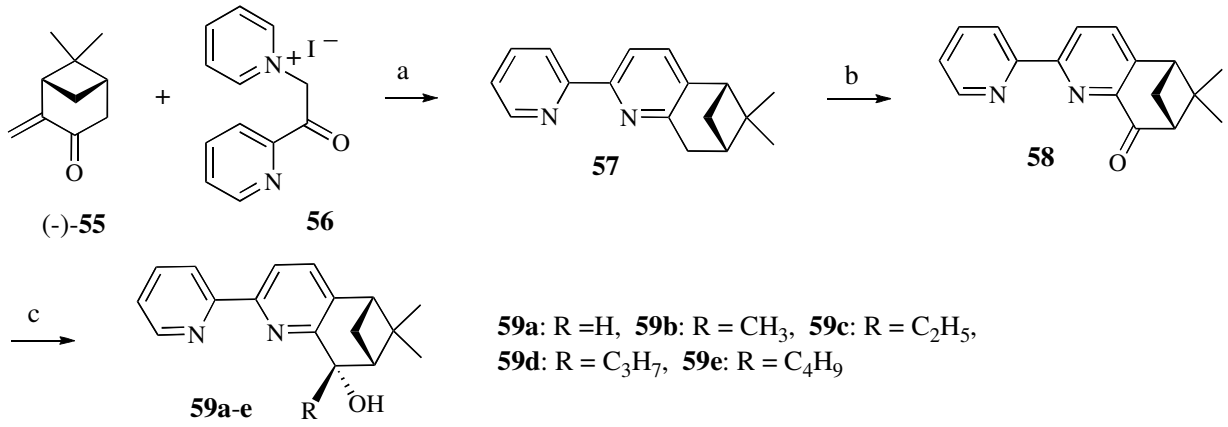
a: acetylacetone, r.t., 2 h, then PPA, 75 °C, 48 h, 69%; b: BuLi, Et_2O, 0 °C, then $(Me_3SiO)_2$, -75 °C, then H_3O^+, 75%; c: pyridinium dichromate, CH_2Cl_2, 25 °C, 12 h, 94%; d: H_2O_2, HCOOH, 4 °C, 2 h; e: CH_2N_2, DDE, 25 °C, 82%; f: PhMgBr (2.5 equiv), THF, 25 °C, 84%.

Scheme 8

2.3. Addition of organometallic reagents to pyridyl ketones and nitriles

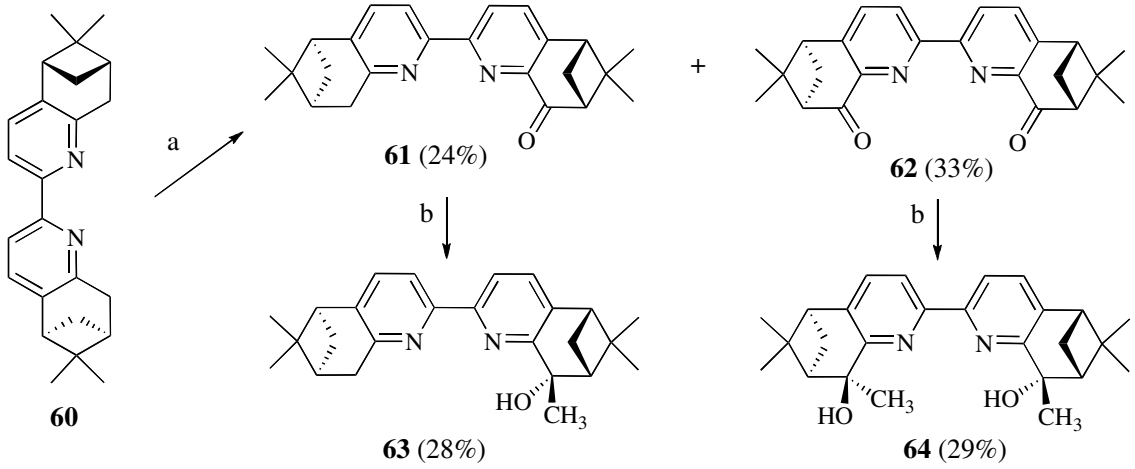
Chen and Lin reported the preparation of various bipyridine alcohols derived from (–)-pinocarvone **55** (Schemes 9 and 10).[16] Compound **55** and pyridinium salt **56** were heated with ammonium acetate in glacial acetic acid to yield bipyridine **57**, which was oxidized to ketone **58** using potassium permanganate (Scheme 9). This compound was reduced using sodium borohydride, lithium aluminum hydride or diisobutyl-aluminum hydride to yield the diastereomeric *sec*-alcohol **59a**. When $NaBH_4$ (97% de) and $LiAlH_4$ (97% de) were used as reducing agents, the reaction was more diastereoselective with respect to DIBAL-H (81% de). On the other hand, *tert*-alcohols **59b–e** were prepared as single stereoisomers by reacting compound **58** with the proper Grignard reagents.

Bipyridine **60** (for its synthesis, see Scheme 31)[17] was treated with potassium permanganate to produce ketone **61** (24% yield) and diketone **62** (33% yield). Pure compounds **61** and **62** were reacted with methylmagnesium iodide to yield the alcohol **63** (28% yield) and diol **64** (29% yield), respectively (Scheme 10).



a: AcOH, $AcONH_4$, 100-110 °C, 74%; b: $KMnO_4$, *t*-BuOH, 75-80 °C, 24 h, 77%; c: $LiAlH_4$, THF; or RMgI(Br), Et_2O, r.t., 1 h, **59a**: 87%, **59b**: 62%, **59c**: 9%, **59d**: 20%, **59e**: 18%.

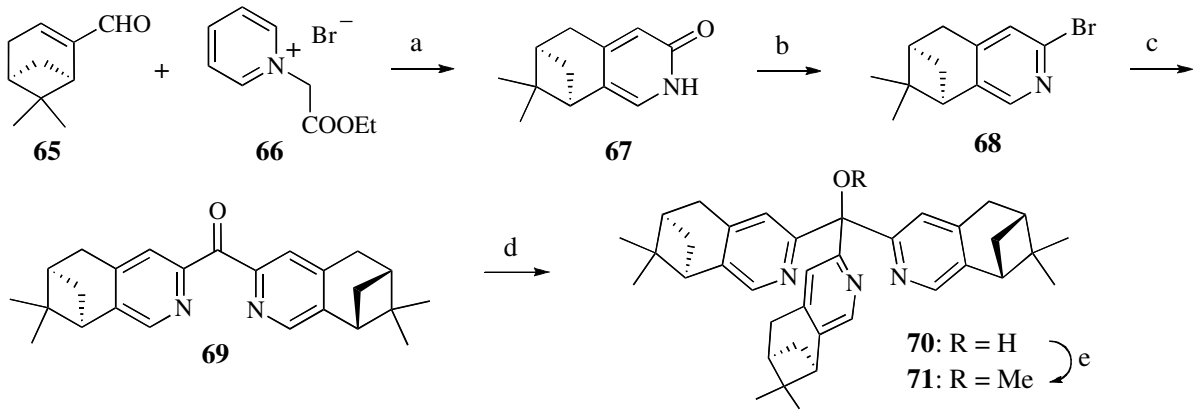
Scheme 9



a: $KMnO_4$, *t*-BuOH, 75-80 °C, 24 h; b: CH_3MgI, Et_2O, r.t., 1 h.

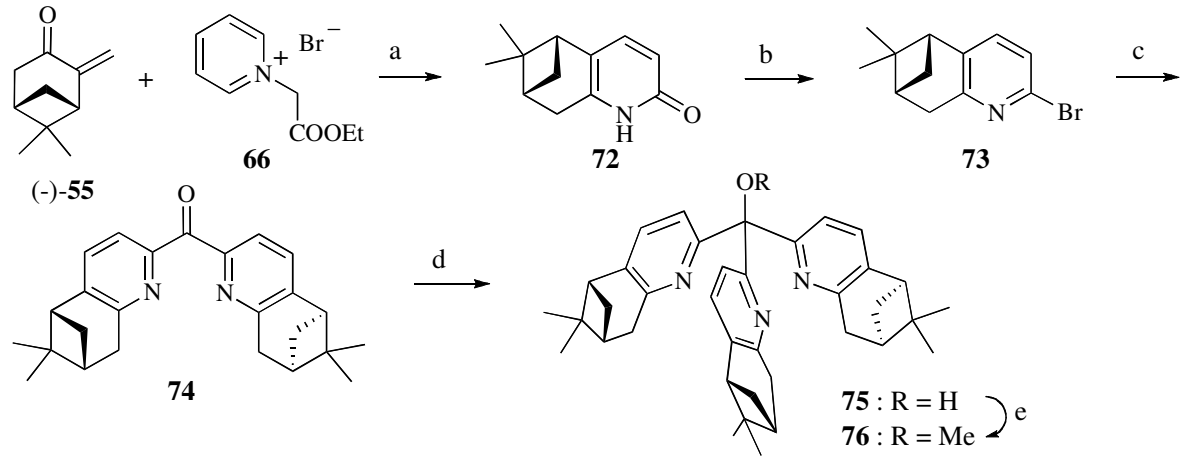
Scheme 10

Two C_3-symmetrical trispyridyl alcohols were prepared from (−)-myrtenal **65** and (−)-pinocarvone **55** *via* a *de novo* construction of the pyridine nucleus (Schemes 11 and 12).[18] Pyridone (−)-**67** was prepared by condensation of the aldehyde (−)-**65** with the pyridinium salt **66** and dry ammonium acetate under Kröhnke conditions. Bromination of **67** with $POBr_3$ without any solvent afforded **68** with moderate yield (30%). Lithiation of **68** *via* metal-halogen exchange with *n*-BuLi followed by slow addition of a solution of diethyl carbonate gave the expected ketone **69** in reasonable yield (51%). Ketone (−)-**69** was then itself treated with the lithiated **68** to generate the trispyridyl methanol ligand **70** with 56% yield. Light modification of this procedure and the use of (+)-pinocarvone **55** as the starting material allowed to gain the trispyridyl alcohol **75** (Scheme 12). Condensation of **55** with salt **66** led in 45% yield to pyridone **72**, which was brominated to give bromopyridine **73** in moderate yield (31%). Diethyl carbonate was slowly added to a solution of the lithium derivative of **73**, affording the ketone **74** in moderate yield (42%). Finally, slow addition of **74** over lithiated **73** afforded ligand **75** in 69% yield.



a: $AcONH_4$, HCHO, 40 °C, 3 days, then 80 °C, 3 days, 150 °C, 6 h, 27%; b: $POBr_3$, 140 °C, 2.5 h, 30%; c: *n*-BuLi, THF, -78 °C, then $CO(OEt)_2$, THF, -78 °C, 2 h, 51%; d: **68**, *n*-BuLi, THF, -40 °C, 56%; d: NaH, MeI, THF

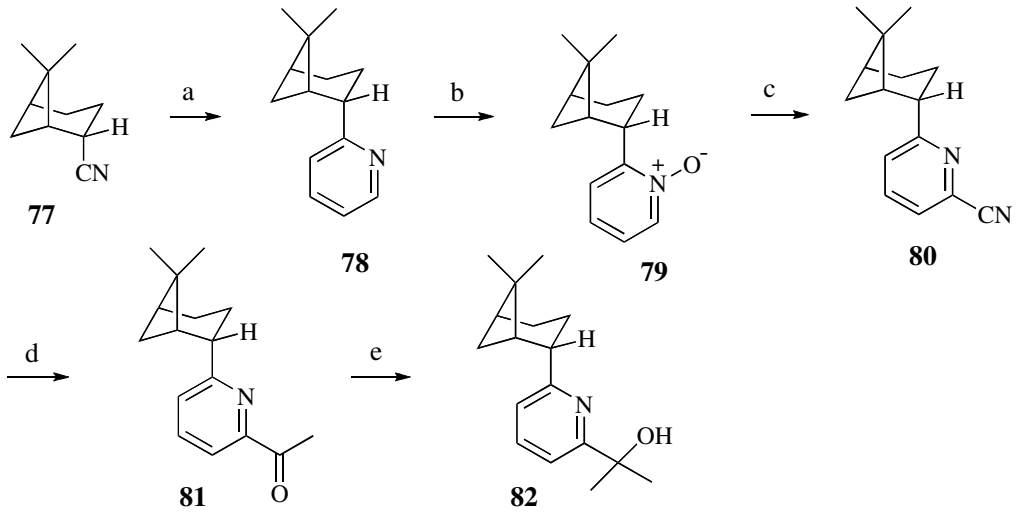
Scheme 11



a: $AcONH_4$, piperidine, EtOH, 80 °C, 1 h, then $HCONH_2$, acetic acid, 210 °C, 1 h, 45%; b: 1.4 equiv of $POBr_3$, 2.5 h, then 1.4 equiv of $POBr_3$, 2.5 h, 31%; c: *n*-BuLi, THF, -78 °C, then $CO(OEt)_2$, THF, -78 °C; d: **73**, *n*-BuLi, THF, -78 °C, 2 h to r.t, 69%; d: NaH, MeI, THF

Scheme 12

Pyridyl alcohol **82** was formed by two consecutive addition of methyl magnesium bromide to the nitrile **80** (32% yield) and then to the resulting ketone **81** (70% yield) (Scheme 13).[19,20] Nitrile **80** was prepared starting from the nitrile **77**, which was converted into the pyridine **78** by cobalt(I)-catalyzed cyclotrimerization with acetylene (95% yield). This was oxidized with *m*-CPBA to the corresponding *N*-oxide **79** (95% yield), which afforded the nitrile **80** by treatment with trimethylsilyl cyanide and dimethylcarbamoyl chloride (95% yield).



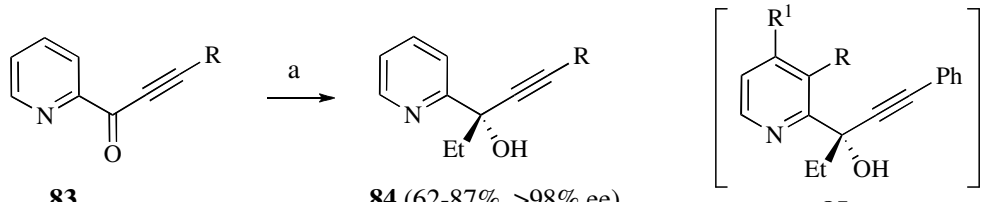
77 **78** **79** **80** **81** **82**

a: CpCo(COD), acetylene, 8 atm., 140 °C, 95%; b: *m*-CPBA, CH_2Cl_2, >95%; c: $(CH_3)_3SiCN$, $(CH_3)_2NCOCl$, CH_2Cl_2, rt, 5 d, 95%; d: CH_3MgBr, Et_2O, 32%; e: CH_3MgBr, Et_2O, 70%.

Scheme 13

2.4. Catalytic addition of organozinc reagents to pyridyl ketones

Recently, a protocol for the catalytic enantioselective synthesis of tertiary propargyl alcohols bearing a 2-pyridyl substituent has been developed.[21]

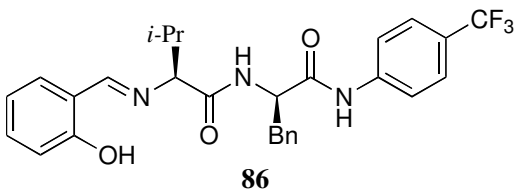


83 **84** (62-87%, >98% ee) **85a-c**

R = Ph, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$CF_3C_6H_4$, *p*-IC_6H_4, *p,m*-$Cl_2C_6H_3$, *o*-BrC_6H_4, 3-thienyl, *n*-hexyl, C_6H_{11}, $(i\text{-}Pr)_3Si$

85a: R = Br, R^1 = H, 88%, >98% ee
85b: R = H, R^1 = OMe, 78%, >98% ee
85c: R - R^1 = CH=CH-CH=CH, 74%, >98% ee

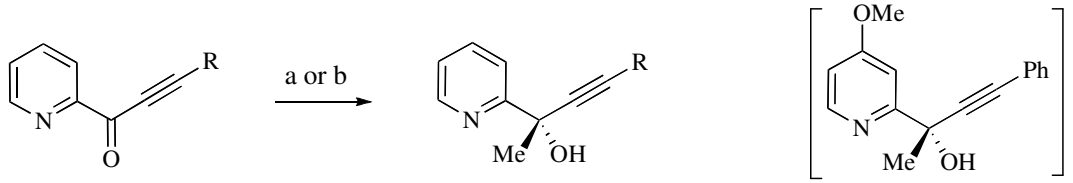
a: $ZnEt_2$ (3 eq), **86** (5-10 mol%), $Al(O\text{-}i\text{-}Pr)_3$ (5-10 mol%), $H_2NP(O)(OEt)_2$ (50 mol%), MeC_6H_5, - 78 °C, 20 min.



86

Scheme 14

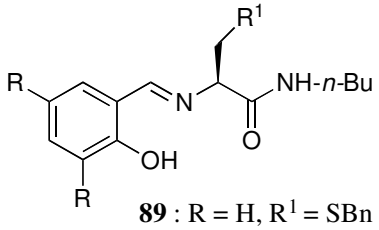
The method is based on the alkylations of pyridyl substituted ynones with $ZnEt_2$ or $ZnMe_2$ promoted by amino acid-based chiral ligands in the presence of aluminium-based alkoxides. In this way, pyridyl *tert*-alcohols were efficiently obtained with >98% ee with $ZnEt_2$ and 57 to 96% ees with $ZnMe_2$ (Schemes 14 and 15). After probing a variety of amino acid-based chiral ligands, two of them were identified as optimal for the reactions of these dialkylzinc reagents. Catalytic alkylations with $ZnEt_2$ required the chiral ligand **86** carrying two amino acid moieties (valine and phenylalanine) along with a *p*-trifluoromethylphenylamide *C*-terminus (Scheme 14). In contrast, reactions with $ZnMe_2$ were most effectively promoted in the presence of the chiral ligand **89** containing a single amino acid (benzyl cysteine) capped by an *n*-butylamide group (Scheme 15). Some pyridyl ynones substituted on the pyridine ring were also effectively alkylated with both $ZnEt_2$ and $ZnMe_2$. These enantiomerically enriched alcohols, with a quaternary carbon stereogenic centre bearing three highly versatile substituents (a hydroxy group, a pyridine and an alkyne) were functionalized in a variety of manners to furnish a wide range of difficult-to-access acyclic and heterocyclic structures.



83 **87** (53-74%, 79-96% ee) **88** (53%, 77% ee)

R = Ph, *p*-$MeOC_6H_4$, *p*-$CF_3C_6H_4$, *p*-IC_6H_4, *p,m*-$Cl_2C_6H_3$, *o*-BrC_6H_4, 3-thienyl, *n*-hexyl, $(i\text{-}Pr)_3Si$

a: $ZnMe_2$ (5 eq), **89** (15 mol%), $Al(O\text{-}i\text{-}Pr)_3$ (15 mol%), $H_2NP(O)(OEt)_2$ (50 mol%), MeC_6H_5, -30 °C, 12 h;
b: R = $(i\text{-}Pr)_3Si$, $ZnMe_2$ (5 eq), **90** (15 mol%), $Al(O\text{-}i\text{-}Pr)_3$ (15 mol%), $H_2NP(O)(OEt)_2$ (50 mol%), MeC_6H_5, - 50 °C, 12 h, 65%, 57% ee.



89 : R = H, R^1 = SBn
90 : R = Cl, R^1 = Ph

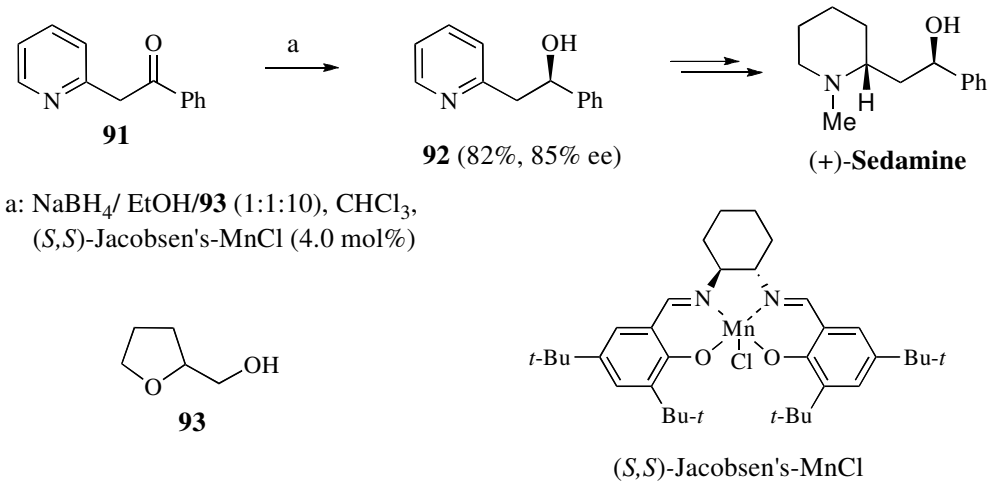
Scheme 15

3. β-(2-Pyridyl) *sec*-alcohols

3.1. Reduction of pyridine ketones

In a study aimed at the generation of both enantiomers of sedamine [l-methyl-2-(2-phenyl-2-hydroxyethyl)piperidine] with high optical purity, the reduction of 1-phenyl-2-(pyridin-2-yl)ethanone **91** was examined (Scheme 16).[22] The reduction of **91** by Baker's yeast proved without effect. (+)-β-Chlorodiisopinocampheylborane[23] gave only moderate yield (65%) and enantiomeric excess (61%) of the (*R*)-(+)-alcohol **92**. Corey's (*R*)-2-CBS-oxazaborolidine[24] was ineffective, as was the hydrogenation catalysed by (*R*)-(+)-BINAP-(*p*-cymene)RuCl[25] that gave the alcohol with zero enantiomeric excess, or (*R*)-(+)-BINAP-PdCl that was totally without effect. It appeared that the ketone (perhaps as its enol,[26] 3:1 keto-to-enol in $CDCl_3$ solution) is a potent ligand and thereby inactivates the above systems. Therefore, the use of a chiral Lewis acid, which would utilize this ligand character and thereby present facial selectivity to a borohydride reagent, was pursued. While equimolar aluminium chloride/(+)-diethyl tartrate in CH_2Cl_2/ethanol solution with $NaBH_4$ gave (*R*)-**92** with low enatioselectivity (22% ee), Jacobsen's catalyst[27] was remarkably effective.

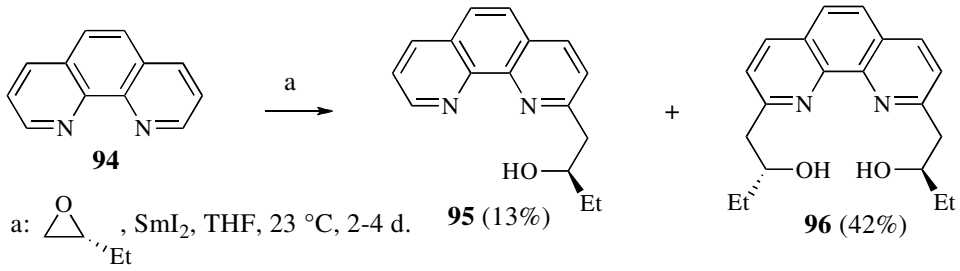
Thus, using modified $NaBH_4$ as used by Mukaiyama[28] [$NaBH_4$/EtOH/tetrahydrofurfuryl alcohol (1:1:10 molar) in chloroform and 4.0 mol% Jacobsen's Mn(III)Cl catalyst at −20 °C], the (*R*,*R*)-catalyst converted 2-phenacylpyridine **91** into the (*S*)-alcohol **92** in 76% yield, while the (*S*,*S*)-catalyst gave the (*R*)-alcohol in 82% yield and 85% ee (Scheme 16). Both enantiomers produced >96% ee material on one recrystallization. Other pyridyl-CH_2COR derivatives reacted similarly with aliphatic derivatives (1-adamantyl, for instance) requiring however lower temperatures (≤−50 °C) for efficient stereoselective reduction [*e.g.*, using (*R*,*R*)-catalyst, 80% yield, 72% ee]. Cobalt(II) Jacobsen's catalyst was without effect on the reduction.



Scheme 16

3.2. Addition of chiral 2-pyridyllithium derivatives to chiral epoxides

Helquist and co-workers demonstrated the utility of samarium diiodide for effecting coupling reactions between 1,10-phenanthroline and chiral non-racemic epoxides.[29] In particular, the reaction performed by combining 1,10-phenanthroline with (*R*)-1,2-epoxybutane and SmI_2 provided both mono- and bis-2-(2-hydroxyalkyl)-1,10-phenanthroline derivatives **95** and **96**, respectively (Scheme 17). The isolated yields varied in different runs with up to 13% for **95** as the minor product and up to 42% for **96** as the major product as one pure diastereomer. Longer run times resulted in no additional product formation as the SmI_2 appeared to be completely consumed after 4 days. Analysis of the crude products by ^1H NMR typically showed nearly total conversion of the 1,10-phenanthroline to **96**. Significant material loss occurred in the purification process needed to isolate pure samples of the products.



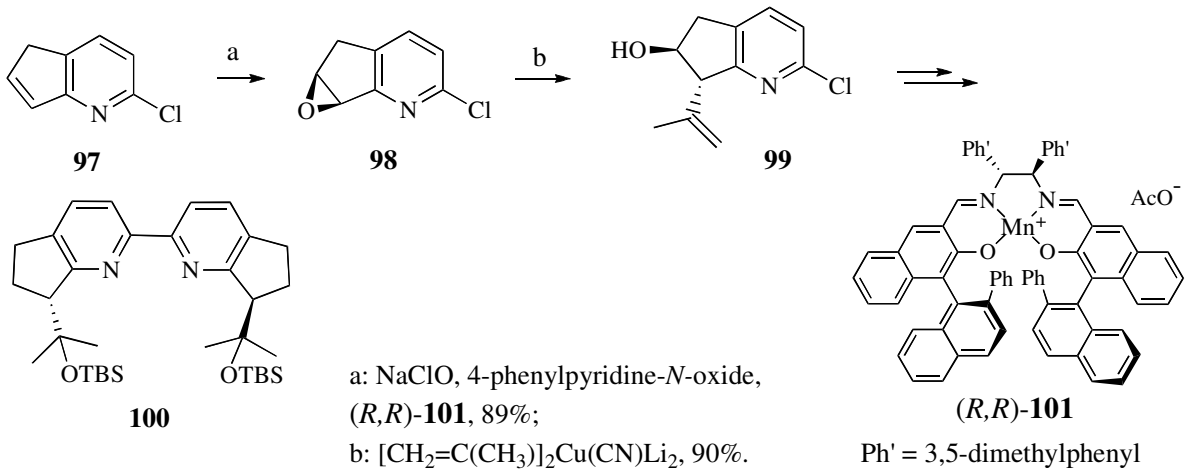
Scheme 17

3.3. Ring opening of chiral pyridine epoxides

Katsuki and co-workers, for the preparation of both bipyridines **100** (Scheme 18)[30] and **105** (Scheme 19),[30] exploited the asymmetric epoxidation of an alkene catalyzed by a chiral manganese-salen complex as

a key step of both syntheses.[31] Asymmetric epoxidation of **97** with the catalyst (*R*,*R*)-**101** proceeded smoothly to give the epoxide **98** with 96% ee (Scheme 18).[30] Treatment of this epoxide with the cuprate $[(CH_2=C(CH_3)]_2Cu(CN)Li_2$ provided β-hydroxyalkylpyridine **99** as a single isomer (90% yield). The absolute configuration of **99** was determined to be 6*S*,7*S*, consistent with the empirical rule on enantioface selectivity in the Mn-salen catalyzed epoxidation.[31] Compound **99** was next converted into bipyridine **100** in several steps (Scheme 31).

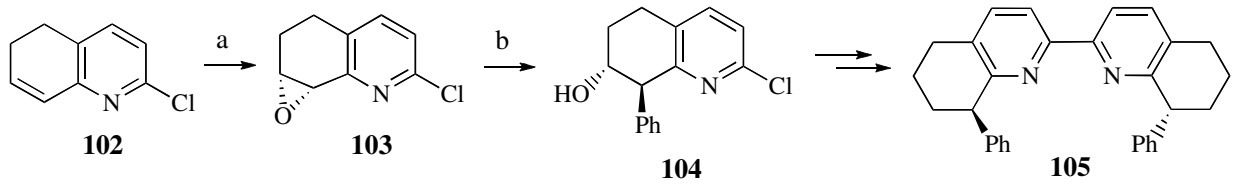
For the synthesis of the bitetrahydroquinoline **105**, the chiral epoxide **103** was prepared in 96% ee by epoxidation of the alkene **102** with the catalyst (*S*,*S*)-**101** (Scheme 19).[30] Treatment of **103** with the cuprate $Ph_2Cu(CN)Li_2$ in the presence of BF_3-Et_2O provided the β-hydroxyalkylpyridine **104** as a single isomer (84% yield). This compound, whose absolute configuration was determined to be 7*R*,8*R*, was next converted into bipyridine **105**.



a: NaClO, 4-phenylpyridine-*N*-oxide, (*R,R*)-**101**, 89%;
b: $[CH_2=C(CH_3)]_2Cu(CN)Li_2$, 90%.

Ph' = 3,5-dimethylphenyl

Scheme 18



a: NaClO, 4-phenylpyridine *N*-oxide, (*S,S*)-**101** (Ph' = Ph), 77%; b: $Ph_2Cu(CN)Li_2$, $BF_3{\cdot}OEt_2$, 84%.

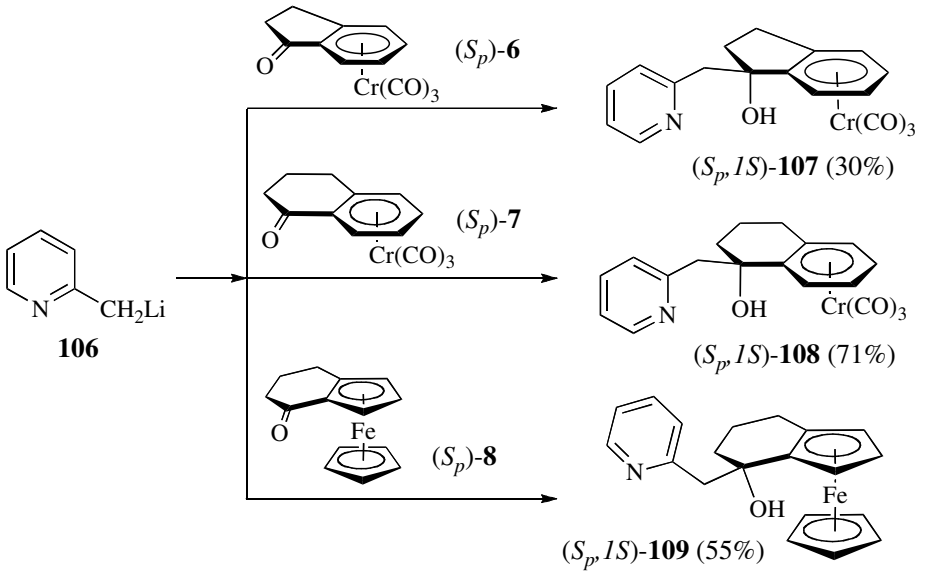
Scheme 19

4. β-(2-Pyridyl) *tert*-alcohols

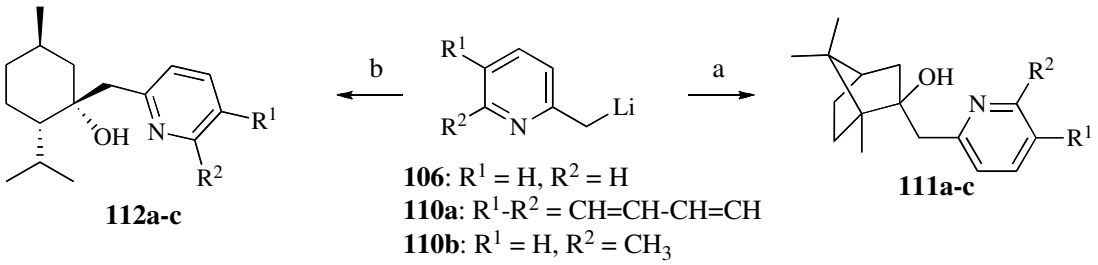
4.1. Addition of 2-picolyllithium derivatives to chiral ketones

Malfait and co-workers prepared in satisfactory yields diastereomeric pure pyridine alcohols (S_p,1*S*)-**107,108** and (S_p,1*S*)-**109** with both central and planar chirality, by addition of 2-picolyllithium to ketones (S_p)-**6**, (S_p)-**7** and (S_p)-**8**, based on arene-chromium and -ferrocene complexes, respectively (Scheme 20).[32]

Xu and co-workers easily synthesized chiral alcohols **111a–c** and **112a–c**, containing a quinoline[33] or pyridine[34] ring, from (+)-camphor **5** or (−)-menthone **4** as depicted in Scheme 21. These ketones were reacted with 2-picolyllithium **106**, 2-quinolylmethyllithium **110a** and [(6-methylpyridin-2-yl)methyl]lithium **110b**, in turn obtained from the parent heterocycles and *n*-BuLi in diethyl ether at 0 °C, to produce compounds **111a–c** and **112a–c** in nearly quantitative yields as single diastereomers.



Scheme 20



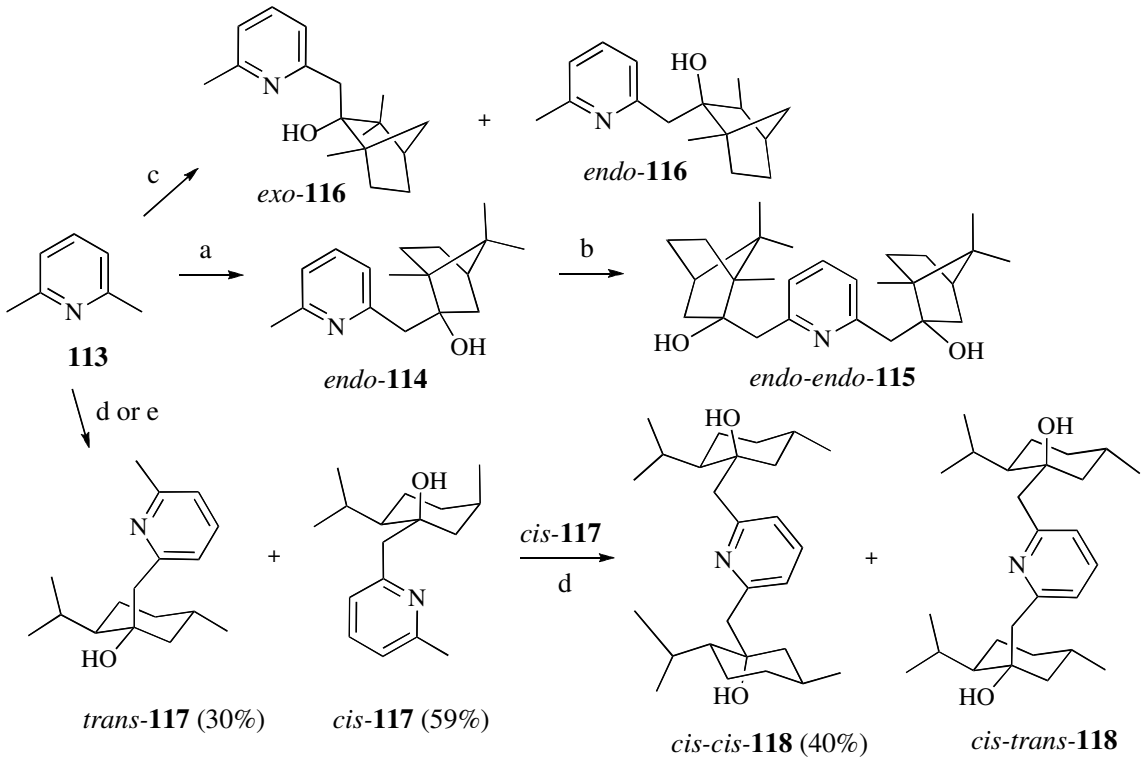
111,**112**: **a**: R^1-R^2 = CH=CH-CH=CH, **b**: R^1 = H, R^2 = CH_3, **c**: R^1 = H, R^2 = H

a: ether, 0 °C, (+)-camphor **5**; b: ether, 0 °C, (-)-menthone **4**.

Scheme 21

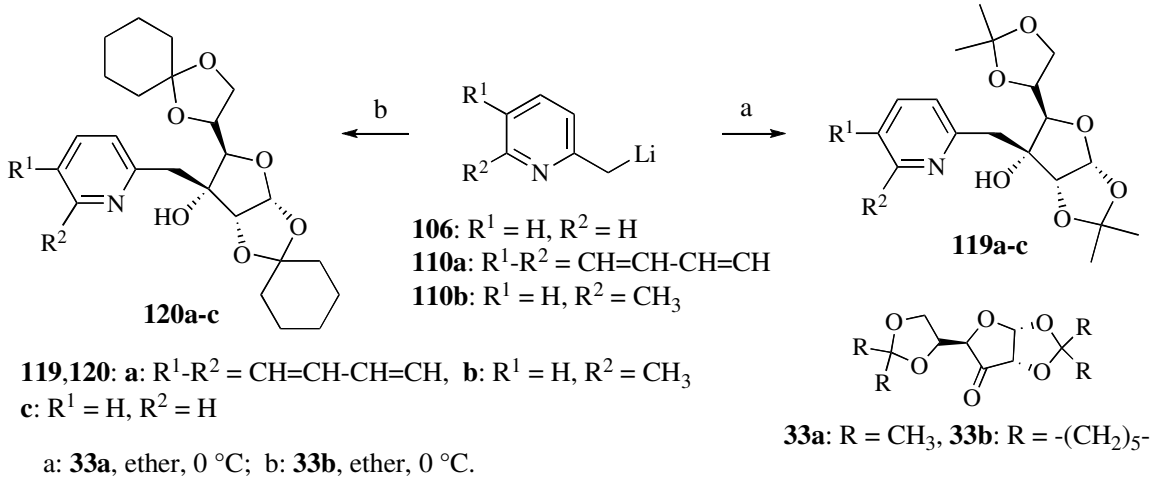
Metalation of 2,6-dimethylpyridine **113**, followed by treatment with various ketones, was studied in order to obtain C_2-symmetric pyridine alcohols.[35] The approach, consisting in one-pot two steps synthesis (treatment of **113** with *n*-BuLi and then with the ketone, followed by a new treatment of the obtained product with *n*-BuLi and then with the ketone), afforded diols in low to moderate yields. For instance, when camphor was employed as the ketone, the yield was 45%. Yields could be improved substantially applying a two-pot reaction in which the mono-adduct is first isolated and then converted into the C_2-symmetric di-adduct by adding slightly more than two equivalents of base, followed by addition of the ketone. Employing this strategy with (+)-camphor, the alcohol *endo*-**114** was isolated in 89% yield (Scheme 22), but the second reaction step was initially less straightforward. The lithiation time strongly influences the yield of the desired C_2-symmetric product. However, when **114** was treated with potassium di-*iso*-propylamide (KDA) (2.1 equivalents) instead of *n*-BuLi and then quenched with (+)-camphor after only 15 minutes of stirring, the diol *endo-endo*-**115** was obtained as a sole product in 95% yield (Scheme 22). The addition of **113** mono-lithiated to other ketones, such as (*R*)-fenchone and (−)-menthone, was less successful, while the addition to (*R*)-fenchone afforded inseparable *exo* and *endo* adducts **116** in equal amounts. Addition to (−)-menthone gave *cis* and *trans* isomers **117** in a ratio of 16:5, respectively (Scheme 22). The separated *cis* isomer **117** was lithiated with two equivalents of *n*-BuLi and treated with (−)-menthone to give the *cis-cis* and *trans-*

trans isomers **118** in a ratio of 16:5, respectively. The *cis-cis* isomer **118** could be selectively isolated in 40% yield by crystallization from a mixture of water/ethanol. Better facial selectivity (*endo*:*exo*=1:4) for (*R*)-fenchone was obtained when lithium in the mono-lithium derivative of **113** was replaced by cerium trichloride and the temperature of the addition was lowered to −80 °C. When this approach was applied to (−)-menthone, only the isomer *cis*-**117** was obtained in 45% yield.



a: *n*-BuLi, THF, -60 °C, then (+)-camphor, 1 h, 89%; b: KDA, THF, -50 °C, 15 min, then (+)-camphor, -50 °C to r.t., 2 h, 95%; c: *n*-BuLi, THF, -70 °C, 15 min then $CeCl_3$, -50 °C, 1 h, then (*R*)-fenchone, 54% (*endo*/*exo* = 4/1); d: *n*-BuLi, THF, -60 °C, then (-)-menthone, 1 h; e: *n*-BuLi, THF, -70 °C, 15 min then $CeCl_3$, -50 °C, 1 h, then (-)-menthone, 3 h, 45% (only *cis*-**117**).

Scheme 22

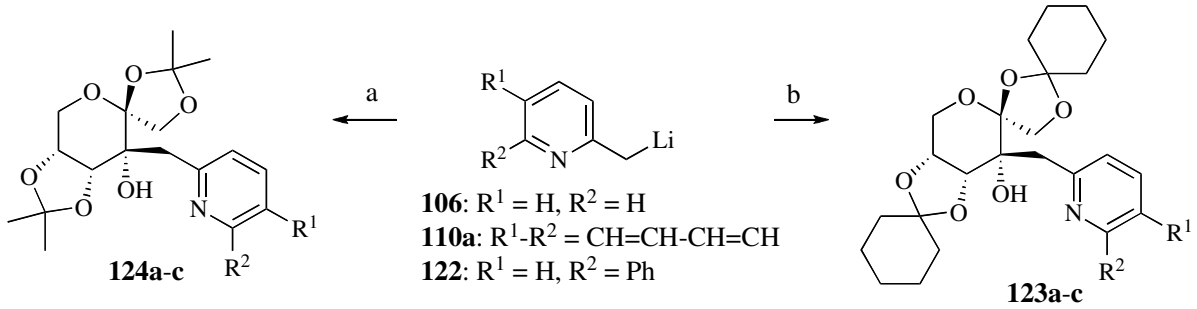


119,**120**: **a**: R^1-R^2 = CH=CH-CH=CH, **b**: R^1 = H, R^2 = CH_3
c: R^1 = H, R^2 = H

a: **33a**, ether, 0 °C; b: **33b**, ether, 0 °C.

Scheme 23

Zheng and co-workers easily synthesized pyridine and quinoline alcohols derived from carbohydrates. Initially, ketones **33** derived from D-glucose (Scheme 23)[36] and then ketones **9a,b** derived from D-fructose (Scheme 24)[37] were synthesized. These ketones were trapped with organolithium reagents, obtained by lithiation of 2-picoline, 2,6-lutidine and 2-methylquinoline with *n*-BuLi, to give the corresponding compounds **119a–c** and **120a–c** (Scheme 23) in 51−78% yields and compounds **123a–c** and **124a–c** (Scheme 24) in 51−78% yields.



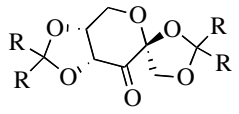
124a-c

106: R^1 = H, R^2 = H
110a: R^1-R^2 = CH=CH-CH=CH
122: R^1 = H, R^2 = Ph

123a-c

123,**124** = **a**: R^1-R^2 = CH=CH-CH=CH, **b**: R^1 = H, R^2 = Ph; **a**: R^1 = H, R^2 = H

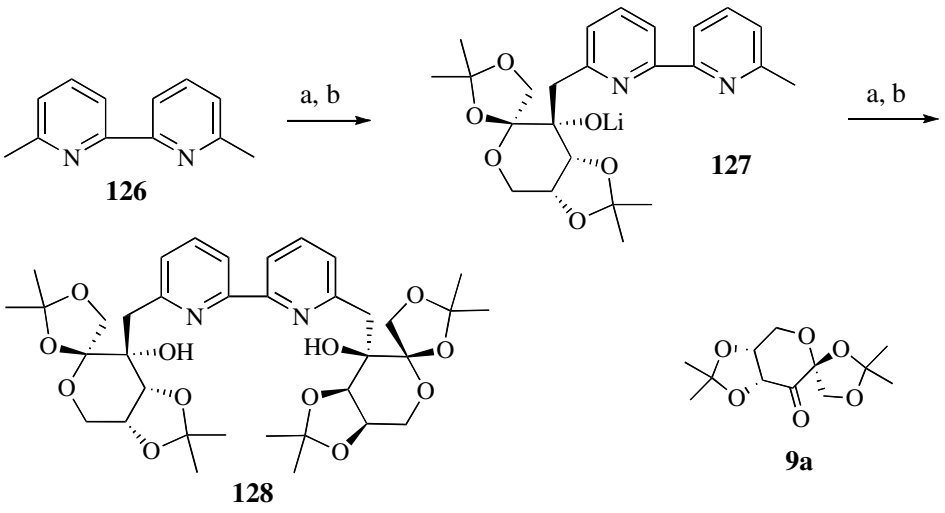
a: **9a**, Et_2O, 0 °C to r.t.; b: **9b**, Et_2O, 0 °C to r.t.



9a: R = Me ; **9b**: R = -$(CH_2)_5$-

Scheme 24

The conformationally flexible C_2-symmetric bipyridine alcohol **128**, which is the dimer of compound **124a**, was also conveniently prepared in 32% yield by reacting 2 equivalents of the chiral ketone **9a** with 6,6'-dimethyl-2,2'-bipyridine **126** in the presence of *n*-BuLi (Scheme 25).



126

127

128

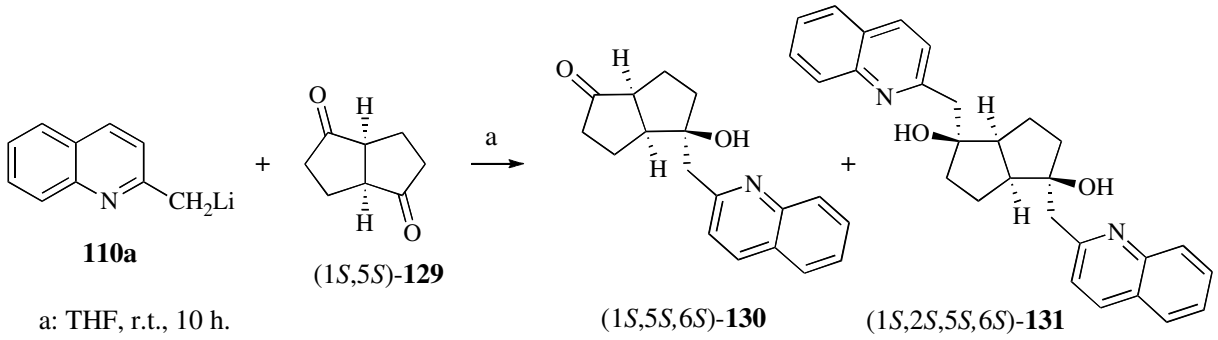
9a

a: *n*-BuLi, Et_2O, 0 °C; b: **9a**, -78 °C to r.t.

Scheme 25

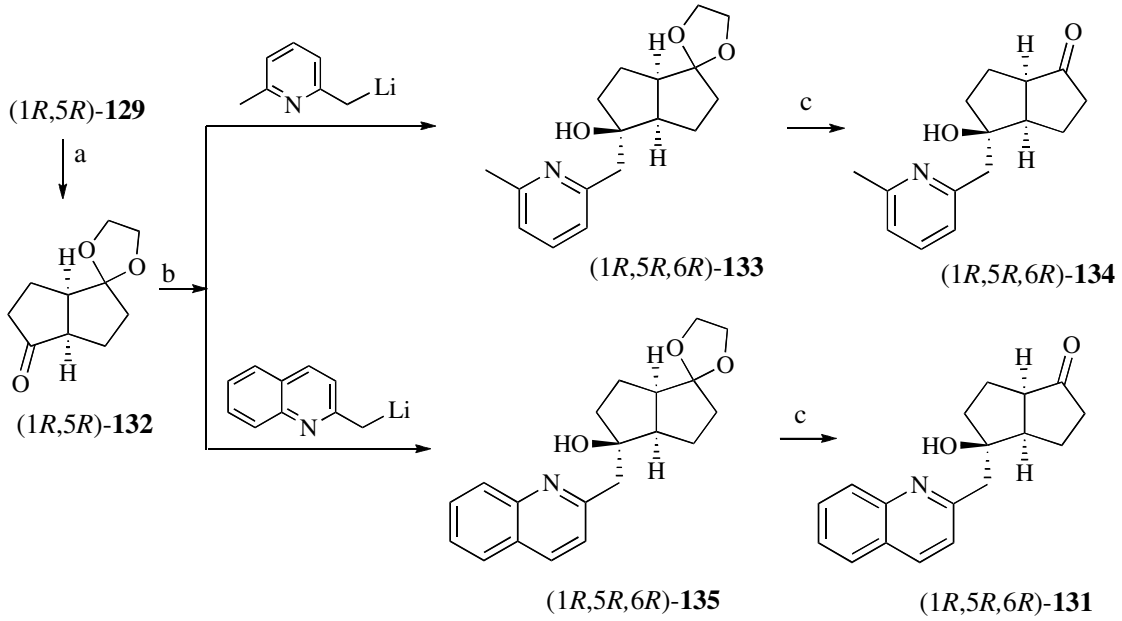
Lin and co-workers easily synthesized pyridine and quinoline alcohols and a diquinoline alcohol from the enantiomeric pure ketone **129** prepared in turn from 1,5-cyclooctadiene (Schemes 26, 27 and 28).[38,39]

Addition of (quinolin-2-ylmethyl)lithium (3.0 equivalents) to (1*S*,5*S*)-**129** (1.0 equivalent) afforded a mixture of the mono-quinoline alcohol (1*S*,5*S*,6*S*)-**130** and C_2-symmetric quinoline alcohol (1*S*,2*S*,5*S*,6*S*)-**131** in 50 and 20% yields, respectively (Scheme 26). *Ent*-**131** was also prepared starting from *ent*-**129** that was first mono-protected as mono-ketal (1*R*,5*R*)-**132**, then treated with (quinolin-2-ylmethyl)lithium and finally deprotected. The same procedure was also followed to obtain pyridine alcohol (1*R*,5*R*,6*R*)-**134** (Scheme 27).



a: THF, r.t., 10 h.

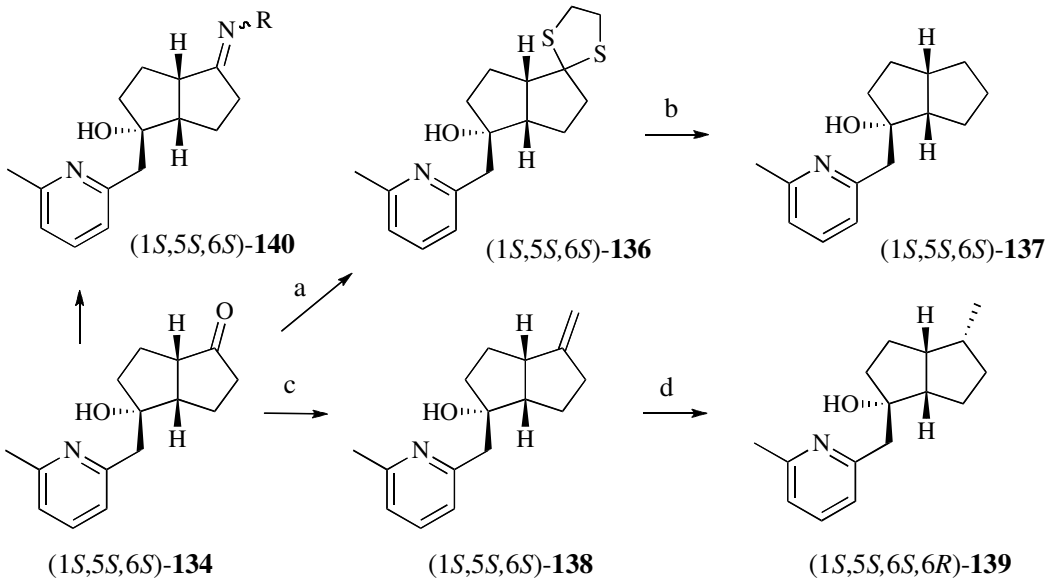
Scheme 26



a: ethylene glycol, *p*-TsOH, toluene, 6 h, 80%;
b: THF, r.t., 10 h, 84-88%; c: HCl, acetone, THF, r.t., 5 h, 100%.

Scheme 27

The carbonyl group of (1*S*,5*S*,6*S*)-**134** was also converted into a methylene, methyl group or *N*-substituted oxime derivative (Scheme 28).[39] Unfortunately, direct reduction, including both Wolff-Kishner-Huang reduction and tosylhydrazone reduction by sodium cyanoborohydride, proved to be unsuccessful. Thus, a different approach was undertaken. As shown in Scheme 28, by converting (1*S*,5*S*,6*S*)-**134** (*ent*-**134**) into its dithioketal **136**, followed by reaction with Raney-nickel in 2-propanol, the designed compound **137** was successfully obtained. In addition, compound **139** was synthesized by Wittig reaction of (1*S*,5*S*,6*S*)-**134** with CH_3PPh_3I, which afforded compound **138**, followed by hydrogenation.

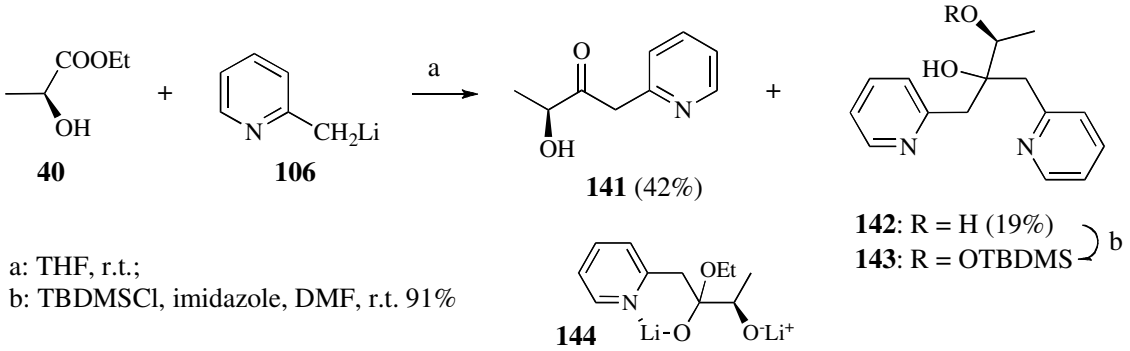


a: $HSCH_2CH_2SH$, BF_3OEt_2, CH_2Cl_2, 100%; b: Raney-nickel, EtOH, reflux, 100%;
c: CH_3PPh_3I, *t*-BuOK, 82%; d: Pd/C, H_2 (1 atm), 85%.

Scheme 28

4.2. Addition of 2-picolyllithium to chiral esters

The addition of 2-picolyllithium to ethyl L-lactate **40** led to ketone **141** and dipyridine **142** as the minor by-product (Scheme 29).[40] This result accounts for the peculiar structure of the tetrahedral carbon intermediate **144**, which is stabilized by six-membered intramolecular coordination of lithium at the pyridine nitrogen. All attempts to convert **141** to **142** were unsuccessful, due to the fairly unstable nature of **141**. Selective protection of the secondary alcohol group of **141** with *tert*-butyldimethylchlorosilane gave the corresponding dipyridylsilyl ester **143** in high yield (91%).



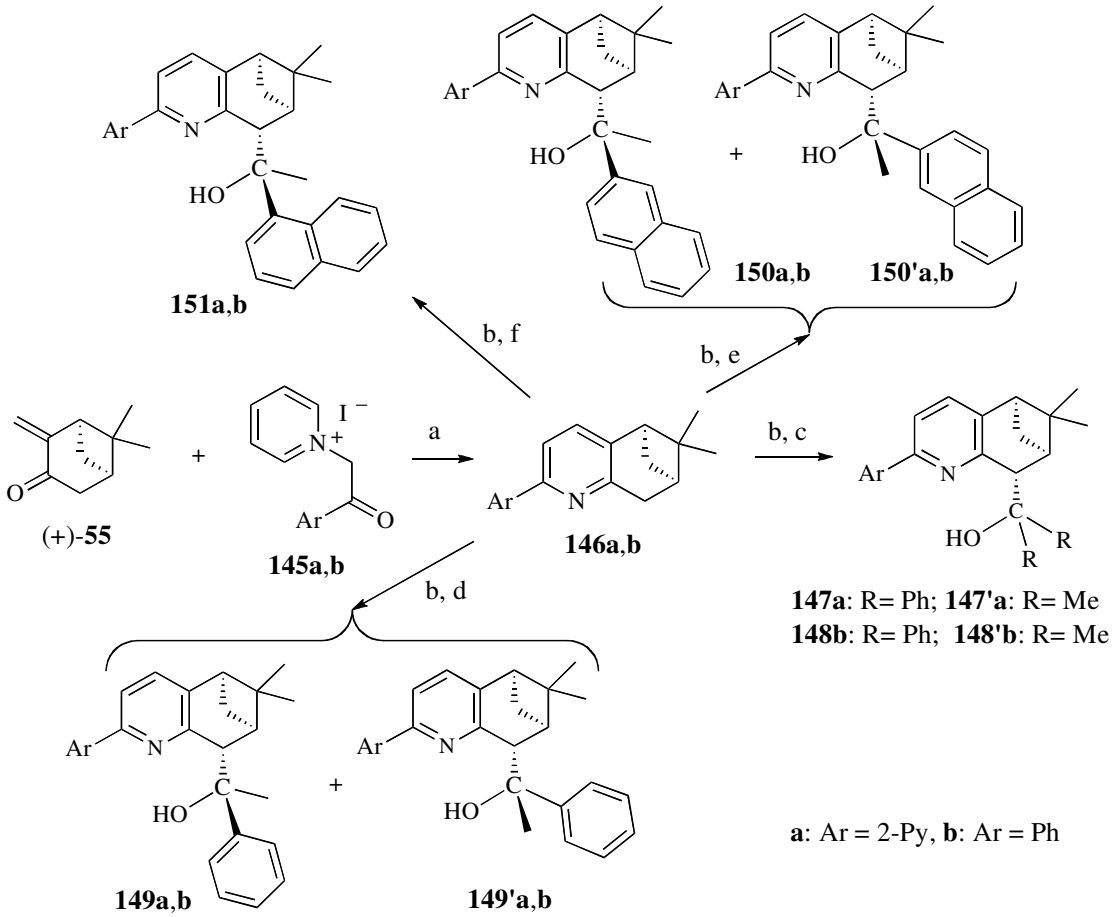
a: THF, r.t.;
b: TBDMSCl, imidazole, DMF, r.t. 91%

Scheme 29

4.3. Addition of chiral pyridine lithium derivatives to carbonyl compounds

Von Zelewsky[41] and Chelucci[42] independently prepared chiral pyridine alcohols from the 2-(pyridin-2-yl)-5,6,7,8-tetrahydroquinoline **146a** and the related 2-phenyl-5,6,7,8-tetrahydroquinoline **146b** (Scheme 30). These compounds were synthesized by reaction of (+)- or (−)-pinocarvone **55** with the pyridinium salts **145a**[43] and **145b**.[41,42] The solution of lithiated **146a** or **146b**, by reaction with several ketones, gave the alcohols **147a** and **151a** or **147b** and **151b**, respectively. When a prochiral ketone was used, a new

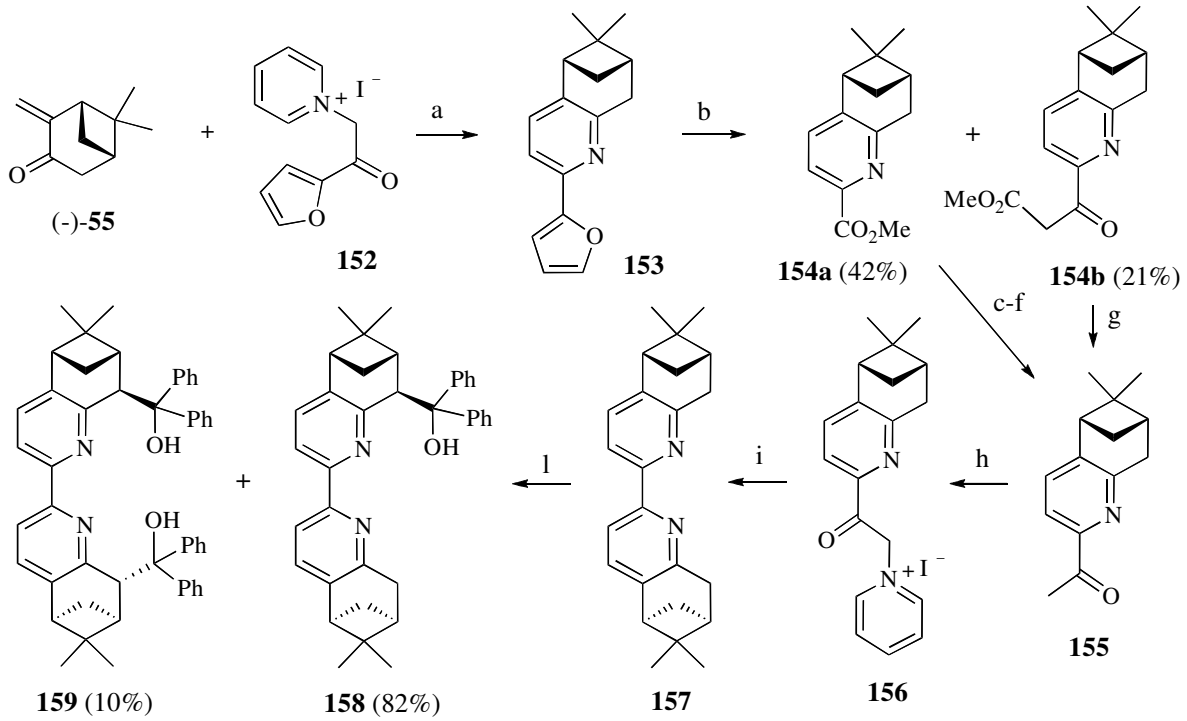
stereogenic centre was introduced in the side chain. Depending on the ketone, either only one diastereomer (with 1-acetonaphthone) or a pair of diastereomers (with acetophenone or 2-acetonaphthone) was obtained.



a: AcOH, $AcONH_4$, 100°C, 20 h, 60%; b: LDA, -60 °C, 2 h; c: benzophenone or acetone, -50 °C, 5 h; d: acetophenone, -50 °C, 5 h; e: 2-acetonaphthone, -50 °C, 5 h; f: 1-acetonaphthone, -50 °C, 5 h.

Scheme 30

Chen and co-workers have recently prepared the bipyridine diol **159** (Scheme 31)[17] that is the corresponding C_2-symmetric ligand of the bipyridine **147a** (see Scheme 30) reported by von Zelewsky.[43] The synthesis of **159** starts from the 2-furylpyridine **153** that was obtained by Kröhnke reaction of (−)-pinocarvone **55** with the pyridinium salt **152**, prepared in turn from 2-acetylfurane (Scheme 31). Compound **153** was ozonolyzed and treated with diazomethane to afford esters **154a** and **154b** in a ratio of about 2:1. Compound **154a** was reduced by $LiAlH_4$ to produce a primary alcohol that was oxidized *via* a Swern oxidation to an aldehyde. This aldehyde was then reacted with MeMgBr to form a secondary alcohol that was oxidized *via* a Swern oxidation to give the ketone **155**. On the other hand, the compound **154b** could be converted into the ketone **155** by decarboxylation with H_2SO_4. Compound **155** was treated with iodine in pyridine to yield the pyridinium salt **156** that, when reacted with enone (−)-**55** and ammonium acetate, produced the bipyridine **157** in 39% yield. This latter compound was treated in a one-pot process with *n*-BuLi and then with benzophenone to produce in a ratio of about 1:8, the C_1- and C_2-symmetric bipyridine diols **158** and **159**, which were separated by chromatography. It was also possible to convert compound **158** into **159** by treatment with *n*-BuLi and then with benzophenone.

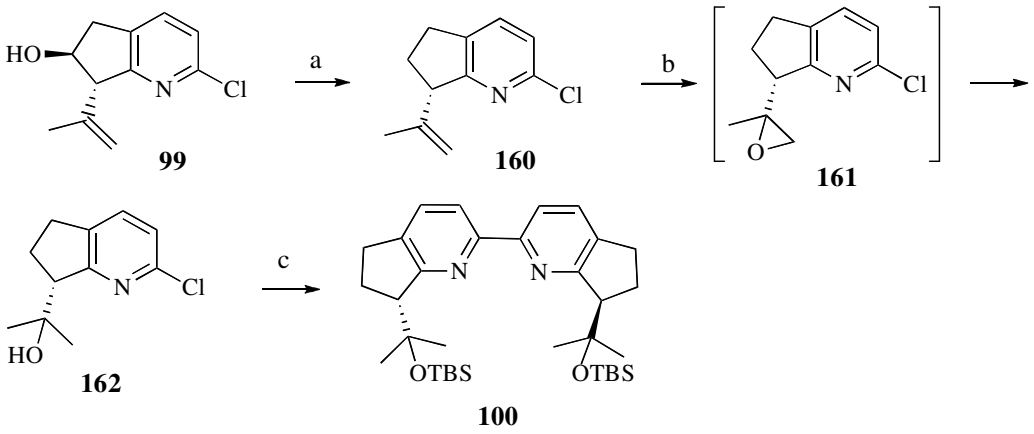


a: AcOH, $AcONH_4$, 100-110 °C, 84%; b: O_3, CH_2Cl_2/CH_3OH (2/1), -78 °C, then CH_2N_2, Et_2O, 0 °C; c: $LiAlH_4$, THF, r.t., 72%; d: $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C, 91%; e: CH_3MgI, EtO_2, r.t., 77%; f: $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C, 100%; g: H_2SO_4, AcOH, H_2O, reflux, 88%; h: I_2, py, 100-110 °C; i: AcOH, $AcONH_4$, 100-110 °C, 39%; l: *n*-BuLi, Et_2O, 0 °C to r.t., then benzophenone, -78 °C.

Scheme 31

4.4. Ring opening of chiral pyridine-epoxides

Katsuki and co-workers prepared bipyridine **100**, whose synthesis has the chiral pyridine alcohol **162** as a key intermediate (Scheme 32).[30] This alcohol was obtained from the alcohol **99** (see Scheme 19) by a three-step sequence.



a: PhOC(S)Cl, DMPA then *n*-Bu_3SnH, BEt_3, 45%; (b) *m*-CPBA then $LiBEt_3H$, 57%; (c) TBDMSOTf, 2,6-lutidine, 91% then $NiCl_2$, PPh_3, Zn, 91%.

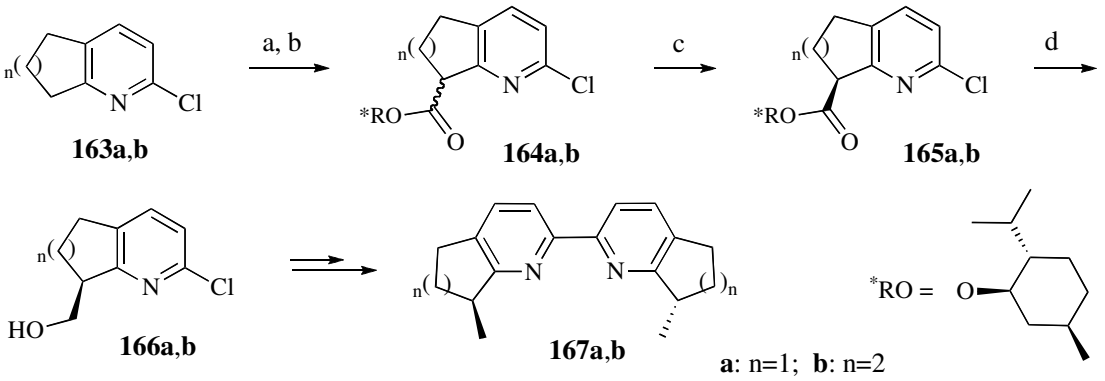
Scheme 32

Treatment of **99** with phenyl chlorothionoformate in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMPA), followed by reaction of the resulting thiocarbonate with tri-*n*-butyltin hydride in the presence of

triethylborane, gave the alkene **160** (45% yield), which, by oxidation with *m*-chloroperbenzoic acid, afforded the epoxide intermediate **161**. This compound was then reduced with super hydride to give the alcohol **162**. From this compound, the bipyridine derivative **100** was ultimately obtained by nickel(0)-mediated homocoupling.

5. β-(2-Pyridyl) *prim*-alcohols

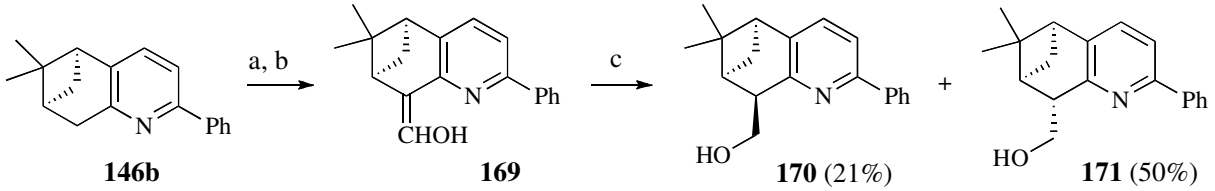
In a series of papers, Katsuki and co-workers reported the synthesis of a number of chiral C_2-symmetric 5,6-cycloalkeno-fused bipyridines with a stereogenic centre bound to the α-position of the cycloalkene ring.[44] As a first example, the preparation of the enantiomerically pure methyl-substituted bipyridines **167a** and **167b** was reported (Scheme 33).[44a] Key intermediates in these syntheses are the primary alcohols **166a** and **166b**. The synthesis of these compounds starts from 6-chloro-2,3-cyclopenteno- and 6-chloro-2,3-cyclohexenopyridine **163a** and **163b**, which were successively treated with LDA and then with (−)-menthyl chloroformate at −78 °C to give the respective carboxylates **164a** and **164b** as mixtures of diastereomers.



a: LDA, -78 °C; b: (-)-menthyl chloroformate **168**, -78 °C; c: chromatographic separation; d: AlH_3.

Scheme 33

From these mixtures, the more polar diastereomers with (*S*)-configuration **165a** and **165b** were separated by chromatography on silica gel and then converted to the corresponding primary alcohols (*S*)-**166a** and (*S*)-**16b** by reduction with AlH_3. From these compounds the related bipyridines **167a** and **167b** were then obtained.



a: BuLi, TMEDA, THF, 1h at -78 °C then 2h at -30 °C; b: DMF at -60 °C; c: $NaBH_4$, MeOH, then chromatographic separation.

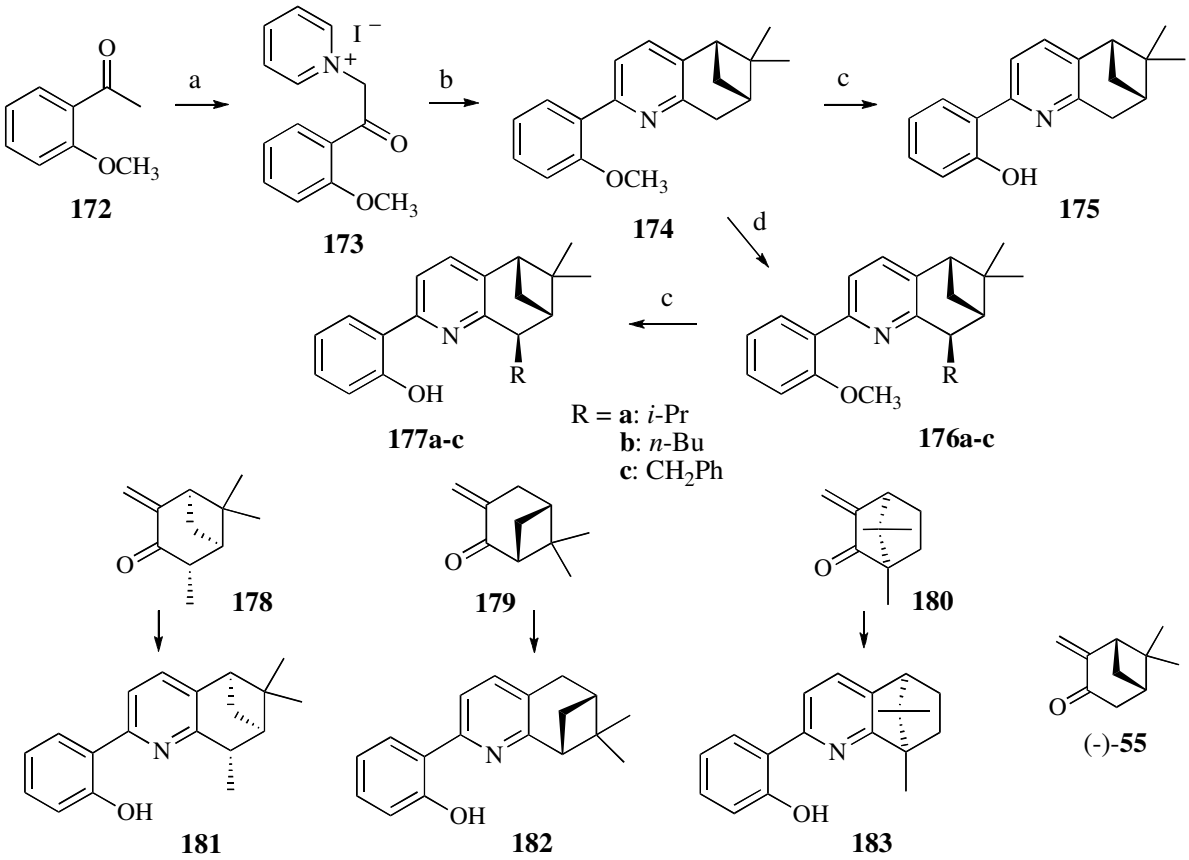
Scheme 34

The chiral tetrahydroquinolines **146b** (obtained from (−)-**55**) was used as starting point to obtain a pyridine *prim*-carbinols (Scheme 34).[42,45] Thus, the lithium derivative of **146b** was treated with DMF at

−60 °C to give the enol **169**, which, by reduction with sodium borohydride, gave a 3:7 mixture of diastereomeric alcohols **170** and **171**, which were finally isolated after chromatography in 21 and 50% yields based on **146**.[42]

6. Pyridines bound to phenolic groups

Chelucci and co-workers prepared a number of chiral 2-(2-hydroxyphenyl)-5,6,7,8-tetrahydroquinolines from naturally occurring monoterpenes (Scheme 35).[46,47] The key intermediate **174** was readily accessible (82% yield) by reaction of (−)-pinocarvone **55** (obtained by oxidation of (+)-α-pinene), with 1-phenacylpyridinium iodide **173** that was in turn prepared by reaction of 2-methoxyacetophenone **172** with iodine in pyridine (Scheme 35).[46] Then, the red solution of lithiated **174**, obtained by treatment with lithium diisopropylamine (LDA) at −78 °C for 1 hour and then 1 hour at 0 °C, was quenched with the proper electrophile (*i*-PrI or *n*-BuBr or $PhCH_2Br$) to give compounds **176a–c**. Finally, ligands **174** and **176a–c** were demethylated with pyridinium chloride at 200 °C to afford the phenol derivatives **175** and **177a–c**, respectively. This protocol was later extended to other chiral α-methylene ketones (Scheme 35).[47] Thus, compounds **178**, **179** and **180**, obtained from (−)-isopinocampheol, (−)-β-pinene and (+)-camphor, respectively, gave the corresponding phenol derivatives **181**, **182** and **183**.

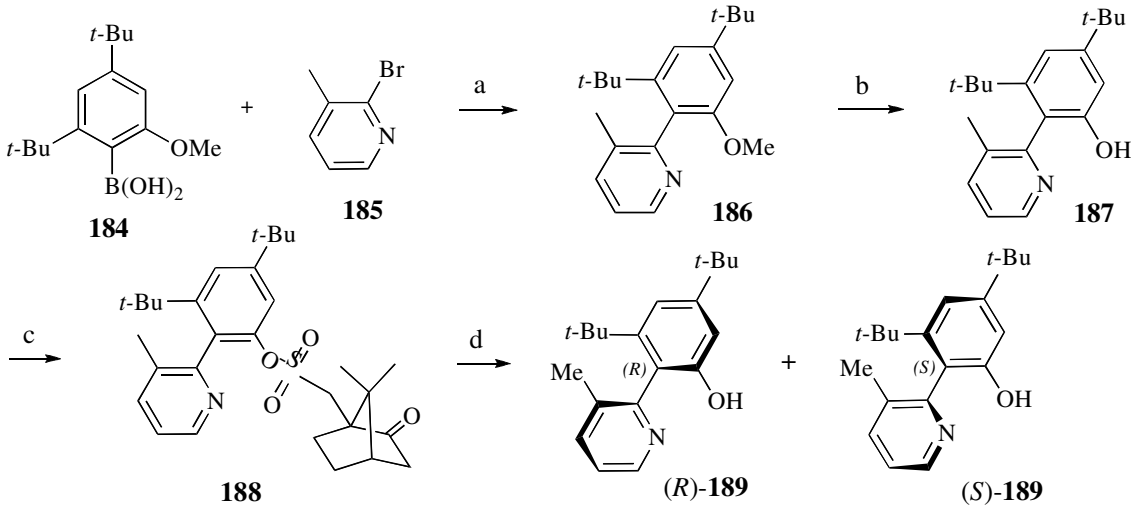


a: I_2, Pyridine; b: (-)-**55**, AcOH, $AcONH_4$, 120°C, 4h; c: Pyridine hydrochloride, 200 °C, 14 h; d: LDA, THF, 1 h at -78 °C and 1 h at 0 °C; then *i*-PrI or *n*-BuBr or $PhCH_2Br$, THF, -78 °C, then slowly r.t.

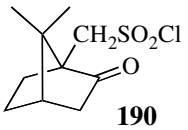
Scheme 35

Chan and co-workers described the synthesis of the optically active atropisomeric pyridyl and bipyridyl phenols (*R*)- and (*S*)-**189** and (*S*,*S*)-**194**, respectively (Schemes 36 and 37).[48] Racemic **187** was obtained

through Suzuki cross-coupling of the boronic acid **184** with 2-bromo-3-methylpyridine **185** using $Pd(PPh_3)_4$ as the catalyst and potassium *tert*-butoxide as the base (83% yield), followed by demethylation of the obtained derivative **186** with pyridine hydrochloride (83% yield) (Scheme 36). Pure (*R*)- and (*S*)-**189** were obtained by chromatographic separation of the diastereomeric sulfonates **188** obtained by reaction of racemic **187** with (*S*)-(+)-camphorsulphonyl chloride. Bipyridines (*S*,*S*)-**194** and (*S*,*S*)-**195** were obtained from **186** according to Scheme 37.[48] A bromo group was introduced at the 6-position of the pyridine ring of **186** by lithiation with *tert*-butyllithium and quenching with 1,2-dibromoethane (71% yield).

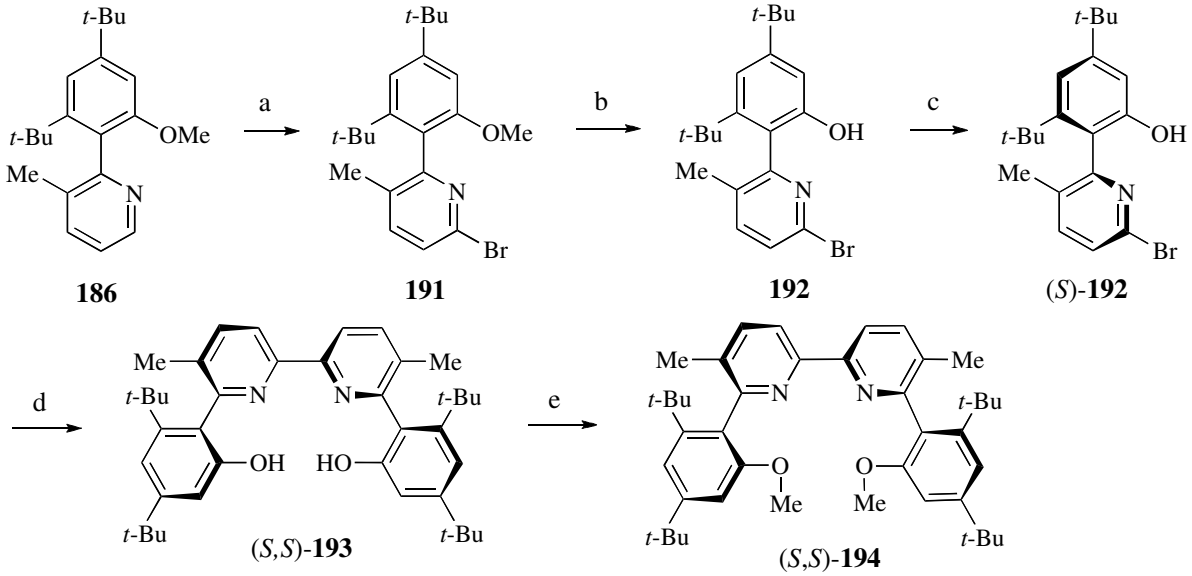


a: $Pd(PPh_3)_4$, KO^{t}Bu, DME, reflux, 83%; b: PyHCl, 200 °C, 83%; c: **190**, pyridine, CCl_4, 98%; d: chromatographic separation, then NaOH, MeOH, H_2O, 60 °C, 24 h.



190

Scheme 36



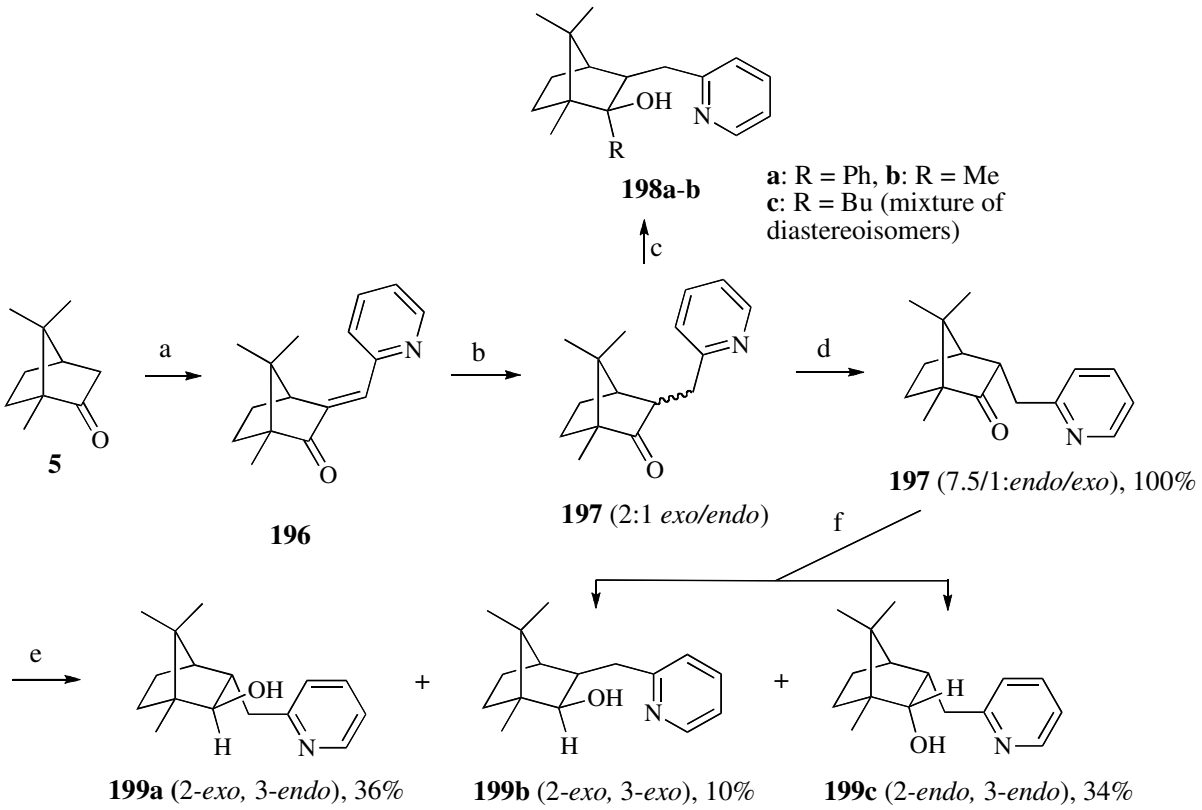
a: *t*-BuLi, THF, -78 °C, 1 h; then $BrCH_2CH_2Br$, THF, -78 °C, 4 h, 71%; b: 48% HBr, AcOH, 120 °C, 8h, 95%; c: enantiomeric separation by chiral HPLC; d: 30% $NiCl_2(Ph_3P)_2$, Zn, Et_4NI, THF, 60 °C, 8 h, 89%; e: NaOH, MeOH, rt, 1 h, Me_2SO_4, 40 °C, 2 h, 90%.

Scheme 37

Demethylation of 2-bromopyridylanisole **191** with 48% HBr in AcOH gave **192** (95% yield) which was subsequently separated into its enantiomers by chiral HPLC. Nickel(0)-catalyzed homo-coupling of (*S*)-**192** gave (*S*,*S*)-**193** without any racemization (89% yield). Methylation of the tetradentate ligand (*S*,*S*)-**193** gave the bipyridine (*S*,*S*)-**194** (90% yield).

7. Miscellaneous pyridine-alcohols

Nevalainen and co-workers prepared a variety of 2-(γ-hydroxyalkyl)pyridines derived from (+)-camphor, which were used in the enantioselective addition of diethylzinc to aldehydes.[49] The introduction of a pyridylmethyl group into the α-position of the carbonyl group of (+)-camphor was obtained following a method described in the literature,[50] which requires the treatment of the sodium enolate of camphor with pyridine-2-carboxaldehyde to give the enone **196**. This compound was hydrogenated on Pd/C in ethanol to yield the ketone **197** as a 2:1 *exo*/*endo* mixture of diastereoisomers (Scheme 38). This mixture was isomerized by treatment with sodium methoxide in methanol to give the *endo* diastereomer **197** as the more abundant epimer. Reduction of the ketone **197** (7.5:1 *endo*/*exo* diastereomeric mixture) with $LiAlH_4$ in THF afforded the alcohol **199** as a 1:1.3 mixture of *trans*-**199a** and *cis* diastereomers **199b,c**. The relative stereochemistry of the newly formed stereocentre was assigned on the basis of coupling constants ($J_{H2,H3}$), taking the benzylidene analog of **199** as a model.[50a] Separation of that mixture by flash chromatography gave *trans*-**199a** (*2-exo, 3-endo*) as a pure isomer and *cis*-**199b**,**c** as a 3.2:1 mixture of *2-endo*, *3-exo* **199**/*2-endo*, *3-endo* **199c** diastereomeric alcohols (Scheme 38).



a: Na, 2-Py-CHO, 28%; b: H_2, Pd/C, EtOH, 83%; c: PhLi (18%) or MeLi (21%) or BuLi (27%); d: MeONa, MeOH; e: $LiAlH_4$; f: EtMgBr.

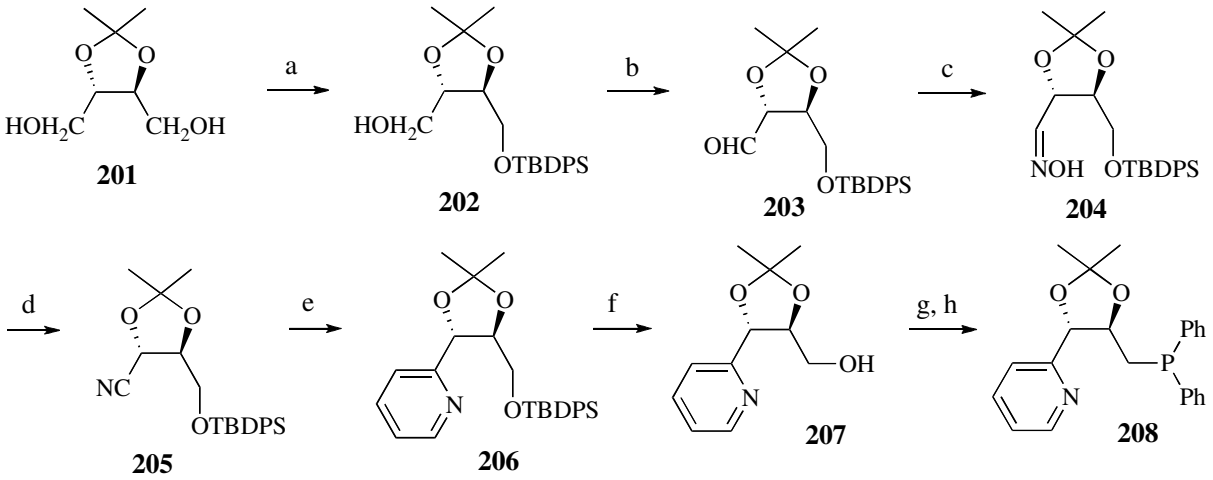
Scheme 38

The small size of hydride allowed the formation of both the *endo* and *exo* diastereomers, whereas more bulky nucleophiles such as PhLi or MeLi added to ketone *exo*-**197** in polar solvents from the less hindered *endo* side[51] afforded **198a** and **198b**, respectively. Moreover, a competing base-promoted enolization takes place, as indicated by the deep red colours of the reaction mixtures. In contrast to these results, the addition of *n*-BuLi to a 2:1 *exo*/*endo* mixture of **197** in hexane provided an inseparable mixture of diastereomeric alcohols **198c**. Probably, the *exo* attack was in that case possible as a result of the increased nucleophilicity of the *n*-BuLi in an apolar solvent.

When the ketone **199** (7.5:1 *endo*/*exo* diastereomeric mixture) was treated with EtMgBr in THF, no ethyl addition product was formed, but the *cis* alcohols **200b**,**c** were obtained as a 1:6 mixture of *2-exo*,*3-exo*/*2-endo*,*3-endo* isomers. It is interesting to note that EtMgBr is a more facially selective reducing agent than $LiAlH_4$ for the preparation of *2-endo*, *3-endo*-**200a** *via* reduction of **197**.

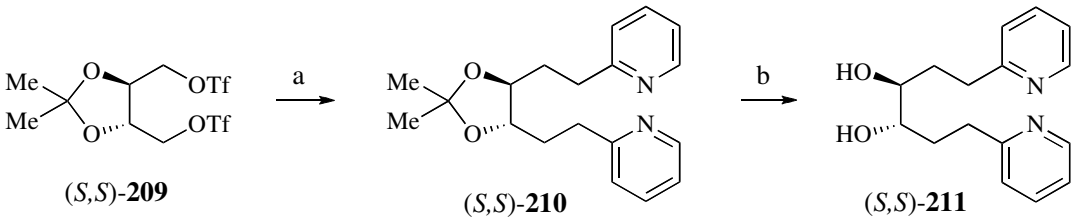
Chelucci and co-workers described the preparation of the phosphine-pyridine-based ligand PYDIPHOS **208**, which has the pyridine carbinol **207** as a key intermediate (Scheme 39).[52,53] The synthesis started from the aldehyde **203** that was prepared by selective protection of the known diol **201**[54] with *tert*-butyldiphenylsilyl chloride, followed by Swern's oxidation of **202**. The aldehyde **203**[55] was converted into the nitrile **205** *via* the formation of the corresponding oxime **204**, followed by dehydration with *N*,*N'*-carbonyldiimidazole. Cobalt-catalyzed cyclotrimerization of the nitrile **205** with acetylene[56] afforded the pyridine **206** in 62% overall yield based on **203**. The hydroxy group was then easily deprotected using a 0.1 M solution of Bu_4NF in THF to give the alcohol **207** that was converted into PYDIPHOS **208** by tosylation, followed by nucleophilic displacement of the tosyl group with a Na/K diphenylphosphide mixture.

Kotsuki and co-workers prepared the pyridine alcohols (*S*,*S*)- and (*R*,*R*)-**211** from the ditriflates (*S*,*S*)- and (*R*,*R*)-**209**, which were in turn synthesized using L- or D-tartaric acid as starting materials (Scheme 39).[57] Reaction of (*S*,*S*)-**209** with 2-picolyllithium afforded the acetonide **210** in 80% yield, which was hydrolyzed to give (*S*,*S*)-**211**. In the same way, (*R*,*R*)-**209** was converted into (*R*,*R*)-**211**. It should be noted that the reaction of 2-pyridyllithium with both **209** and the corresponding diiodide failed (Scheme 40).



a: NaH (1 equiv), *t*-$BuPh_2SiCl$ (TBDPSCl), 75%; b: $(COCl)_2$, DMSO, Et_3N, -78 °C, 89%; c: $NH_2OH{\cdot}HCl$, 10% K_2CO_3; d: *N,N'*-carbonyldiimidazole, 89%; e: CpCo(COD), acetylene, toluene, 120 °C, 14 atm, 94%; f: Bu_4NF, THF, 83%; g: TsCl, Et_3N, DMPA, CH_2Cl_2; h: Ph_3P, Na/K, dioxane, 67%.

Scheme 39



(*S,S*)-**209** (*S,S*)-**210** (*S,S*)-**211**

a: 2-picolyllithium, 80%; b: H_3O^+

Scheme 40

8. Optically active pyridyl alcohols by optical activation methods

The production of optically active pyridyl alcohols from racemic precursors by optical activation methods, including both classical diastereomer-mediated separation and chromatographic techniques has been widely pursued. Recently, kinetic resolution procedures are also finding increasing interest. In this section an overview of these methods is given.

8.1. Diastereomer-mediated separation

Racemic pyridyl alcohols can be resolved into the corresponding enantiomers exploiting either the basicity of the pyridine nitrogen or the carbinol function. In the first case, diastereomeric salts, formed when pyridines are treated with enantiopure acids, are separated by fractional crystallization. (*R*)-Tartaric acid and its acyl derivative dibenzoyltartaric acid, and (+)-10-camphorsulphonic acid are widely used for this purpose. Thus, for instance, the three isomeric pyridyl ethanols,[58] 1,1,1-trichloro-3-(3-ethylpyridin-4-yl)propan-2-ol[59] and 1-phenyl-1-(pyridin-4-yl)nonan-1-ol[60] were resolved with tartaric acid, whereas 1-(pyridin-2-yl)propan-1-ol[61] and 1-(pyridin-2-yl)propan-2-ol[62] with dibenzoyltartaric acid. (+)-10-Camphor-sulphonic acid was instead preferred for 1-phenyl-1-(pyridin-2-yl)nonan-1-ol,[63] cyclohexyl(phenyl)(pyridin-2-yl)methanol,[64] 1-(2-methylpyridin-3-yl)-1-phenylethanol[65] and 1-phenyl-1-(pyridin-4-yl)ethanol.[66]

On the other hand, by reacting racemic pyridyl alcohols with enantiopure acid derivatives, diastereomeric esters are obtained, which can be separated by crystallization or chromatography.

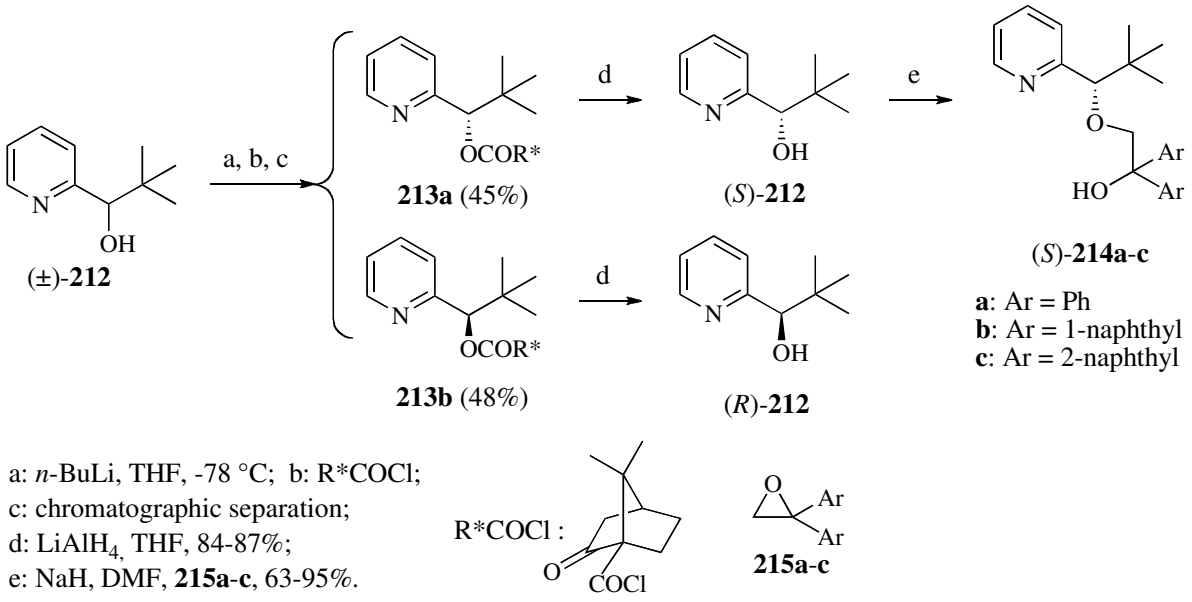
A significant example of this procedure concerns the preparation of the enantiopure pyridyl phenol (*R*)- and (*S*)-**189** obtained by chromatographic separation of the diastereomeric sulfonates **188** formed by reaction of racemic **187** with (*S*)-(+)-camphorsulphonyl chloride, followed by hydrolysis with diluted NaOH (Scheme 36).[48]

Enantiomerically pure pyridyl alcohols **212** were prepared by Hoshino and co-workers through separation of the diastereomeric esters **213a** and **213b**, prepared by reaction of **212** with D-ketopinic acid chloride.[67] The separation was accomplished by medium-pressure liquid chromatography in 45 and 48% yields, respectively (Scheme 41). These esters were reduced with $LiAlH_4$ to afford the corresponding enantiomerically pure (*S*)- and (*R*)-**212**, in 84 and 87% yields. By reaction of (*S*)-**212** with the epoxides **215a–c** in the presence of NaH in DMF, the tridentate ligands (*S*)-**214a–c** were obtained in 63 to 95% yields (Scheme 41).

Kang and co-workers reported an interesting pyridyl alcohol resolution by a protocol that facilitates diastereomer separation (Scheme 42).[68] Thus, alcohol **216** was converted by reaction with (–)-menthyl chloroformate into the diastereomeric carbonates **217**. This mixture was oxidized with *m*-CPBA to give the *N*-oxide carbonates **218** that were so easily separated through fractional crystallization. Subsequent

deoxygenation with PCl_3 and hydrolysis of the diastereomeric pure carbonates (*R*)- and (*S*)-**218** gave (*R*)- and (*S*)-**216**, respectively.

Besides the alcohol **216**, Kang and co-workers designed the slightly modified pyridyl alcohol **221** (Scheme 42). Oxidation of **216** with pyridinium chlorochromate afforded the ketone **222**, which was further α-dialkylated with iodoethane to give the α,α-diethyl-substituted ketone **223** in 28% yield. Reduction of this ketone with $LiAlH_4$ gave the racemic alcohol **221**, which was converted into the corresponding carbamic diatereomers **222** using (*R*)-(+)-α-methylbenzyl isocyanate. Subsequent oxidation with *m*-CPBA afforded the diastereomeric *N*-oxide carbonates **222** (97% for the two steps) that were separated by fractional crystallization. Finally, deoxygenation, followed by hydrolysis of the pure diastereomers, afforded (*R*)- and (*S*)-**221** in 85 and 92% yields, respectively.



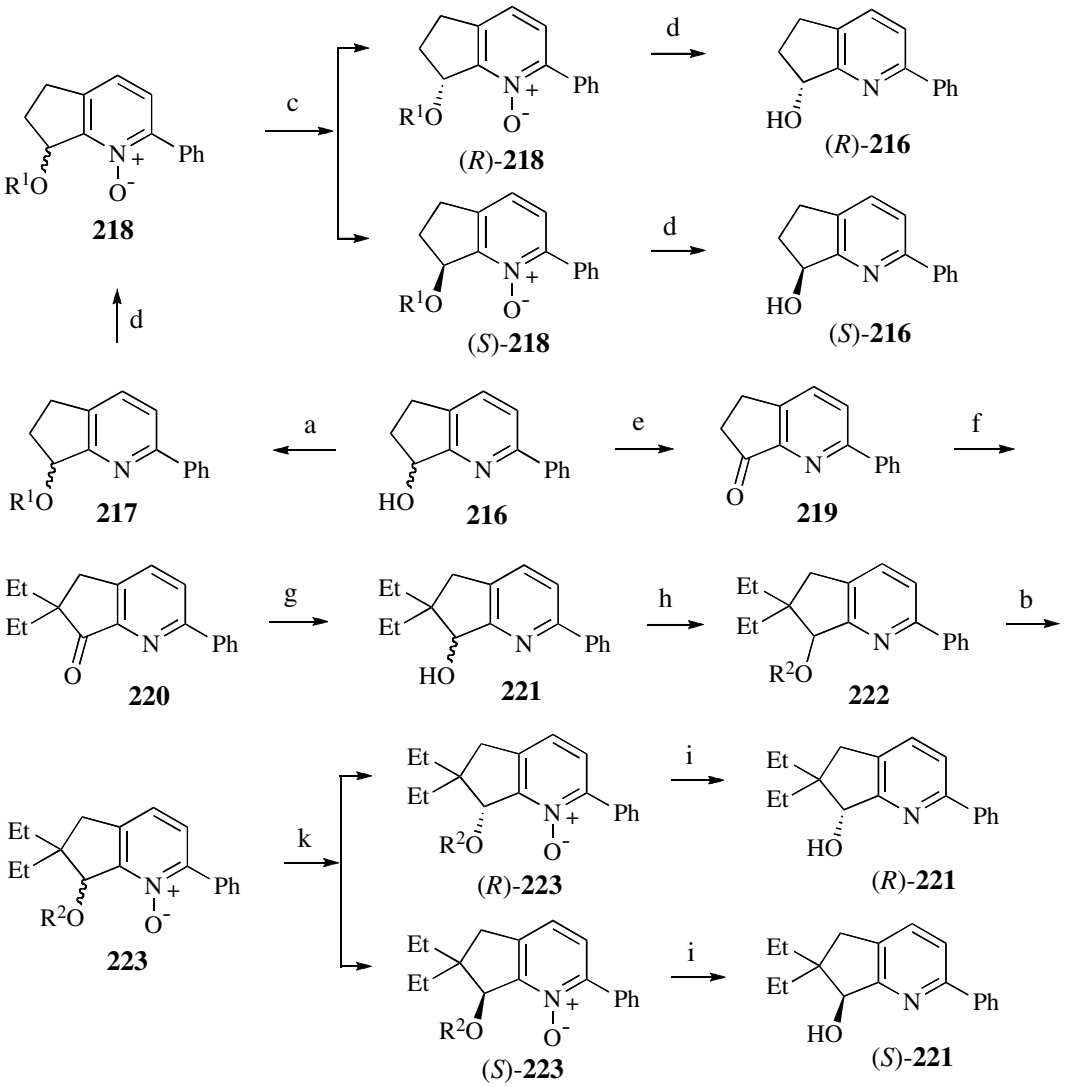
Scheme 41

8.2. Kinetic resolution

Kinetic resolution of *sec*-alcohols by asymmetric acylation with non-enzymatic reagents or catalysts is attracting increasing attention[69] and a number of pyridyl *sec*-alcohols have been resolved using this approach.

Yamada and co-workers reported that the kinetic resolution of various *sec*-alcohols resulted in good to excellent selectivities in the presence of 0.05 to 0.5 mol% of the catalyst 4-dimethylaminopyridine derivative **227**.[70] Among the examined substrates, racemic 1-(pyridin-3-yl)ethanol **224** was selectively acylated with *iso*-butyric anhydride in the presence of 0.5 mol% of **227** (Scheme 43) to afford the (*S*)-alcohol **225** with good enantioselectivity (60% conv, 92% ee).

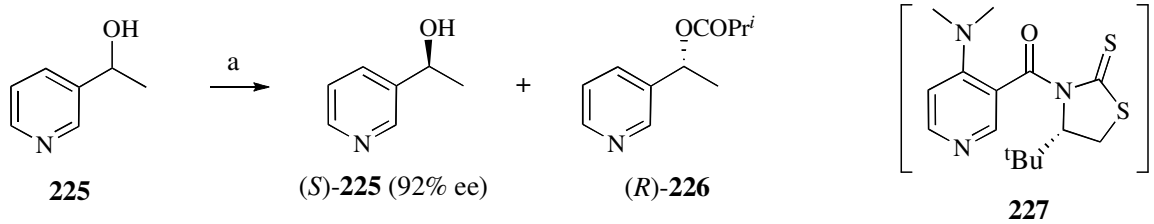
Pfaltz and co-workers, in a study aimed at developing a catalytic system for the kinetic resolution of 1,2-diols and pyridyl alcohols by copper(II)-catalyzed benzoylation, used bisoxazolines **230** and boron-bridged bisoxazolines **231** as ligands (Scheme 44).[71] Pyridyl alcohols **216** and **228a–d** were scrutinized since these compounds were estimated to be able to chelate copper(II). This fact is thought to be an essential requirement for achieving high enantioselectivties.[72]



R^1 = (+)-menthoxycarbonyl R^2 = (*R*)-(+)-α-methylbenzylcarbamyl

a: *n*-BuLi, (-)-menthyl chloroformate, THF, 0 °C to r.t., 99%; b: *m*-CPBA, $CHCl_3$, r.t., 100%; c: fractional crystallization, Et_2O/hexane, r.t., 16 h; d: PCl_3, $CHCl_3$, r.t.. then KOH, 60 °C, 71-92%; e: PCC, CH_2Cl_2, 45 °C, 72%; f: *t*-BuOH, EtI, CH_2Cl_2, r.t.; g: $LiAlH_4$, THF, r.t., 45%; h: (*R*)-(+)-α-methylbenzyl isocyanate, toluene, 100 °C, 97%; k: fractional crystallization, $CHCl_3$/hexane, 0 °C, 16 h; i: PCl_3, r.t., then Et_3N, $HSiCl_3$, toluene, 100 °C, 85-92%.

Scheme 42

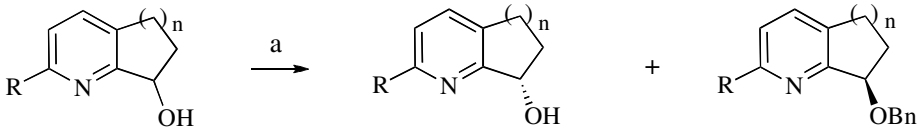


a: **227** (0.5 mol %), (*i*-PrCO)$_2$O (0.8 equiv), Et_3N (0.9 equiv), CH_2Cl_2, r.t., 12 h.

Scheme 43

They found that ligands **231** induce higher (*S*)-selectivities than ligands **230**. The obtained data indicate that, when the pyridine is fused with a six-membered ring, the enantioselectivity can be higher than

that with a five-membered ring analog. Moreover, the substitution at the α-CH of the pyridine ring with a phenyl group greatly enhances the selectivity. The best results achieved for each substrate are reported in Table 1.

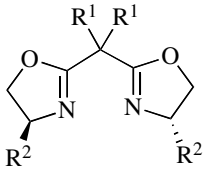


216, **228a-d** (*S*)-**216**, (*S*)-**228a-d** (*R*)-**229a-e**

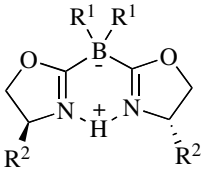
216: R = Ph, n = 1; **228a**: R = H, n = 1; **228b**: R= H, n= 2; **228c**: R = Ph, n = 2; **228d**: R = Cl, n = 2.

229a: R= H, n= 1; **229b**: R= Ph, n= 1; **229c**: R= H, n= 2; **229d**: R= Ph, n= 2; **229e**: R= Cl, n= 2.

a: ligand (1.0 mol%), $CuCl_2$ (1.0 mol%), PhCOCl (0.51 equiv), *i*-$PrNEt_2$ (1 equiv), CH_2Cl_2, 0 °C, 2 h.



230a: R^1= Me, R^2= Ph
230b: R^1= Ph, R^2= Bn



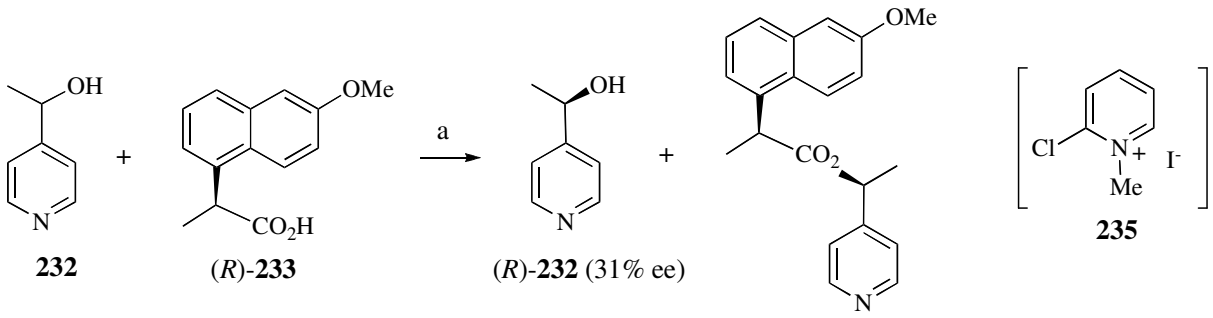
231a: R^1= Et, R^2= *t*-Bu; **231b**: R^1= Ph, R^2= *t*-Bu
231c: R^1= Ph, R^2= Bn; **231d**: R^1= Et, R^2= Bn
231e: R^1= 3,5-bis(trifluoromethyl)phenyl, R^2= Bn

Scheme 44

Table 1. Kinetic resolution of pyridyl alcohols **216** and **228a–d** using ligand **231** (Scheme 44).[a]

substrate	ligand	alcohol ee (%)	benzoate ee (%)	conversion (%)	selectivity
216	**231d**	16	3	33	2
228a	**231e**	76	91	45	51
228b	**231d**	>99	60	62	9
228c	**231e**	70	97	42	125
228d	**231d**	62	80	44	17

[a]Only the best results are reported.



232 (*R*)-**233** (*R*)-**232** (31% ee) **235**

a: **235**, Et_3N, toluene, r.t., 1 h (*R,S*)-**234** (60% de)

Scheme 45

Mukayama reagent **235** was used for the kinetic resolution of racemic 1-(pyridin-4-yl)ethanol **232** with the enantionerically pure (*R*)-naproxen **233** in the presence of triethylamine (Scheme 45). Enantiomerically

enriched (*R*)-**232** (up to 31% ee) and diastereomerically enriched ester (*R,S*)-**234** (up to 60% de) were obtained.[73]

9. Conclusions

This account is the second part of a series of reviews dedicated to chemical and bioorganic syntheses and application in asymmetric catalysis of chiral non-racemic pyridyl alcohols. In this occasion the stereoselective synthesis of optically active pyridyl alcohols with a *tert*-carbinol chiral centre bound to a pyridine ring and the synthesis of some examples of pyridyl *tert*-alcohols without this topological element are explained. Other kinds of these chiral non-racemic compounds such as pyridyl β-carbinols and pyridines bound to a phenolic ring are illustrated too. In addition, the production of some representative optically active pyridyl alcohols from racemic precursors by optical activation methods is described. Although many routes toward the asymmetric synthesis to these compounds with comparably simple structures have been developed, new opportunities are yet to be explored. It is hoped that this review will stimulate further research on this subject so that new chiral pyridyl alcohols can be prepared and applied in many areas of the organic and organometallic chemistry.

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SYNTHESIS AND FUNCTIONALIZATION OF 4-SUBSTITUTED QUINAZOLINES AS KINASE TEMPLATES

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Abstract. *Over the last two decades, substituted quinazolines have attracted much interest as kinase inhibitors from the pharmaceutical industry and academic groups. The quinazoline core represents a relatively simple and accessible scaffold that can be substituted via a number of key vectors to give potent and selective inhibitors of a wide range of kinase targets. Here, we will attempt to condense over 20 years of medicinal chemistry library research on this scaffold carried out in AstraZeneca's laboratories and externally into what we regard as the key "savoir-faire".*

Contents

1. Introduction

There are about 530 known protein kinases, meaning that they are one of the largest protein families of the human genome.[1] Kinases play roles in just about every aspect of physiological processes. Therefore, the human kinome offers a very important drugable target notably for oncology but also for other therapeutic areas. Almost all kinases have a discrete catalytic domain and use adenosine 5'-triphosphate (ATP) as a co-substrate which transfers its γ-phosphate onto a hydroxyl acceptor group (*e.g.*, serine, threonine or tyrosine) of an acceptor–protein, peptide or lipid. The role of phosphorylation represents a key step in many vital cell processes such as proliferation, differentiation and apoptosis. Modulation of the role of kinases in signal transduction has thus been a key area of pharmaceutical research over the last two decades.[2]

1.1. Significance of quinazolines for the pharmaceutical industry

At present, there are nine small-molecule kinase inhibitors which have received approval for the treatment of cancer. All of these compounds are in the class of ATP-competitive kinase inhibitors.[3] 4-Substituted quinazolines represent a very important class, with two compounds in *gefitinib*,[4] *erlotinib*[5]

already commercialized for the treatment of non-small cell lung cancer and *lapatinib*[6] for hormone-positive and HER2-positive advanced breast cancer. In addition, there are several compounds (*e.g.*, *afatinib*,[7] *cediranib*[8] and *barasertib*[9]) in late phase clinical trials (Figure 1).

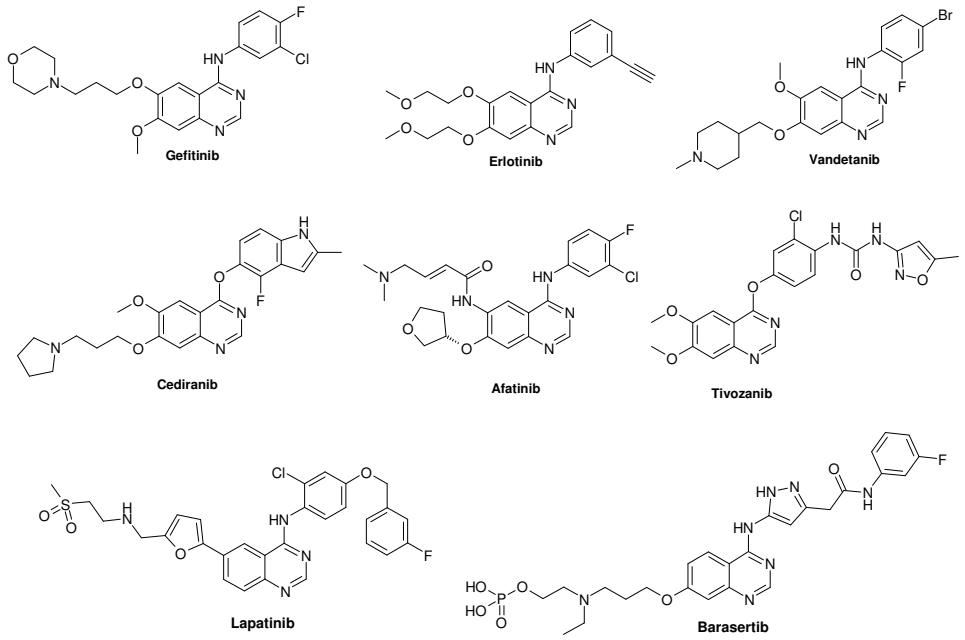
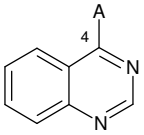
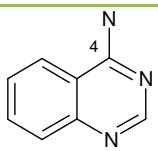
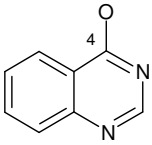
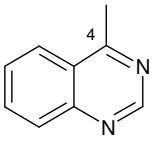
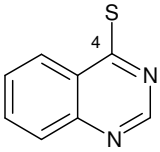


Figure 1

Table 1. Current distribution of 4-substituted quinazolines in the public domain. A=Any atom except H.

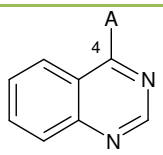
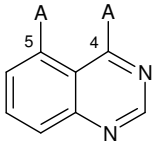
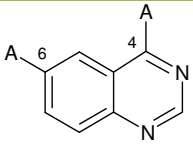
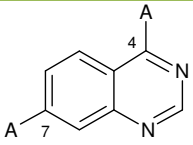
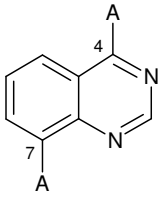
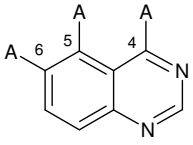
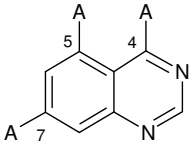
Entry	Substructure	CAS Nos	No. of Ref	No. of journal ref	No. of patents	% Share of CAS Nos / patents
1		144293	12485	6091	**3843**	N/A
2		129026	9574	6643	2654	89.4/69.1
3		8339	2503	1278	1203	5.8/31.3
4		3653	1245	638	593	2.5/15.4
5		2634	263	177	85	1.8/2.21

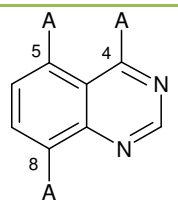
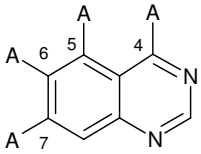
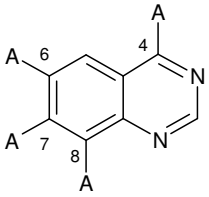
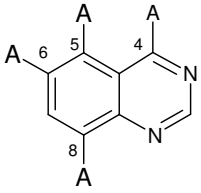
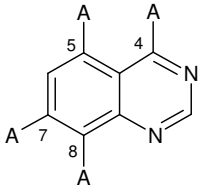
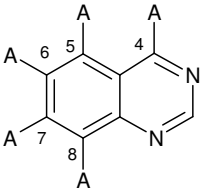
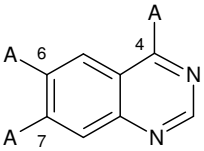
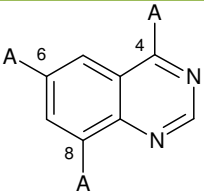
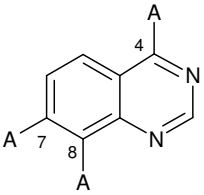
As a consequence of such a profound industrial interest in this heterocycle, finding new intellectual property has become somewhat challenging. For example, if we focus simply on 4-aniline substituted

quinazolines with ether substitution at positions 6 and 7, a substructure present in 3 out of the 8 compounds depicted in Figure 1, there are 9,616 CAS Nos (chemical abstract service registry numbers) with 7,230 references including 1605 chemistry patents. This class remains the most successful class of quinazolines to date.[10] The following analysis gives an impression of the level of interest in the family of 4-substituted quinazolines to date.

Table 1 shows the level of investment up to the current day[10] in 4-substituted quinazolines (entry 1). Within this large family, it is apparent that the 4-amino substituted subset (entry 2) has received the most attention, accounting for 89% of the registered compounds cited in 69% of the patents in this class. The second class of quinazolines, the most studied, is the 4-ether class (entry 3), accounting for approximately 6% of total CAS numbers followed by 4-carbon linked (entry 4) with 2.5% and 4-sulfur linked derivatives (entry 5) with just less than 2%.

Table 2. Current literature distribution looking at substitution on the phenyl ring moiety of the 4-substituted quinazoline family.

Entry	Substructure	CAS Nos	No. of Refs	No. of journal refs	No. of patent refs	% Share of CAS Nos / patents
1		144293	12485	6091	3843	N/A
6		1925	558	261	295	1.3/7.7
7		45726	1804	844	955	31.7/ 25.0
8		24468	545	208	366	17.0/9.5
9		1695	178	92	92	1.2/2.4
10		12252	291	117	111	8.5/2.9
11		1111	131	44	87	0.8/2.3

12		426	210	67	142	0.3/3.7
13		151	41	19	21	0.1/0.6
14		533	97	45	51	0.4/1.3
15		118	51	28	20	0.1/ 0.5
16		62	111	3	103	0.04/2.7
17		519	144	61	82	0.4/2.1
18		40641	8167	5821	1999	28.2/ 52.0
19		4352	127	66	61	3.1/1.6
20		367	95	47	48	0.3/1.3

If we take a closer inspection of this family and look specifically at substitution on the neighbouring phenyl ring, the level of interest is even more pronounced in one particular subset, 4,6,7-trisubstituted

quinazolines featuring in 1999 patents, thus accounting for around 50% of the investment in C-4-substituted quinazolines.

Inspection of Table 2 reveals that within the family of 4-substituted quinazolines (entry 1), substitution at positions 6 and/or 7 (*e.g.*, entries 7, 8 and 18) are most present accounting for almost 77% of all CAS numbers and cited in 80% of the total patents. The 5 position has also attracted significant interest as kinase templates (*e.g.*, entries 6, 10, 11), accounting for 10.6% of the total CAS numbers in this family. In conclusion, almost 90% of the total CAS numbers are represented by mono-substitution at positions 5, 6 or 7 or a combination of substitution at these positions.

Table 3. Distribution of literature in the 4,6,7-trisubstituted quinazoline family looking specifically at some important atom links on the phenyl ring.

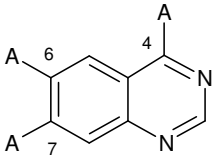
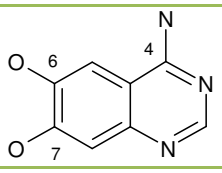
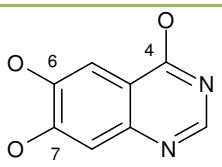
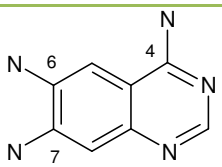
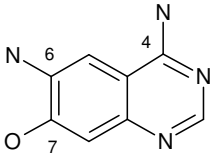
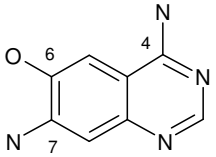
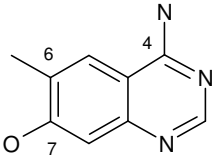
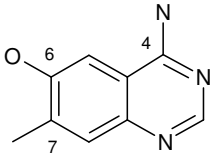
Entry	Substructure	CAS Nos	No. of refs	No. of journal refs	No. of patent refs	% Share of CAS Nos / patents
21		40641	8167	5821	1999	N/A
22		15688	7840	5447	1758	38.6/87.9
23		2517	546	172	372	6.2/18.6
24		4670	157	110	45	11.5/2.3
25		2166	428	130	297	5.3/14.9
26		220	11	2	9	0.5/0.5
27		517	36	5	51	1.3/2.6
28		337	17	2	15	0.83/0.75

Table 3 shows clearly the major interest in this important subset surrounds the 4-amino-6,7-bis-(ether)quinazoline family (entry 22). This family is present in almost 90% of the total number of patents and the interest in this class does not seem to be fading despite heavy investment since the early 90s from major pharmaceutical companies (see Figures 1 and 2). The 4-ether-6,7-bis(ether)quinazoline family follows accounting for almost 19% of patent coverage (within this class, we find late stage development compounds such as *tivozanib*) which is closely followed by 4-amino substitution with 6-N-7-O substitution (*e.g.*, *afatinib*, *canertinib*) accounting for approximately 15% of total patents in this class.

Figure 2 shows quite clearly that the interest in 4-substituted quinazolines is not fading, with 415 individual patents filed in 2009 compared with just 58 in 1999, a total increase of over 700%. This is a general trend within every major sub-family having notable increases in patents filed from 1999 to 2009. The family is quite clearly dominated by 4-amino-6,7-O substituted quinazolines, representing 63% of the total patents in this family in 2009. The second most important family is 4,6 disubstituted quinazolines, exemplified in 144 patents filed in 2009. Perhaps surprisingly given the development success of *afitinib*, the 4-N-6-N-7-O family is much scarcer with just 48 patents filed in 2009. In conclusion and despite the heavy investment from industry and academia since the early 1990s, the interest in this substructure is not fading rather increasing, therefore, articulation of the key synthetic chemistry employed to manipulate this scaffold is of interest. This chapter will focus on the manipulation of positions 4, 5, 6 and 7 which have been the most studied as vectors for kinase templates.

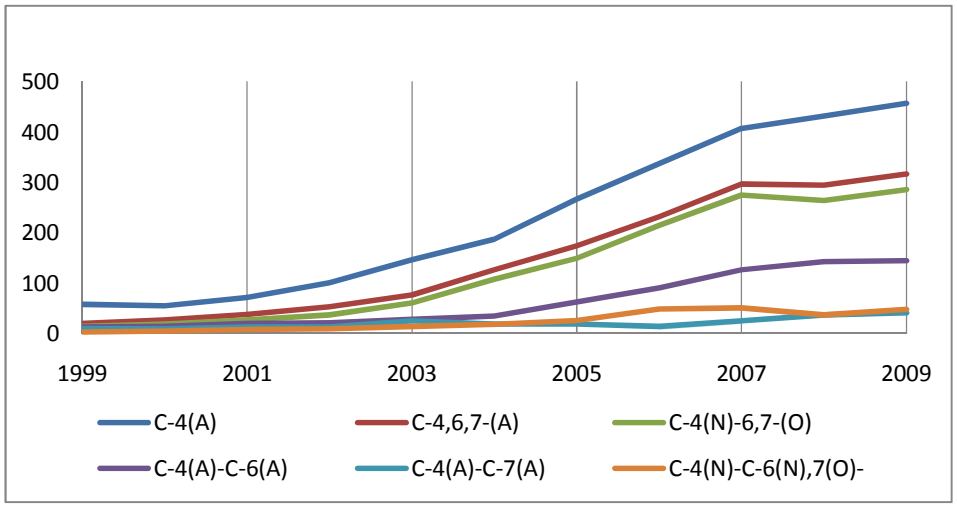


Figure 2. The number of patents published during the last ten years concerning the 4-substituted quinazolines series.

1.2. Generalized binding mode of quinazolines in kinases

Quinazolines compete with adenosine 5'-triphosphate (ATP) by binding to the hinge region of the kinase backbone, a model proposed by Traxler.[11] ATP binds to the backbone hinge region through a H-bond acceptor interaction with N-3 and a H-bond donor interaction with the exocyclic free amino group (Figure 3).

ATP-competitive kinase inhibitors bind to the hinge region through one or more H-bond interactions. 4-Substituted quinazolines bind to the hinge-binding region through a H-bond acceptor interaction at N1, mimicking the adenine core, while substitution at 4 usually occupies a hydrophobic back-pocket which

offers extensive scope to improve potency and selectivity. Finally, substituents at 6 and/or 7 occupy the sugar pocket or solvent channel and offer avenues for improving notably physicochemical properties (Figure 4).

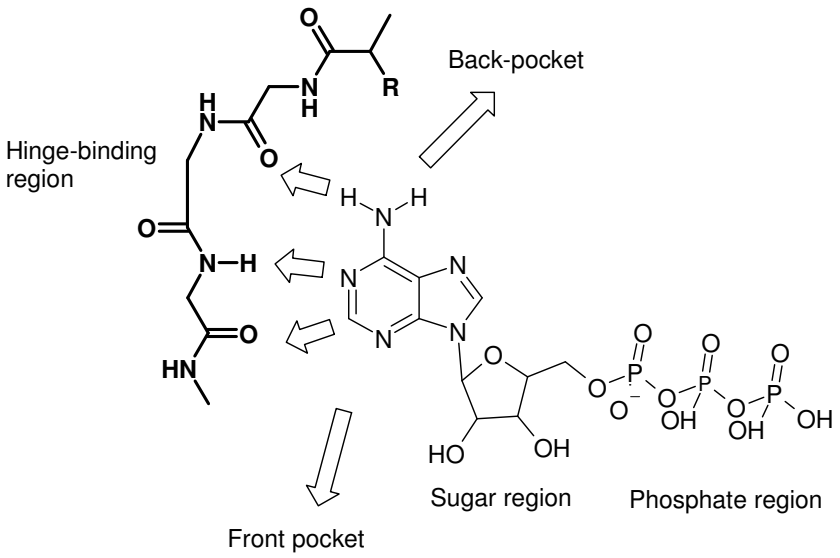


Figure 3. Binding mode of ATP to the hinge region.

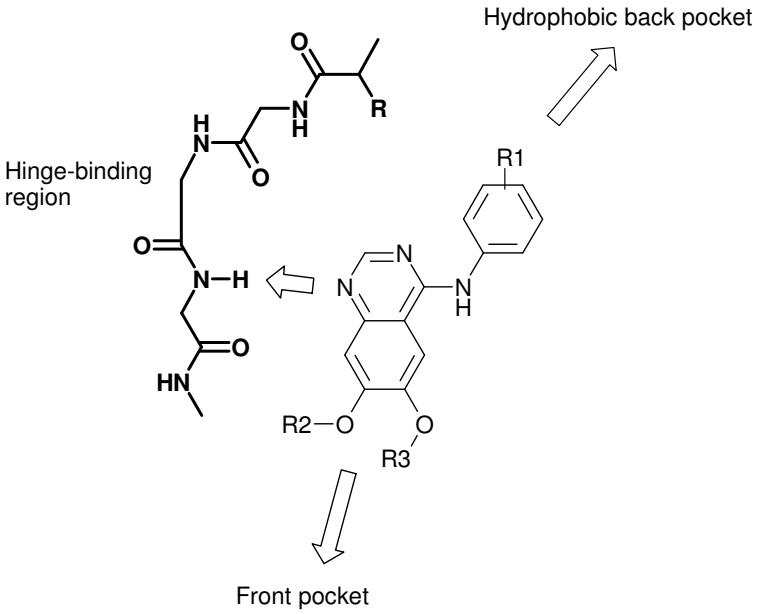


Figure 4. Generic binding mode of 4-anilinoquinazolines.

2. Synthetic manipulation of quinazolines

2.1. General reactivity of quinazolines

The quinazoline ring represents an attractive scaffold for chemical diversification thanks to four differentially activated positions at 2, 4, 5 and 7 allowing for inclusion of straightforward nucleophilic aromatic substitution strategies while positions 8 and 6 are relatively electron-rich centres. The generalized reactivity pattern of quinazolines can be summarized in Figure 5.[12]

As the positions 4, 5 and 7 are activated by the quinazoline ring, direct nuceophilic aromatic substiution (S_NAr) is generally achievable under mild conditions, with the order of reactivity being

4>>2>5>7. Indeed, this relationship was nicely illustrated in a recent article by Ford *et al.* at AstraZeneca Process Research and Development, Cheshire, U.K.[13]

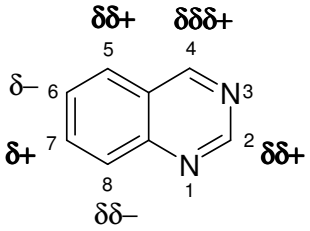
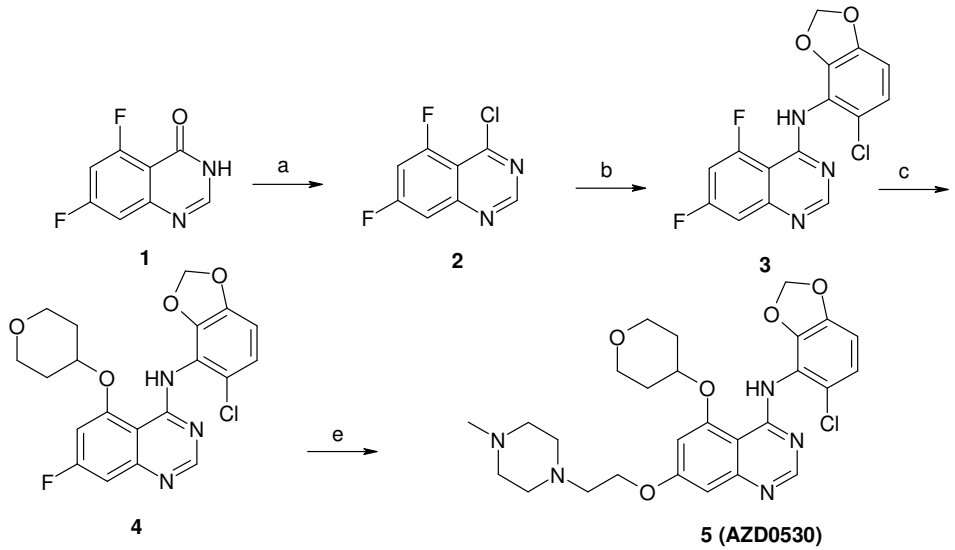


Figure 5. Generalized reactvity core of the quinazoline ring.

Their strategy towards the synthesis of AZD0530, a potent c-Src inhibitor, relied on sequential S_NAr reactions on 5,7-difluoro-4-chloroquinazoline (**2**). The first substitution at position 4 was achieved with 6-chloro-2,3-methylenedioxyaniline under acid-catalyzed conditions to afford **3**. The second displacement was achieved using a 2 fold excess of the potassium salt of 4-hydroxytetrahydropyran in refluxing THF to afford **4**. Finally, the synthesis of AZD0530 (**5**) was terminated by the final S_NAr, requiring a 3.36 fold excess of the potassium salt of 1-(2-hydroxyethyl)-4-methylpiperazine in 1,2-dimethoxyethane (DME) at 120 °C (Scheme 1).

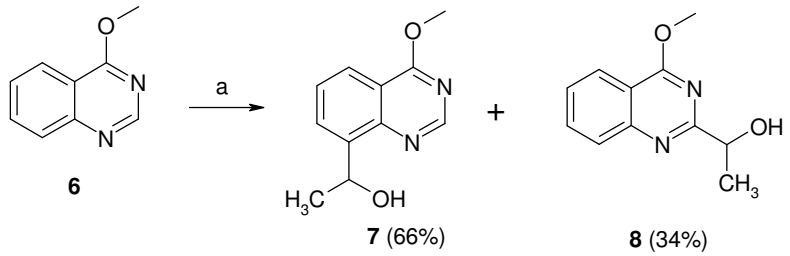


Process research route to AZD0530. Reagents and conditions: a) $POCl_3$, *N,N*-diisopropylethylamine (DIPEA), MeCN, reflux, not isolated; b) 6-chloro-2,3-methylenedioxyaniline, 80 °C, 16 h, 85%; c) 4-hydroxypyran, KO*t*-Bu, THF, reflux, 74%; d) 1-(2-hydroxyethyl)-4-methylpiperazine, KOH, DME, 120 °C, 69%.[13]

Scheme 1

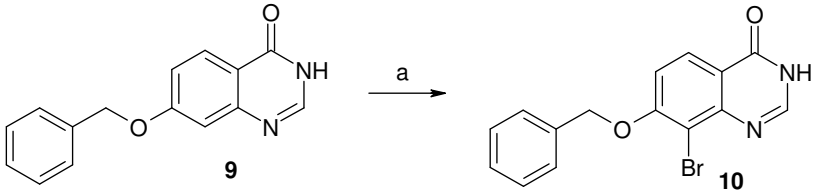
Positions 6 and 8 are not activated and, as a consequence, are the most problematic positions to derivatize. Selective C-8 functionalization can be conveniently achieved *via* deprotonation using a 4-fold excess of lithium tetramethylpiperidine as demonstrated by Quéguiner and co-workers at Rouen University, France (Scheme 2).[14]

In our own laboratories, we have demonstrated that electrophilic substitution takes place preferentially at the 8 position with benzyloxy substitution at the 7 position, albeit under forcing conditions, to afford excellent yields of 8-brominated quinazoline **10** with no traces of bromination at the 6 position (Scheme 3).[15]



Reagents and conditions: a) LiTMP (4 equiv.), THF, −78 °C, 30 min., followed by addition of of CH_3CHO (1 equiv.).

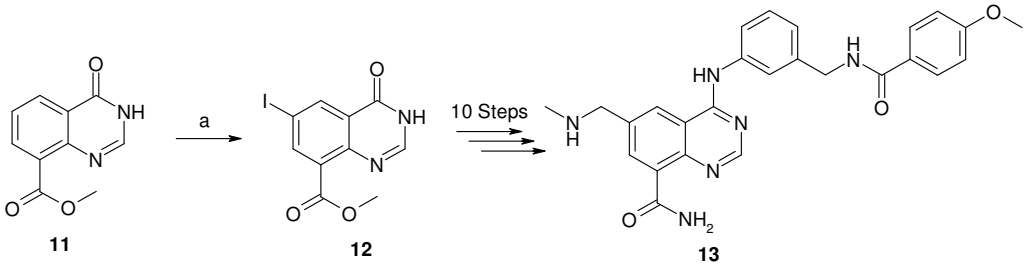
Scheme 2



Reagents and conditions: a) *N*-bromosuccinimide (NBS), AcOH, reflux, 95%.

Scheme 3

A rather direct example exploiting the electron-rich 6 position was recently provided by Merck scientists specifically looking for novel azabicyclic inhibitors of the Aurora and PDK1 kinases, with carboxamide substitution at the 8 position. Electrophilic iodination of **11** was achieved using *N*-iodo-succinimide (NIS) in concentrated sulfuric acid at 40 °C for 8 days to give **12**. This key step permitted derivatization at positions 4, 6 and 8 to prepare large libraries of desired final kinase inhibitors (*i.e.*, **13**) in a convergent manner (Scheme 4).[16]

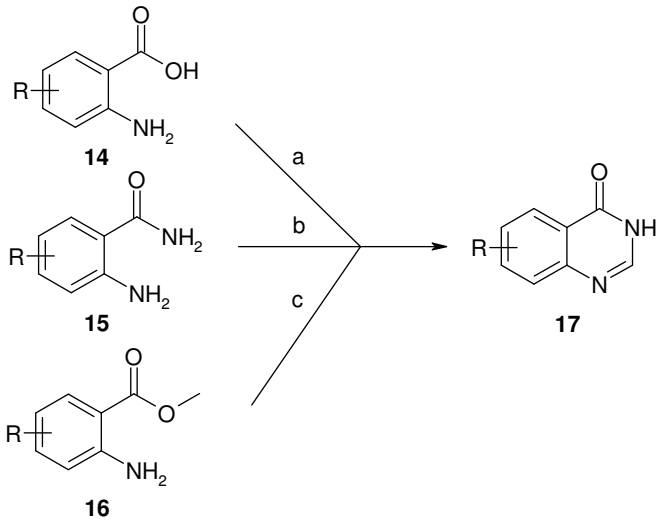


Reagents and conditions: a) NIS, H_2SO_4, r.t., 21 h followed by 8 days at 40 °C, 43%.

Scheme 4

2.2. Synthesis of substituted quinazolin-4(3*H*)-ones

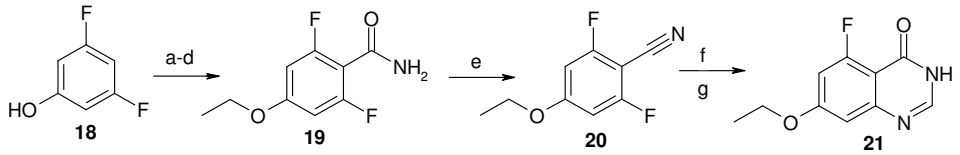
Synthetic strategies to access these key templates for quinazoline exploration have principally depended on cyclization of derivatives of *o*-aminobenzoic acids also known as "anthranilic acids" (Scheme 1).[12] There are three commonly used cyclization protocols to access the key 4(*3H*)-quinazolinone skeleton (**17**) based on the Niementowski's synthesis.[17] This classically involves cyclization of *o*-aminobenzoic acids (**14**) and their derivatives (*e.g.*, **15** and **16**) in neat formamide at elevated temperatures, typically in excess of 150 °C (Scheme 5).[18] The cyclization may also be carried out under milder conditions using formamidine acetate in refluxing 2-methoxyethanol.[19] In certain cases, research groups opt to pre-synthesise the *o*-amino- benzamides allowing for cyclization in the presence of formic acid, Gold's reagent $[(CH_3)_2NCH{=}NCH{=}N(CH_3)_2Cl]$[20] and triethylorthoformate.[21]



Commonly employed processes include: a) formamide, >150 °C; b) formamidine acetate, 2-methoxyethanol, reflux or Gold's reagent [$(CH_3)_2NCH=NCH=N(CH_3)_2Cl$ or [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride], dioxane, reflux or HCOOH, reflux; c) formamide, >150 °C or formamidine acetate, 2-methoxyethanol, reflux.

Scheme 5

During efforts to discover selective EGFR (epidermal growth factor receptor) and c-Src kinase inhibitors, Foote and co-workers recently synthesized a 7-ethoxy-5-fluoroquinazolin-4(*3H*)-one (**21**) by cyclizing the appropriate 2-aminobenzonitrile precursor in formic acid with a catalytic amount of concentrated H_2SO_4. The key transformation of 3,5-difluorophenol (**18**) to the 4-carboxamide (**19**) was achieved through direct lithiation followed by carbonylation with dry ice. Transformation of the acid to the resulting carbonyl chloride followed by ammonia afforded **19** in 71% overall yield. In order to effect the cyclizaton step efficiently, Foote found it was preferential to dehydrate to the nitrile **20** which, after displacement of the fluorine atom *ortho* to the nitrile with ammonia, was cyclized to afford **21** in good yield (Scheme 6).[22]

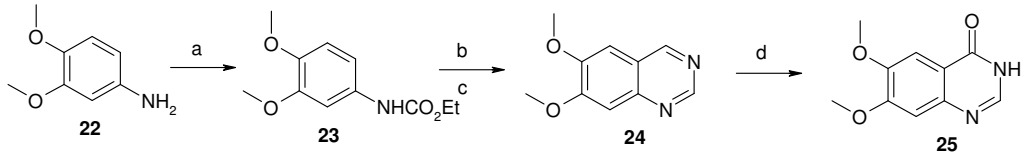


Reagents and conditions: a) Et_2SO_4, K_2CO_3, DMF, 80 °C, 86%; b) *n*-BuLi, THF, CO_2, 89%; c) $(COCl)_2$, DCM; d) NH_3 (aq.), THF, 93%; e) Cl_3CCOCl, Et_3N, DCM, 89%; f) NH_3(EtOH), 150 °C, 77%; g) HCO_2H, conc. H_2SO_4 (cat.), 100 °C, 70%.

Scheme 6

Recently, Chilin and co-workers have developed an efficient route towards this key building block starting from simple anilines as the starting material.[23] The advantage of this approach is that there are a great deal more anilines commercially available, with at least one free *ortho*-position on which to cyclize, than anthranilic acids. The anilines (*e.g.*, **22**) were first transformed to their corresponding ethoxycarbamates (*e.g.*, **23**) and subjected to a microwave assisted organic synthesis (MAOS) protocol using hexamethylene-tetramine (HMTA) in the presence of TFA to effect the aminomethylation step and enable subsequent cyclization to the dihydropyrimidine ring. The reaction mixtures were simply diluted to make them alkaline

and treated with $K_3Fe(CN)_6$ at 100 °C to afford the quinazolines (*e.g.*, **24**) in good overall yields. The subsequent quinazolines were transformed to the corresponding quinazolin-4(3*H*)-ones (*e.g.*, **25**) using ceric ammonium nitrate (CAN) in acetic acid at 100 °C (Scheme 7).[24]

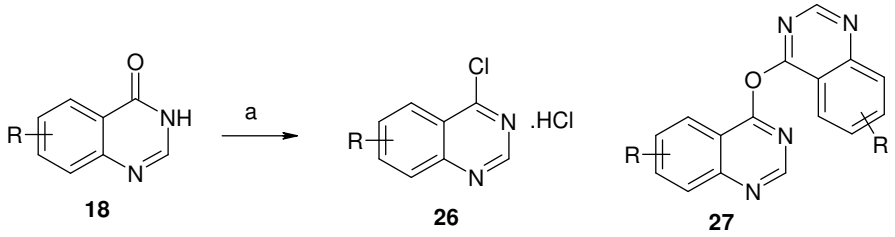


Reagents and conditions: a) $ClCO_2Et$, THF, Et_3N, r.t., 30 min., 98%; b) HMTA, TFA, MW, 110 °C, 10 min.; c) KOH (aq) EtOH, $K_3Fe(CN)_6$, reflux, 4 h, 86%; d) CAN, AcOH, 100 °C, 5 min., 86%.

Scheme 7

2.3. Functionalization of quinazolin-4(3*H*)-ones

Derivatization at the 4-position of the quinazoline nucleus usually requires first transformation of the quinazolin-4(3*H*)-one to the corresponding 4-chloride precursor (**26**) (Scheme 8). This is commonly achieved by treatment with range of common chlorination agents in large excess such as phosphorous oxychloride ($POCl_3$),[25] thionyl chloride ($SOCl_2$),[26] triphenylphosphine and carbon tetrachloride[27] or oxalyl chloride.[28] In most cases, after chlorination, the hydrochloride salt can be isolated by simply removing the excess chlorinating agent and precipitating the final compound with a suitable anti-solvent such as diethyl ether. Occasionally, when the quinazolin-4(3*H*)-one is particularly hindered (*e.g.*, substitution at the 5 position), dimer (**27**) formation occurs due to a particularly slow chlorination step (Scheme 8).[27]

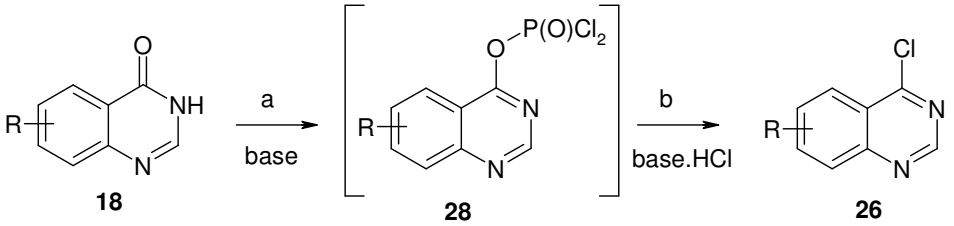


Reagents and conditions: a) excess chlorinating agent ($POCl_3$, $SOCl_2$ or oxalyl chloride), reflux.

Scheme 8

In our experience, 4-chloroquinazoline substrates are not stable when isolated as their hydrochloride salts, being very prone to hydrolysis. Therefore, to preserve their shelf-life, we recommend that they are stocked under anhydrous conditions. In addition, if subsequent chemistry requires more sensitive chemical manipulation (*e.g.*, Mitsunobu alkylation[29] of phenol substituted 4-chloroquinazolines) before substitution at the 4 position, it is advantageous to isolate the free-base. This was maybe achieved by carrying out the chlorination in the presence of an excess of a non-nucleophilic base such as *N,N*-diisopropylethylamine (DIPEA),[30] or by carrying out a careful work-up. The isolation of 4-chloroquinazolines as free bases after chlorination can present problems itself, particularly if electron-withdrawing groups are present on the phenyl ring enhancing the reactivity of the 4 position. The general method employed to minimize *in situ* hydrolysis during work-up is achieved by dropwise addition of the crude residue to a rapidly stirred biphasic mixture of an extraction solvent (*e.g.*, dichloromethane) in the presence of a saturated solution of sodium hydrogencarbonate. Thus, once the free-base is liberated, it enters immediately the organic phase.

In certain cases for particularly sensitive substitution, *e.g.*, O-COC$(CH_3)_3$ substitution[30] on the phenyl ring, we found the best way to proceed was to concentrate to dryness, basify with a non-nucleophilic base such as DIPEA and absorb the residue without any work-up on silica gel for purification by normal-phase chromatography. Our colleagues at AstraZeneca Process Research and Development, Cheshire, U.K., discovered that the chlorination process was best formally recognized as a two step process. First, $POCl_3$ is added dropwise to the reaction mixture containing the quinazolin-4(3*H*)-one derivative (**18**) and base at 0 °C and left to stir for 1–2 hours to form the trichlorophosphonate ester (**28**) quantitatively. This is in effect the rate-determining step. Failure to leave sufficient time for the ester **28** to form can encourage dimerization, particularly in the case of sterically hindered quinazolin-4(3*H*)-ones and when the chlorinating agent is not employed in excess. After this period, the reaction mixture is heated to 40–70 °C to liberate phosphorodichloridic acid by nucleophilic aromatic substitution (S_NAr) by a Cl^- anion provided by the hydrochloride salt of the base (Scheme 9).[13,30]

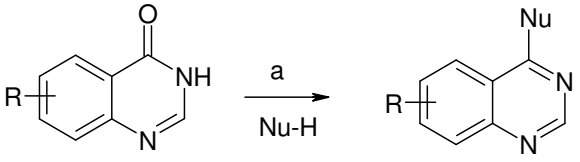


18 **28** **26**

Reagents and conditions: a) $POCl_3$, base (*e.g.*, DIPEA or TEA), toluene, 0 °C, 2 h; b) 40–70 °C, 2 h.

Scheme 9

Wan and co-workers at Wyeth Laboratories, U.S.A. have managed to transform directly quinazolin-4(3*H*)-ones (**18**) to a broad range of carbon, nitrogen and sulfur-based substituted products (**29**) by using benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP), a reagent more commonly used for amide coupling.[31] This phosphonium-mediated process represents a convenient way of introducing the nucleophiles directly at C-4 without having to transform the stable quinazolin-4(3*H*)-ones to reactive and relatively unstable 4-chloroquinazolines (Scheme 10).

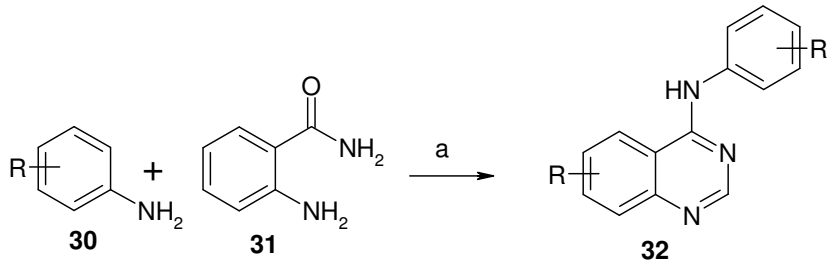


18 **29**

Reagents and conditions: a) BOP (1.3 equiv.), DBU (1.5 equiv.), nucleophile (Nu–H) (1.5–3.0 equiv.), MeCN, r.t.–60 °C, 54–95%.

Scheme 10

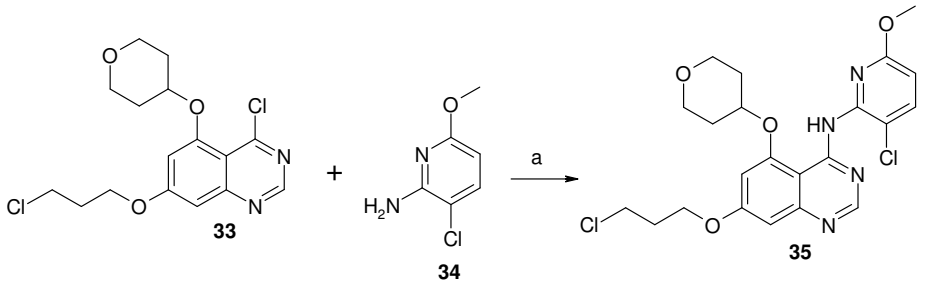
Recent work from Heravi *et al.* demonstrated that 4-arylaminoquinazolines (**32**) can be directly prepared from 2-aminobenzamides (**31**) in good yields. This process simply involves heating the 2-aminobenzamide (**31**), aniline (**30**) and triethylorthoformate in the presence of a heteropolyacid catalyst such as $H_6[PMo_9V_3O_{40}]$.[32] The substrate panel was limited to relatively simple anilines but these mild conditions should indeed have tolerance for a more diverse substrate panel (Scheme 11).



Reagents and conditions: a) $CH(OEt)_3$, cat. $H_6[PMo_9V_3O_{40}]$, MeCN, reflux, 73–93%.

Scheme 11

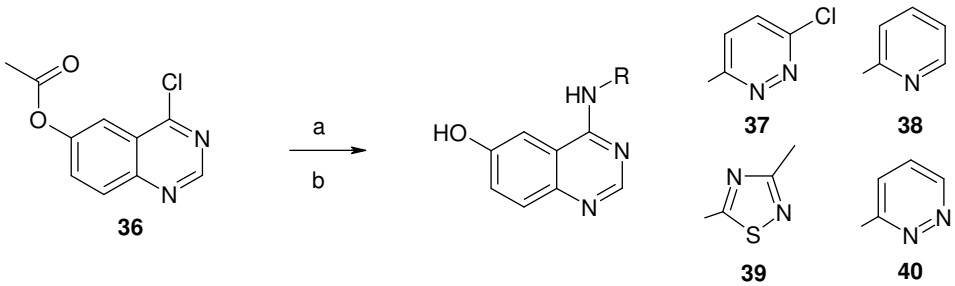
The introduction of substituents at the 4 position generally relies on nucleophilic aromatic substitution (S_NAr) on 4-chloroquinazolines with the appropriate nucleophile. In general, to introduce anilines, these processes are carried out under acid catalysis in a protic solvent (*e.g.*, HCl in refluxing 2-propanol). However, for more hindered electron deficient aromatic amines, acid-catalyzed protocol may result in very poor conversions. In our own laboratories, we found that only the generation of the anilide anion of **34** in the presence of sodium hexamethyldisilazide (NaHDMS) permitted access to good yields of a key intermediate (**35**), used for further elaboration into potent and selective c-Src kinase inhibitors (Scheme 12).[33]



Reagents and conditions: a) NaHDMS (2 equiv.), THF, 0 °C to r.t., 74%.

Scheme 12

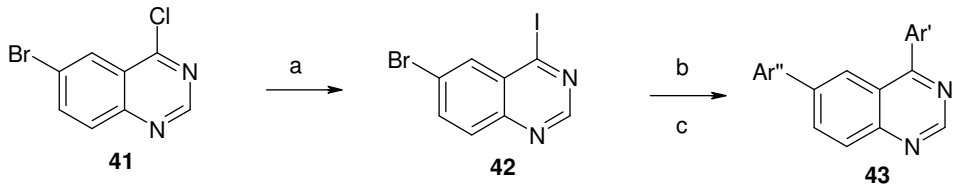
In general, platinum-group metal (PGM) catalysis is seldom used to introduce amine substituents at the activated 4 position. In a majority of cases, 4-chloroquinazolines are easily displaced under base or acid catalyzed S_NAr conditions in good yield with a wide range of nucleophiles. Recently, however, during a project looking for novel 4,6-disubstituted quinazoline glucokinase activators, Iiano *et al.* found it necessary to employ Buchwald-Hartwig conditions to obtain satisfactory conversions to 4-aminated products **37–40** for a certain subset of weakly nucleophilic heteroaromatic amines (Scheme 13).[34]



Reagents and conditions: a) BINAP (0.1 equiv.), $Pd_2(dba)_3$, Cs_2CO_3 (2 equiv.), toluene, 120 °C, 3 h; b) NH_3/MeOH, 50%.

Scheme 13

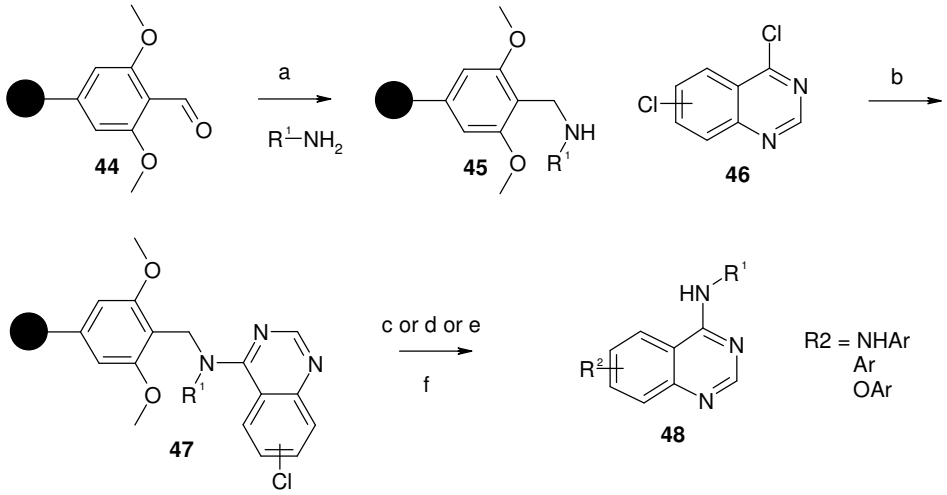
Another example of the application of PGM-catalyzed reactions to prepare libraries of quinazolines was provided by GlaxoSmithKline researchers, who were looking at inhibitors of the phosphoinositide 3'OH (PI3K) kinase family and identified 4,6-disubstituted quinazolines as potent and selective inhibitors, notably of PI3Kα.[35] In order to ensure selectivity at the 4 position, the 4-iodo-6-bromoquinazoline (**42**) was synthesized *via* nucleophilic aromatic substitution of the 4-Cl precursor (**41**) with sodium iodide in refluxing proprionitrile. The key intermediate **42** was subsequently elaborated into libraries of potent inhibitors (**43**) using a series of *Suzuki* cross-coupling reactions (Scheme 14).



Reagents and conditions: a) sodium iodide, proprionitrile, 100 °C, quantitative; b) Ar'-$B(OH)_2$, $Pd(PPh_3)_4$, 2M K_2CO_3, 1,4-dioxane, 100 °C; c) bis(pinacolato)diboron, $Pd(dppf)Cl_2$, KOAc followed by the addition of Ar''-Br, $Pd(dppf)Cl_2$, 2M K_2CO_3, 1,4-dioxane, 100 °C.

Scheme 14

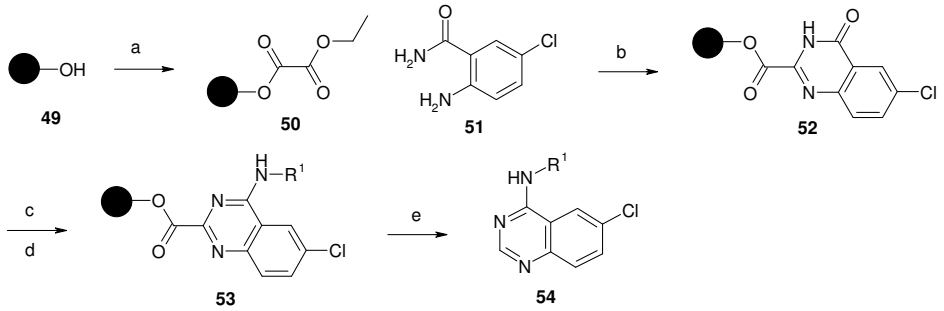
The application of solid-phase synthesis to the preparation of 4-substituted quinazolines has received particular interest[36] due in part to the ease of preparation of the 4-chloroquinazoline precursors. Schultz *et al.* demonstrated an elegant approach to synthesize mono-functionalized 4-aminoquinazolines on PAL-resin (**44**).[37] Reductive amination using standard conditions permitted the introduction of the first variable attached to the resin (**45**). Nucleophilic displacement of the 4-Cl quinazoline (**46**) was followed by a series of palladium-catalyzed cross couplings to introduce aryl ether, aryl amine and aryl substitution on the phenyl ring. Final cleavage of the desired compounds (**48**) from the resin was achieved under hydrolytic conditions in acceptable yields (Scheme 15).



Reagents and conditions: a) $NaBH(OAc)_3$, 1% AcOH in THF, r.t.; b) DIPEA, *n*-BuOH, 90 °C; c) R^2=$ArNH_2$, $Pd_2(dba)_3$, phosphine ligand, KO*t*-Bu, 1,4-dioxane, 90 °C, 12 h; d) R^2=Ar-$B(OH)_2$, $Pd_2(dba)_3$, carbene ligand, Cs_2CO_3, 1,4-dioxane, 90 °C, 12 h; e) R^2=Ar-OH, $(dba)_3$, carbene ligand, Cs_2CO_3, 1,4-dioxane, 90 °C, 12 h; f) TFA/DCM/Me_2S/H_2O (45:45:5:5).

Scheme 15

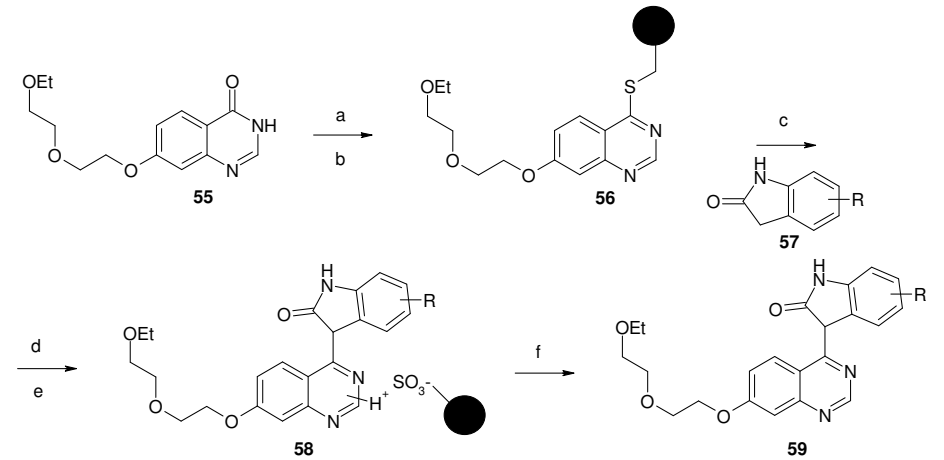
Another intriguing traceless solid-phase process was reported by Abell *et al.* who highlighted the preparation of the quinazoline ring by cyclization of substituted anthranilamides (**51**) onto an oxalate ester linker resin (**50**).[38] Chlorination of the resulting substituted quinazolin-4(3*H*)-ones (**52**) was followed by acid-catalyzed S_NAr to introduce the amine variable at the 4 position (**53**). Finally, cleavage of the ester linkage with concomitant decarboxylation afforded the desired 4,6-disubstituted quinazoline libraries (**54**) (Scheme 16).



Reagents and conditions: a) ethyl oxalyl chloride, DMAP, TEA, DCM, r.t.; b) CSA monohydrate, 1,4-dioxane, reflux, 48 h; c) $SOCl_2$, DMF, reflux, 3 h; d) R^1–NH_2, *i*-PrOH, DMF, HCl, r.t., 18 h; e) TMSCl, NaI, MeCN, 1,4-dioxane, 75 °C.

Scheme 16

In our own laboratories, Hennequin and co-workers developed a novel synthesis of oxindole 4-substituted quinazolines on Merrifield's resin. The synthesis of the substituted quinazolin-4(3*H*)-one (**55**) was followed by thionation using P_4S_{10} in refluxing pyridine. Alkylation onto Merrifield's resin was achieved under basic conditions affording **56** which was subjected to direct S_NAr at the 4 position with a range of oxindoles (**57**) to afford the final compounds (**59**) in respectable yields. Use of a SCX resin in a type of catch-release mode proved to be vital in the process in order to eliminate the oxindole polymers formed during the S_NAr process (Scheme 17).[39]

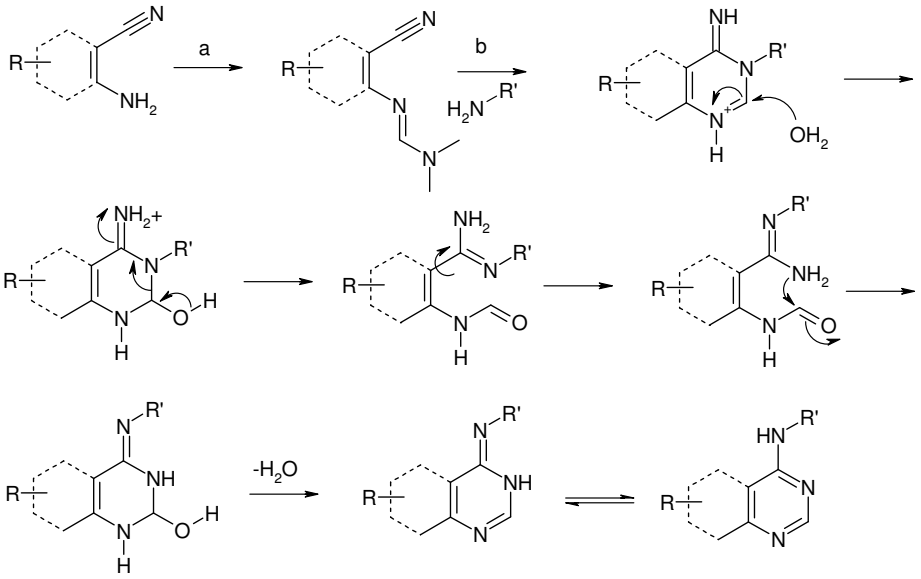


Reagents and conditions: a) P_4S_{10}, pyridine, reflux; b) Merrifield resin (1.24 mmol/g), DBU, DMF, r.t.; c) NaH (10 equiv.), oxindole, DMSO, 100 °C; d) filtration through SCX-silica; e) washing with DCM/MeOH; f) 2% NH_3 in MeOH / DCM (1:1), 35–68% (7 examples).

Scheme 17

Another widely-used direct method to access 4-substituted quinazolines from *ortho*-cyanoaryl- and heteroaryl-*N,N*-dimethylformamidines relies on the Dimroth rearrangement, whereby a substituted

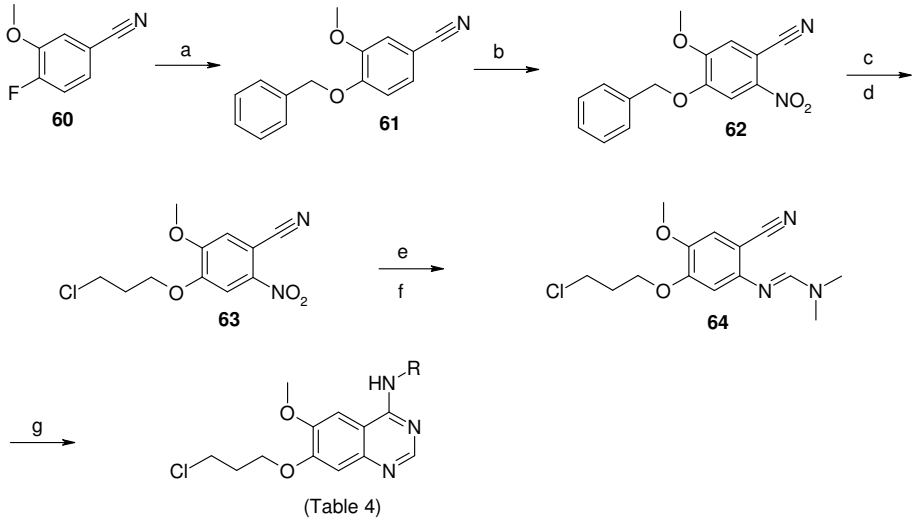
endocyclic nitrogen and a free exocyclic amino group in effect switch place.[40] Initially *ortho*-cyanoaryl- and heteroarylamines were condensed with dimethylformamide dimethylacetal (DMF.DMA) at reflux to introduce the *N,N*-dimethylformamidine moiety. The 4-aminoquinazolines were prepared by heating the intermediate *N,N*-dimethylformamidines and chosen amine usually in refluxing AcOH (Scheme 18)[41] or under microwave irradiation.[42] This process is also very tolerant not just for aromatic amines but also for aliphatic amines.[43]



Reagents and conditions: a) DMF.DMA, reflux; b) AcOH, reflux or NaOH, MeOH, reflux.

Scheme 18. Mechanism of the Dimroth rearrangement.

In our own laboratories, during work on the Aurora kinase program, we were particularly dependant on the Dimroth reaction to introduce weak nucleophiles, such as 2-aminoazoles (*e.g.*, 2-aminothiazoles) and 2-aminoazines (*e.g.*, 2-aminopyrimidines),[9, 41] which gave very poor yields under standard acid or base catalyzed nucleophilic aromatic substitution conditions with 4-chloroquinazoline precursors.



(Table 4)

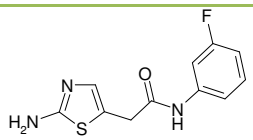
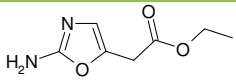
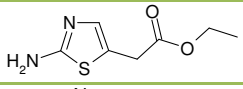
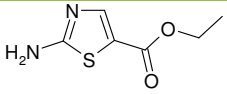
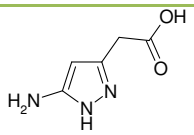
Reagents and conditions: a) benzyl alcohol, NaH, DMF, 80%; b) HNO_3, H_2SO_4, 67%; c) TFA, water, 95%; d) 1-bromo-3-chloropropane, K_2CO_3, DMF; e) H_2, Pd/C, EtOH, 89%; f) DMF.DMA, reflux; g) amine, AcOH, reflux (see Table 4).

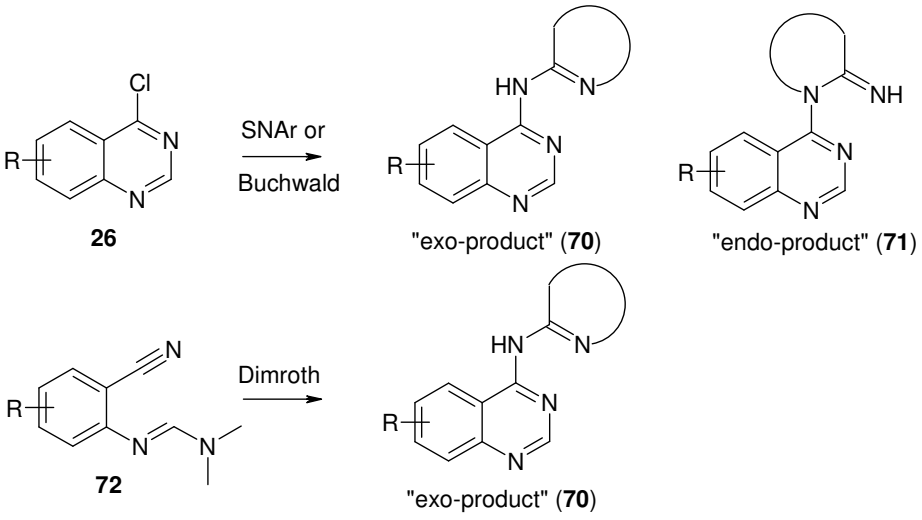
Scheme 19

We managed to devise a very convergent strategy by synthesising the Dimroth precursor **64** with side chain substitution already in place at the 7 position. This allowed for the introduction of a very diverse set of aromatic amines at the 4 position, which would have been very difficult to achieve by nucleophilic aromatic substitution or by using transition metal catalysis (Scheme 19).

The results shown in Table 4 illustrate nicely the scope of diversity that one can obtain by including a Dimroth cyclization in the overall strategy to access substituted quinazolines. Weak nucleophile classes such as 2-aminoazoles (entries **65–69**) participate in the cyclization to afford respectable yields of 4-amino-quinazolines. It is of note that due to the mechanistic nature of the Dimroth rearrangement, these reactions have also the advantage of being totally regiospecific, *i.e.*, quinazoline substitution on the exocyclic nitrogen affording **70** (Scheme 20). Employment of S_NAr and Buchwald-Hartwig conditions to introduce notably, 2-aminoazines and in some cases 2-aminoazoles can occasionally result in mixtures of *endo*- (**71**) and *exo*-products (**70**) that can be difficult to separate.

Table 4. Selected results obtained from a multi-parallel synthesis experiment cyclizing **64** and selected amines in refluxing AcOH for a period of 6 hours.[9,41]

Cpd	Amine	% Yield
65		77
66		33
67		68
68		62
69		69



Scheme 20

2.4. 4,6,7-Trisubstituted quinazolines

Inspection of the databases reveals that this class of quinazoline has received the most interest with over 40,641 CAS numbers and 1,999 chemistry patents.[10] Representing most of this class is the 6,7-bis-(ether) 4-substituted quinazolines with some 18,779 CAS numbers amongst which include the marketed drugs IRESSA® (*gefitinib*) and TARCEVA® (*erlotinib*). However, closer inspection of this heavily explored sub-series revealed that there were very few examples of bis(heteroalkyloxy)quinazolines with other substitution than methyl, possibly largely due to the limited chemical processes available at the time (Figure 6).

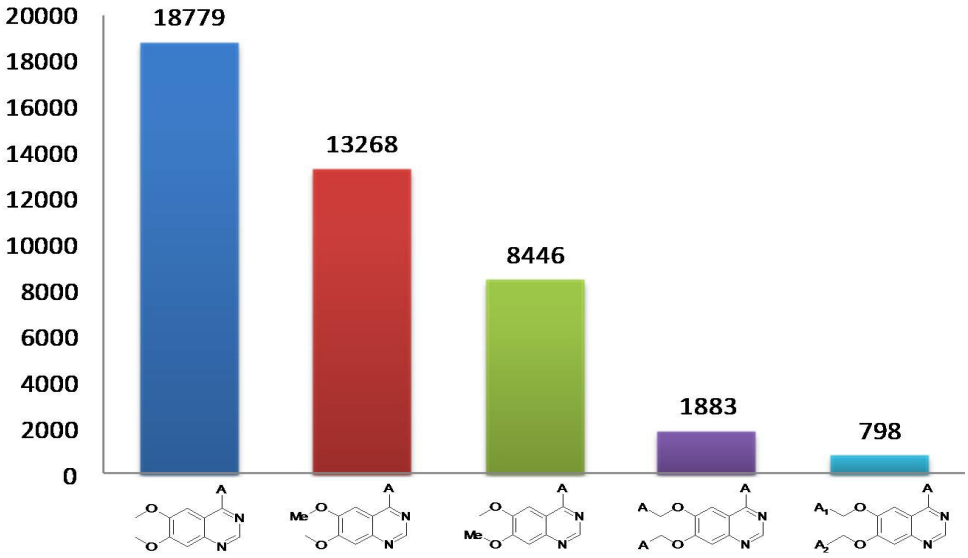
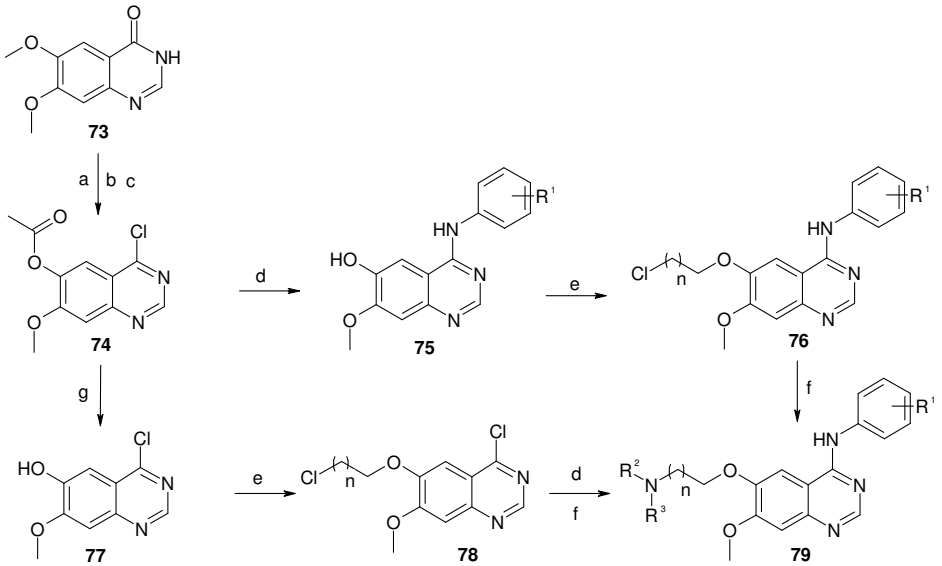


Figure 6. Current CAS distribution in the C-4-substituted-6,7-bis(ether) family. A=Any atom except H; Me=CH_3 fixed; $A_1 \neq A_2$ and not H.

Examination of the literature reveals two key processes which have allowed substitution either at the 6 position while retaining a 7-OCH_3 or *viceversa*. The research routes devised to introduce diversity at positions 6 and 4 relied on developing efficient routes to access large quantities of the 6-OAc-7-OMe-4-Cl quinazoline (**74**). Starting from 6,7-dimethoxyquinazolin-4(3*H*)-one (**73**), a key step was the selective revelation of the 6-OH group using a mixture of DL-methionine in methanesulfonic acid at 100 °C. Acetylation followed by chlorination afforded the key intermediate **74**. Nucleophilic aromatic substitution at the 4 position with *in situ* deprotection of the 6-OAc group afforded the phenol intermediate **75**. Alkylation of the 6-OH can be achieved selectively *via* standard alkylation conditions or using Mitsunobu alkylation conditions. However, in the case of the Mitsunobu reaction, a large excess (3–4 equiv.) of reagents is sometimes necessary to push the reaction to completion which is possibly due to the high pK_a of the 6-OH (*ca.* 10–11 units). The library is finally terminated by substitution with the desired amine at elevated temperatures. For particularly hindered amines, it was advantageous to add a stoichiometric quantity of potassium iodide (KI), thus adopting Finkelstein conditions, to afford acceptable yields of **79** and reduce competing elimination. If substitution at position 4 has already been optimized, the 6-OAc group of **74** can be deprotected with a 7N solution of methanolic ammonia at 0 °C, revealing selectively the 6-OH position while preserving the 4-Cl position of **77**. This intermediate can by alkylated at 6-O using similar chemistry to afford versatile bifunctional intermediates (*e.g.*, **78**) for a selective double substitution approach. Selective substitution at the 4 position followed by substitution of the pendant side chloroakyl chain could even be

achieved in a one pot manner if required by ensuring that step d is carried out in a non-nucleophilic solvent such as DMF, MeCN (Scheme 21).



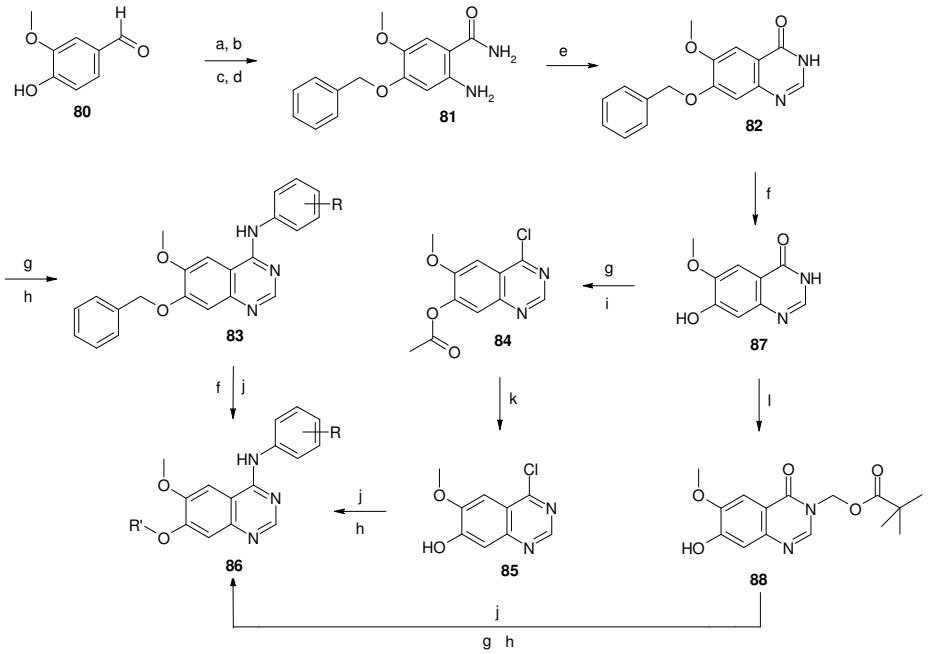
Reagents and general conditions: a) D,L-methionine, methanesulfonic acid, 100 °C, 3 h, 45%; b) Ac_2O, pyridine, 100 °C, quant.; c) $SOCl_2$, reflux, 70%; d) R^1–Ar–NH_2, cat. HCl, IPA, reflux; e) $Cl(CH_2)_nBr$, K_2CO_3, DMF, r.t. or $Cl(CH_2)_nOH$, TPP, DEAD, 0 °C to r.t., DCM; f) R^2R^3NH, DMF, 80 °C; g) methanolic ammonia (7N), 0 °C to r.t.

Scheme 21

A similar strategy was used to access a suitable intermediate for generating libraries of quinazolines with diversity points at positions 4 and at the 7-O.[20] The first approach fixed 4-substitution early on allowing for exploration at off the 7-O at the end of the sequence. Starting from 4-hydroxy-3-methoxybenzaldehyde or vanillin (**80**), benzyl protection of the 4-O position followed by nitration and standard functional group manipulation gave **81**.[44] Cyclization was achieved using Gold's reagent in refluxing dioxane to afford the key quinazolinone precursor **82**. This precursor was subsequently chlorinated to afford **83**, a useful intermediate for positions 4 then 7-O diversification. Displacement of the 4-Cl under acid-catalysed S_NAr conditions and deprotection of the 7-OBn protecting group by either hydrogenolysis or by ionization in refluxing TFA in the presence of a cation scavenger (*e.g.*, H_2O) revealed the 7-OH group for derivatization into final compounds (**86**).

Contrary, the second approach allowed for introducing and fixing alkyl substitution at the 7-O early on and exploring 4-substitution at the end of the sequence.[20] The synthesis started by deprotection of **82** to afford **87**. Alkylation of **87** affords mixtures of alkylated products at N-3 and the 7-O positions, therefore, the key to realize this approach was efficiently protecting N-3 with a pivaloyloxymethyl or a POM group to give **88**. Transformation of **88** into libraries of **86** relied on quite a laborious sequence. Alkylation at 7-O position, followed by ammonolysis of the POM group, chlorination and final displacement of the 4-Cl gave access to libraries of **86** having the C-4-diversity point available at the end of the sequence. While both approaches had their merit and were used to synthesize many libraries of compounds for several kinase programs, they had the disadvantages of being quite rigid, fixing substitution at the 4 or 7-O positions early on in the sequence and several purifications between steps. Both these strategies were later superseded when routes were devised to access large quantities of **84**. The advantage of this approach was that the 7-OAc

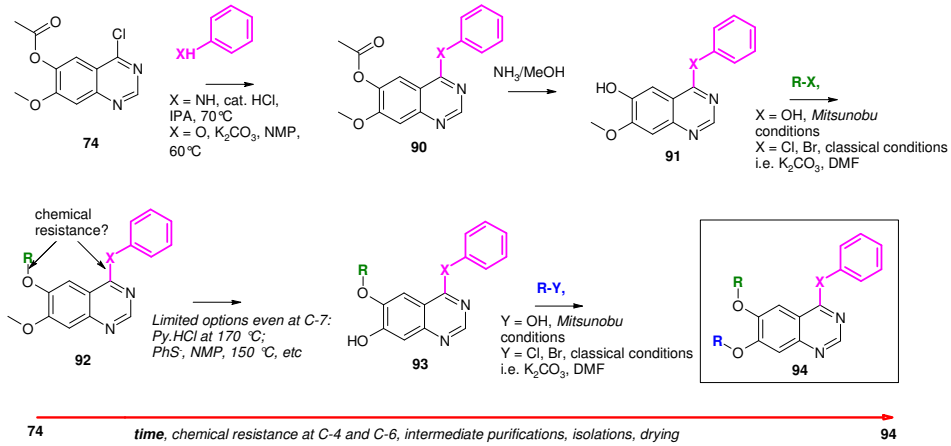
protecting group is easily removed by ammonolysis under mild conditions leaving the 4-Cl in tact for further derivatization in a one-pot manner if required (Scheme 22).



Reagents and general conditions: a) Bn-Cl, K_2CO_3, EtOH, reflux, 2.5 d, 77%; b) conc. HNO_3, 0–15 °C, 89%; c) 10% $KMnO_4$ (aq.), acetone, r.t., 69%; d) $SOCl_2$, reflux, 22 h concentration then NH_3(g), dioxane, r.t., 69%; e) Gold's reagent, dioxane, reflux, 84%; f) H_2, Pd-C, ammonium formate, DMF, 64% or TFA, reflux; g) $SOCl_2$, reflux, 92%; h) $ArNH_2$, IPA/2-pentanol, reflux; i) Ac_2O, pyridine, 90 °C, 76%; j) R'-X, K_2CO_3, DMF, 60 °C or R'-OH, DTAD, TPP, DCM, 0 °C to r.t.; k) (7N) NH_3 in methanol, 0 °C to r.t., 91%; l) POM-Cl, NaH, DMF, 0 °C to r.t.

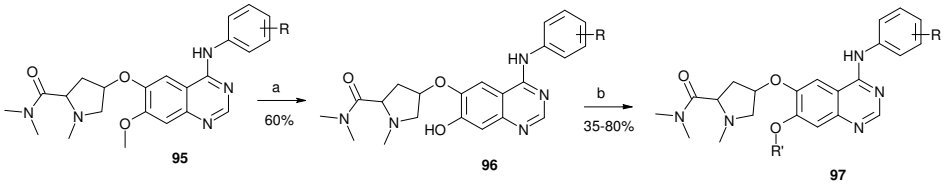
Scheme 22

While both routes were adequate to deliver intermediates (**77** and **85**) having two diversity points, further extension of these routes to allow one to easily vary substitution freely at the 6-O and 7-O positions with other than CH_3 groups were linear, time-consuming and their success was very much dependant on having functionality compatible with the harsh conditions required to deprotect aryl methyl ethers at the 6 or 7 positions (Scheme 23). Indeed, starting from key intermediate **74**, substitution at the 4 position followed by deprotection of the 6-OAc group affords the phenol **90**.



Scheme 23

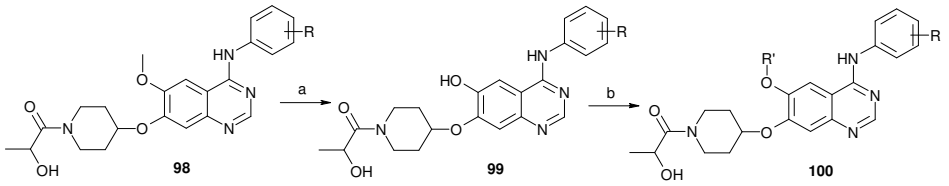
Commonly employed reagents for aryl methyl ether deprotections such as boron tribromide (BBr_3) failed largely due to the poor solubility of starting ether (**92**). The most efficient conditions were molten pyridinium hydrochloride which worked for cases with atypical solubilizing ether side chains (*e.g.*, morpholinopropoxy *alla gefitinib*) but failed when carbonyl functionality was already introduced and even for the methoxyethoxy side chain (*alla erlotinib*). Unable to employ these harsh hydrolytic conditions, we turned our attention to the use of basic conditions. The use of lithium iodide in 2,4,6-collidine at elevated temperatures allowed deprotection of the 7-OCH_3 ether in acceptable yield even in the presence of sensitive amide functionality (Scheme 24).[45]



Reagents and conditions: a) LiI, 2,4,6-collidine, 130 °C, 6 h; b) R'-OH, DTAD, TPP, THF, 0 °C to r.t.

Scheme 24

In addition to the deprotection of the activated 7-OCH_3 ether, we also managed to employ these conditions for the selective deprotection of the 6-OCH_3 ether with a pendant side secondary ether chain present in high yield, proving the product distribution is controlled more by steric rather than electronic factors. The family was completed by Mitsunobu alkylation, assuring the alkylating reagent was pre-formed before adding the phenol **99** (Scheme 25).[45]



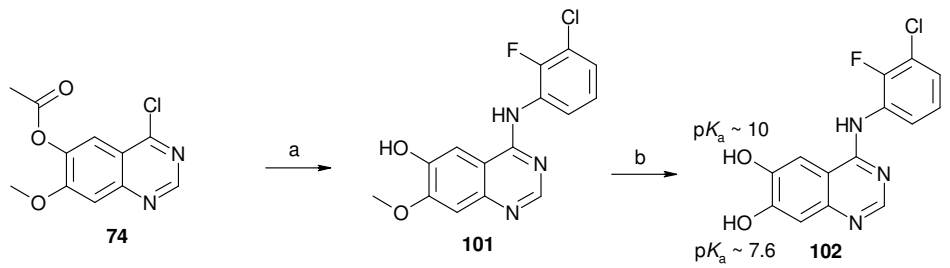
Reagents and conditions: a) LiI, 2,4,6-collidine, 130 °C, 12 h, 69%; b) R'-OH, DTAD, TPP, THF, 0 °C to r.t. then add phenol and heat at 60 °C.

Scheme 25

However, even after taking into account the successful application of lithium iodide in 2,4,6-collidine, the routes to access libraries of 6,7-(heterodialkoxy)-4-anilino-quinazolines still remained very linear and rigid with diversity points fixed early on in the sequence at the 4 position followed by the 7 position. However, in spite of the options available for revelation of the 7-OH, the final route shown in Scheme 22 has the inconvenience of being linear, necessitating purifications between steps and more importantly does not tolerate base-sensitive functionality (*e.g.*, aryl ethers at the 4 position).

During recent efforts looking for potent EGFR kinase inhibitors, we focused our attention to the possibility of synthesizing a central intermediate which would allow diversification initially at the two key points at the 6 and 7 positions in a relatively convergent process with a single purification at the end of the sequence. Our strategy focused on the possible exploitation of the 6,7-diol **102** in the knowledge that the 7 position is activated by the quinazoline ring, therefore, the phenol should be considerably more acidic. Synthesis of **102** was achieved starting from intermediate **74**. Substitution at the 4 position was achieved in

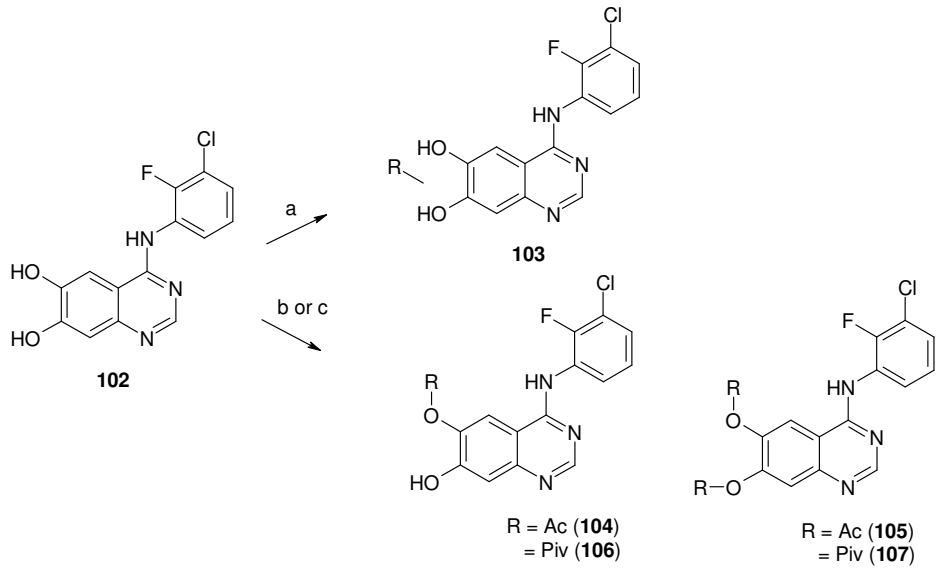
excellent yield with 2-fluoro-3-chloroaniline under acid catalysis and the desired diol **102** was revealed by double deprotection of the 6-OAc and 7-OCH_3 groups using molten pyridinium hydrochloride (Scheme 26).[46]



Reagents and conditions: a) IPA, cat. HCl, reflux, 98%; b) pyridinium hydrochloride, 170 °C, 3 h, 67%.

Scheme 26

The difference in acidity between the 7-phenol (pK_a=7.6), whose delocalization base can be stabilized by conjugation into the quinazoline ring, and the 6-phenol (pK_a=10.02) which cannot be stabilized by the quinazoline, was confirmed by measurement. Our first trails adopting a direct alkylation approach under classical or Mitsunobu conditions on **102** failed, affording complex mixtures due in part to the poor solubility of **102**. To overcome the solubility issue, we envisaged that we could try and selectively esterify **102** with a view to preparing an intermediate, which could be utilized in a 3-step approach to prepare a differentially alkylated 6,7-bis(alkoxy)quinazoline library under mild Mitsunobu conditions (Scheme 27).[46]

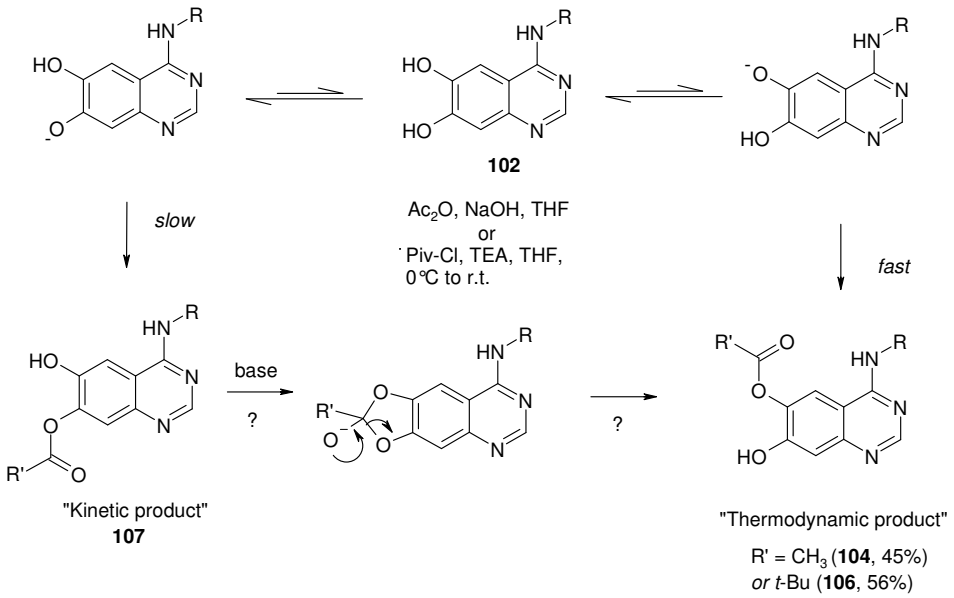


Reagents and conditions: a) R-Br, K_2CO_3, DMF, r.t. or DTAD, TPP, R-OH, THF, r.t., inseparable mixtures; b) Ac_2O, NaOH, THF, 45% (**104**) or Piv-Cl, TEA, THF, 56% (**106**).

Scheme 27

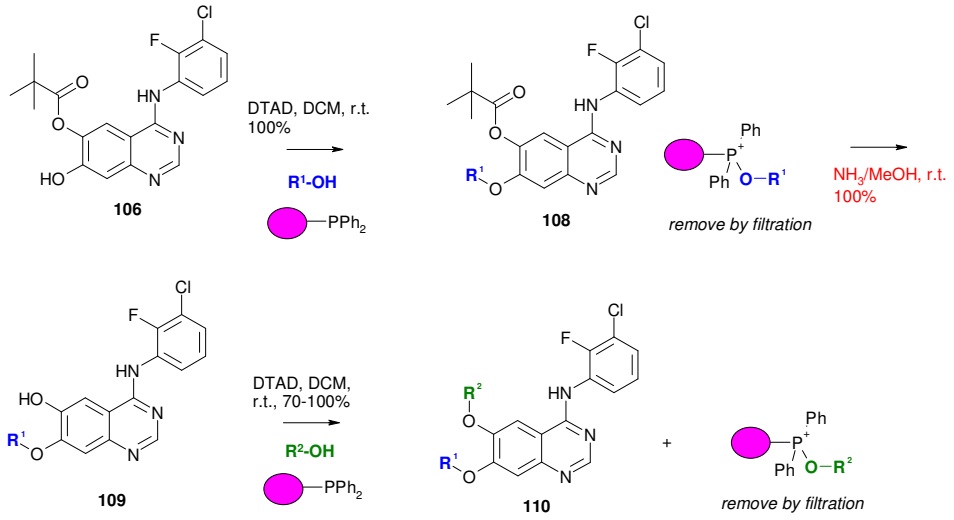
Selective acylation at position 6 was achieved in acceptable yields either using acetic anhydride in the presence of one equivalent of sodium hydroxide or pivaloyl chloride in the presence of triethylamine. The major side products **105** and **107** arising due to di-acylation were easily removed by chromatography and recycled to **102** by ammonolysis. However, no traces of 6-OH-7-OAc product were observed in either process. As mentioned in our first communication on this process,[46] the excellent regioselectivity can be

explained by the Curtin-Hammet principle (Scheme 28).[47] In essence, based on the large difference of 2.4 p*K*a units, the concentration of 6-OH-7-O$^-$ will be much higher than 6-O$^-$-7-OH but the latter is much more nucleophilic; therefore, the rate of acylation is much greater which drives the equilibrium towards selective acylation at position 6 to afford selectively **104** and **106** in acceptable yields. However, one cannot totally exclude the possibility of the kinetic product being the short-lived 6-OH-7-OCOR intermediate (**107**) which undergoes a rearrangement to the thermodynamically more stable 6-OCOR-7-OH intermediate (**104** and **106**) (Scheme 28).



Scheme 28

The 6-OPiv-7-OH intermediate (**106**) proved to be superior to the 6-OAc-7-OH intermediate (**104**) as it was more soluble in commonly-used Mitsunobu solvents (DCM, THF, toluene, etc) and resistant to *in situ* deprotection during the first Mitsunobu alkylation step. Indeed, it was critical to ensure that there was no *in situ* deprotection during the first step as this led to contamination of the final compounds with close-running bis(homodialkyloxy)quinazolines impurities (Scheme 29).



Scheme 29

As for any library process aiming at introducing a significant element of diversity in a very rapid and convergent manner, one of the key aspects of this process was having quick, complete and clean reactions at each step with a low mass of crude product to purify at the end of the sequence. The process presented in Scheme 29 was best effected using low-loading (1–1.2 mmol/g) rather than high-loading (3 mmol/g) polymer-supported triphenylphosphine to ensure that all the first alcohol was captured on the resin and none leached through to the final alkylation step, leading to contamination of the desired final bis(heteroalkyoxy)-quinazolines (**109**) with bis(homoalkoxy)quinazolines. The problem of leaching, thus the need for low-loading polymer-supported triphenylphosphine, was particularly important evidently when using secondary alcohols in the first step. Typical stacked LCMS crude purity profiles for an example can be seen in Figure 7. The intermediate purity profiles, from **106** right up to **113**, were on average never less than 95% permitting purification of the final compounds by a single injection using preparative mass-triggered LCMS reverse-phase chromatography.

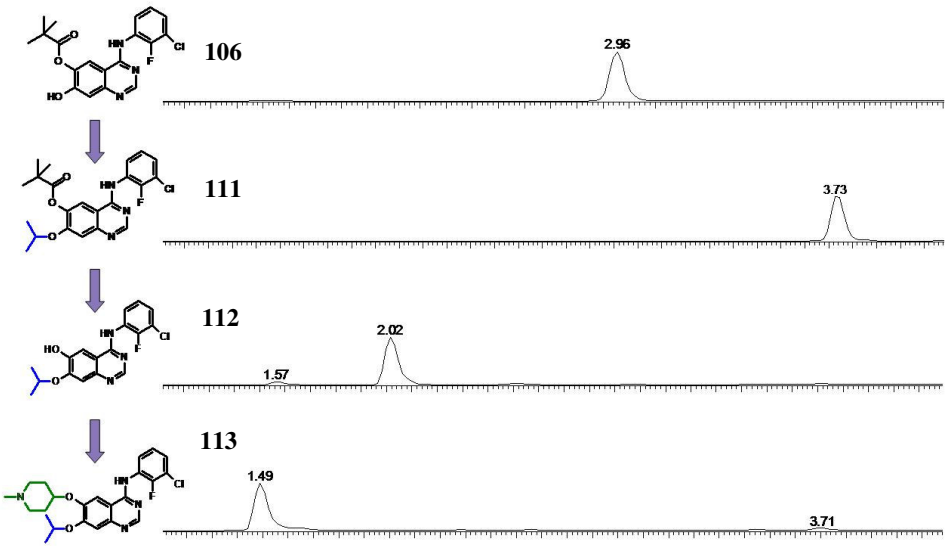
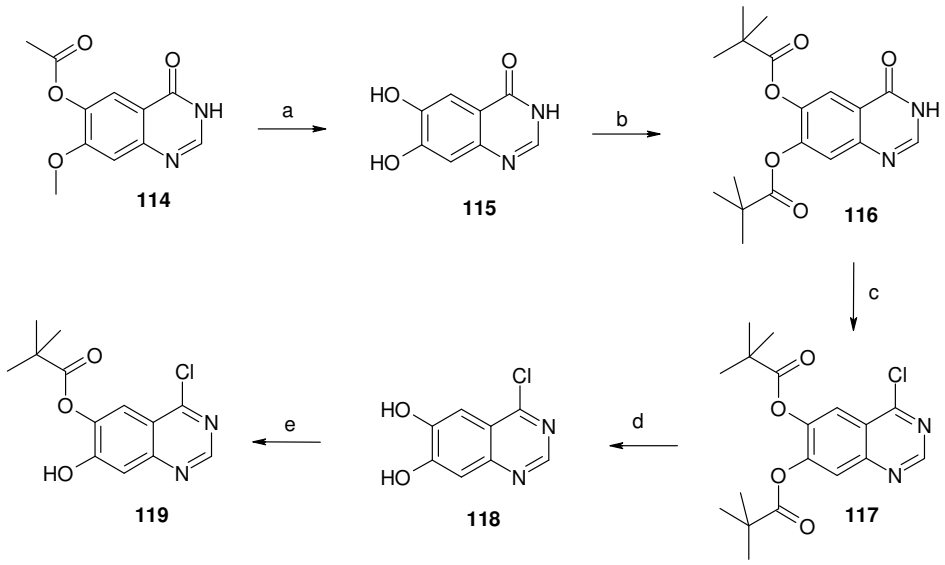


Figure 7

The next challenge for this family was to attempt to go one step further and synthesise an intermediate having all 3-diversification points available. To achieve this, our strategy focused on the synthesis of a similar intermediate to **106** with a chlorine atom at the 4 position (**119**). Therefore, double deprotection of the 6-OAc and the 7-OCH_3 protecting groups of **114** afforded diol **115**. We initially attempted to directly chlorinate **115** followed by regioselective protection at the 6 position with a pivaloyl group but this failed largely due to the poor solubility of the starting quinazolinone affording unidentified side products. The solubility problem was overcome by protecting both the 6 and 7 positions with a pivalolyl group. This key modification afforded intermediate quinazolinone **116** which was soluble in all common organic solvents. Inspite of these modifications, the chlorination process proved to be quite challenging. Exposure of the **116** simply to an excess of chlorinating agent (*e.g.*, $POCl_3$ or $SOCl_2$) results in *in situ* deprotection of the ester groups and subsequent oligomerization to afford unidentified side products. This problem was resolved by allowing the reaction a sufficient amount of time to form the phosphate ester before gently heating to form the 4-chloroquinazoline (**117**). Double deprotection of the pivaloyl groups was achieved using methanolic ammonia to afford **118**, an interesting precursor itself for the generation of bis(homoalkoxy)quinazoline

libraries which we validated to afford the simple example presented Figure 8. Regioselective protection of **118** afforded **119** in acceptable yield with the di-pivaloyl side product easily separated by silica gel chromatography for recycling purposes (Scheme 30).



Reagents and conditions: a) pyridine hydrochloride, 180 °C, 4 h, 95%; b) Piv-Cl, TEA DMF, r.t., 2 h, 71%; c) $POCl_3$, TEA, toluene, r.t.–40 °C, 3 h, 70%; d) NH_3/MeOH, r.t., 2 h, 100%; e) Piv-Cl, TEA DMF, r.t., 2 h, 57%.

Scheme 30

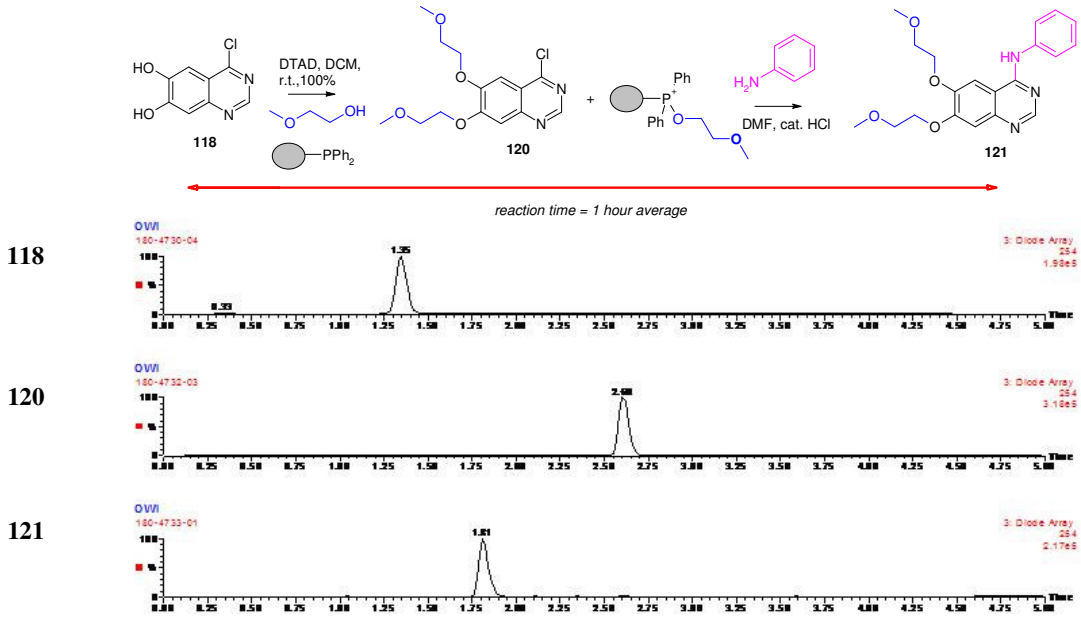


Figure 8

Application of the identical Mitsunobu selective alkylation process as shown in Scheme 28 worked with average inter-step crude purities of >90 %, leaving a final concentration step and exposure of the intermediate to suitable final S_NAr reaction conditions: basic conditions for the introduction of aliphatic amines and phenols or thiophenols in the presence of potassium carbonate or acidic conditions for the introduction of anilines. Typical stacked crude LCMS profiles are shown in Figure 9. The high quality of

crude profiles after each step allowed for the isolation of the desired finals in average yields of >50 % after a 4-step process, from **119** to **125**, requiring one single purification at the end of the sequence. Indeed, this process required just four hours to complete as opposed to several days following existing methodology where applicable.[30]

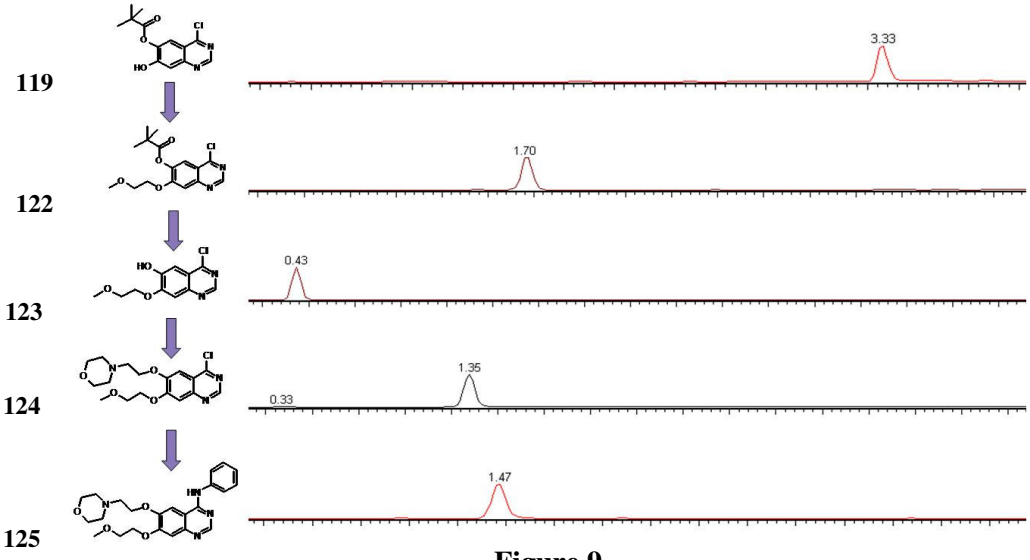
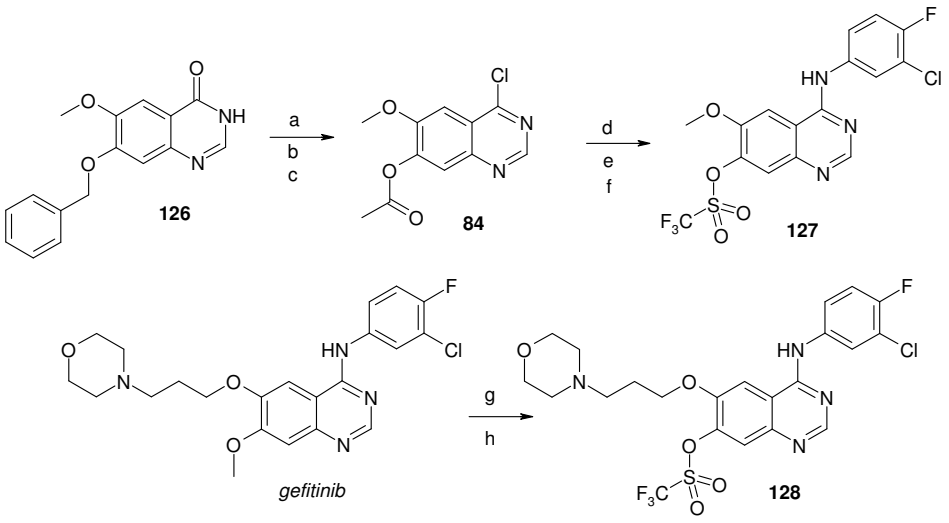


Figure 9

Beyond the 6,7-bis(ether)anilinequinazoline family, we find other classes of 6,7-disubstituted quinazolines that are more challenging to synthesize. During research into our own epidermal growth factor receptor (EGFR) program, we looked at developing convergent methodology to introduce amino functionality at the 7 position in the presence of ether substitution at the 6 position. We managed to furnish a general protocol for the introduction of both secondary and primary amines at the 7 position *via* direct S_NAr, inspite of the positive deactivating mesomeric influence of the C-6-OMe group. In order to achieve this goal, we synthesized the 7-OTf (**128**) and the C-7-F (**133**) precursors.[48]

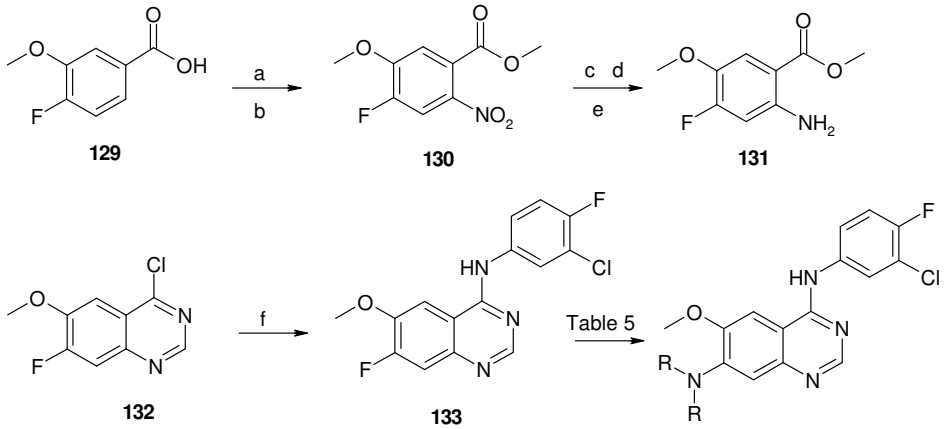


Reagents and conditions: a) TFA-H_2O (3.75:1), reflux, 2 h, 100%; b) Ac_2O, pyridine, reflux, 1 h, 89%; c) $SOCl_2$, reflux, 1.5 h, 69%; d) 3-chloro-4-fluoroaniline, *i*-PrOH, reflux, 91%; e) NH_3/MeOH, r.t., 2 h, 90%; f) $PhN(Tf)_2$, K_2CO_3, THF, r.t., 88%; g) pyridinium hydrochloride, 170°C, 3 h, 80%; h) $PhN(Tf)_2$, K_2CO_3, THF, r.t., 77%.

Scheme 31

The synthesis of **133** started from 6-methoxy-7-benzyloxyoxyquinazolone **126**.[49] Deprotection of the benzyl ether at the 7 position was achieved using TFA in the presence of water to trap the benzyl cation and prevent ring alkylation. The resulting 7-phenol was subsequently acetylated and chlorinated to afford the 4-chloroquinazoline intermediate **84**. Substitution of **84** with 3-chloro-4-fluoroaniline followed by revelation of the 7-OH by treatment with ammonia in methanol and conversion to triflate **127** was realized in 88% yield using an adapted method reported by Hendrickson and Bergeron.[50] Triflate **128** was also prepared directly from *gefitinib* with an overall yield of 62%.[51] Deprotection of the methyl ether at the 7 position was achieved in excellent yield using pyridinium hydrochloride under melt conditions. The resulting 7-OH was transformed to its corresponding triflate using the same conditions as for **127** to afford **128** in acceptable overall yield (Scheme 31).

Direct amination for 7-OTf precursors (**127** and **128**) was best achieved by adding the solid triflate portionwise to a stirred solution of the secondary amine in *N*-methylpyrrolidinone (NMP) at 135 °C. Unfortunately, primary amines could not be used efficiently in this process.[48] Therefore, to permit the substitution of primary amines at the 7 position, we targeted the synthesis of the 7-F analogue (**133**). The preparation of **133** was achieved using straightforward functional group manipulation based on the Niementowski cyclization, starting from the commercially available benzoic acid **129**. Esterification of **129** followed by regiospecific nitration and reduction afforded a good overall yield of anthranilic acid derivative **131**, which was cyclized in the presence of formamide and chlorinated to afford the moisture sensitive 4-chloroquinazoline precursor **132**. Substitution of the 4-Cl with 3-chloro-4-fluoroaniline allowed us to access large quantities of **133** in excellent yield, which was used without further purification (Scheme 32). As expected, the 7-F precursor **133** proved to be a more versatile intermediate affording good to excellent yields of 7-substituted products for both primary and secondary amine substrates (Table 5).



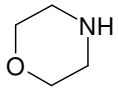
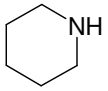
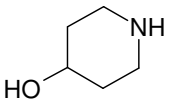
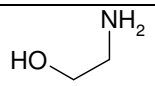
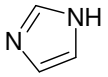
Reagents and conditions: a) MeOH, cat. H_2SO_4, reflux, 16 h, 95%; b) HNO_3, H_2SO_4, 0–10 °C, 0.5 h, 62%; c) H_2, Pd-C, EtOH, r.t., 6 h, 89%; d) formamide, acetic acid, 135 °C, 68%; e) $SOCl_2$, reflux, 16 h, 95%; f) 3-chloro-4-fluoroaniline, *i*-PrOH, reflux, 91%.

Scheme 32

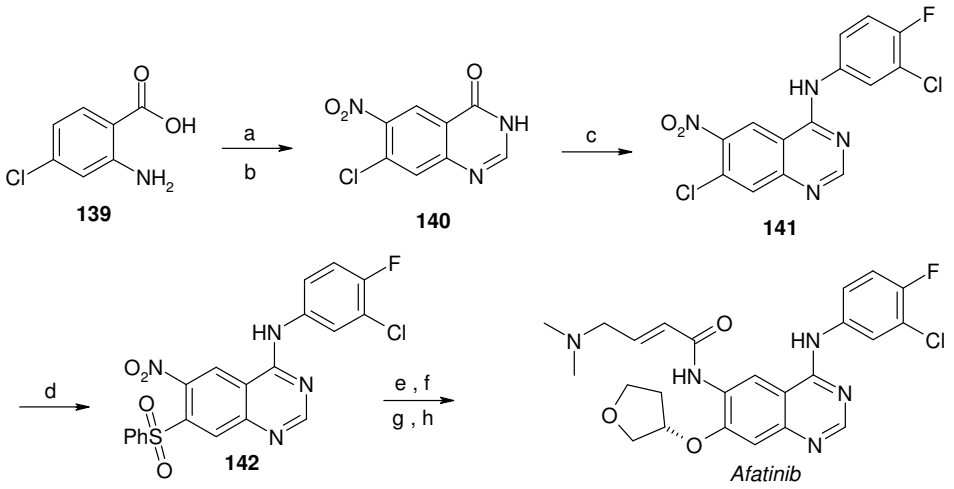
Amine derived substitution at the unactivated C-6 position has also attracted considerable interest with 2166 CAS numbers and 297 patents in the public domain. Within this class, the development candidate, *afatinib*, was identified by Boehringer Ingelheim researchers as a potent and irreversible EGFR inhibitor, having an acrylamide function at the 6 position.[7] The synthesis started from 2-amino-4-chlorobenzoic acid (**139**). Cyclization in neat formamide followed by nitration afforded 6-NO_2-7-Cl-quinazolin-4(3*H*)-one

(**140**). Chlorination followed by condensation with 3-chloro-4-fluoroaniline gave **141**. Displacement of the activated 7-Cl required first exchange of leaving group *via* displacement with the sodium salt of benzene sulfinic acid affording **142**. Transformation of **142** to *afatinib* was realized in good overall yield using standard functional group manipulation passing through a key Wittig-Horner condensation (Scheme 33).

Table 5.

Cpd	Amine	Precursor **127** (Yield)[a]	Precursor **128** (Yield)[a]	Precursor **133** (Yield)[b]
134		72	78	76
135		64	55	83
136		35	55	-
137		-	-	92
138		-	-	89

[a]Triflate **127** or **128** (1 equiv.) added portionwise to a stirred solution of amine (5 equiv.) in NMP (1 ml/g) at 135 °C and heated for 5 hours; [b]fluoride **133** (1 equiv.), amine (5 equiv.) in NMP (1 ml/g) heated at 135 °C for 5 hours.

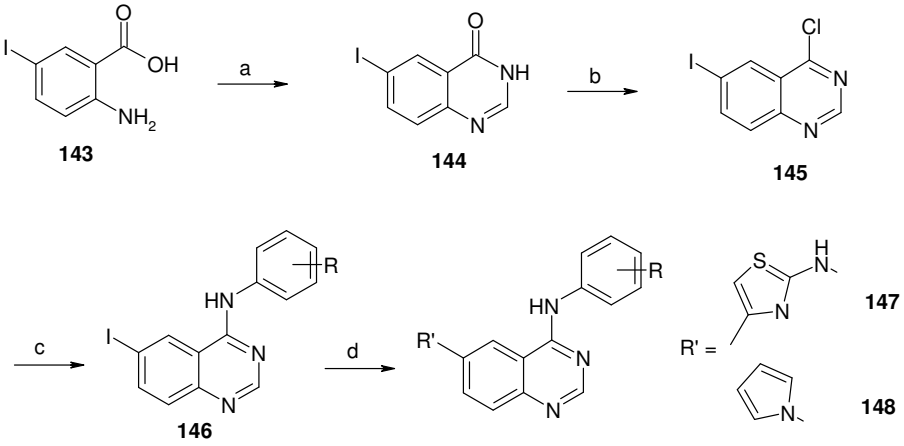


Reagents and conditions: a) NH_2CHO, 160 °C, quant.; b) H_2SO_4, HNO_3, H_2O, 0 °C to 110 °C, 88%; c) $POCl_3$, TEA, MeCN, reflux, 5 h followed by 3-chloro-4-fluoroaniline, 1 h, 90%; d) $PhSO_2Na$, DMF, 90 °C, 6 h, 86%; e) *(S)*-3-hydroxytetrahydrofuran, *t*-BuOK, DMF/*t*-BuOH/THF, r.t.–40 °C, 90%; f) H_2, RaNi, NH_4Cl, DMF, 40 °C, 2.5 h, 97%; g) CDI, diethylphosponoacetic acid, 40 °C, 70%; h) dimethylaminoacetaldehyde-hydrogensulfite adduct, KOH, LiCl, EtOH, −5 °C, 91%.

Scheme 33

Inspection of the literature reveals there are few reported strategies for the introduction of amino substitution directly at the 6 position of a quinazoline core.[52, 53] Researchers at Array Biopharma successfully employed C-6-iodo-4-chloroquinazoline (**145**) as the key building block in a program looking for selective Erb-B inhibitors. Thus, starting from 2-amino-5-iodobenzoic acid (**143**), cyclization in formamide followed

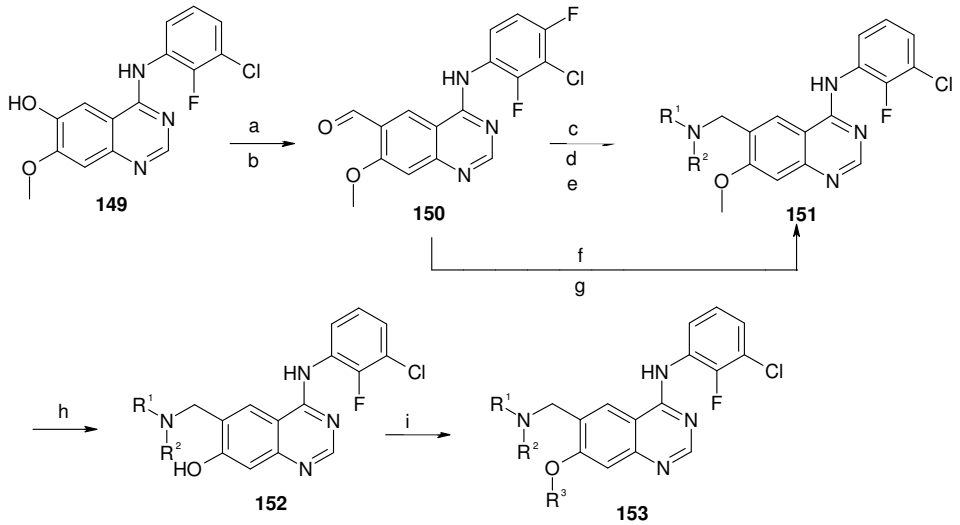
by chlorination afforded **145**. Displacement of the 4-Cl with anilines was achieved under standard acid-catalyzed S_NAr conditions giving **146** in good yield. Finally, substitution at the 6 position was acheived with a selection of heteroaromatic amines under either palladium[52] or copper catalysis.[53] In spite of these recent additions to the literature, there are still no references showing that this can be achieved in the presence of an alkoxy substituent at the 7 position (Scheme 34).



Reagents and conditions: a) $HCONH_2$, 190 °C, 2 h, 90%; b) $POCl_3$, DIPEA, 1,2-dichloroethane, 90 °C, 71%; c) R-Ar-NH_2, *i*-PrOH, r.t. to 80 °C, 4 h, 24%; d) R=2-amino-4-methylthiazole, $Pd_2(dba)_3$, xantphos, *t*-BuONa, toluene, r.t. to 100 °C, 16 h, R=pyrrole, CuI, $CH_3NHCH_2CH_2NHCH_3$, K_2CO_3, toluene, r.t. to reflux, overnight, 95%.

Scheme 34

Another target which attracted our attention during our own EGFR program was based upon having 6-CH_2NRR' substitution and retaining the capacity to vary the alkyl group at the 7 position in order to modify physicochemical parameters. Our synthesis concentrated on exploiting intermediates commonly used in other quinazoline programs.

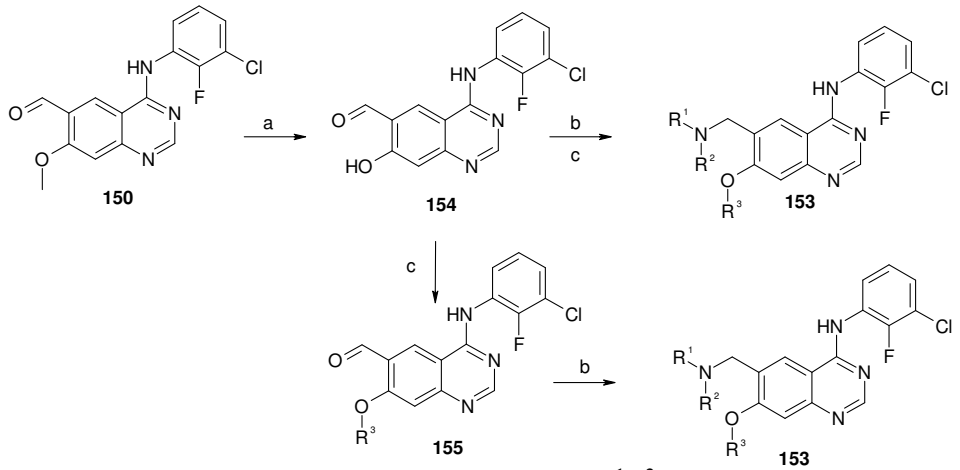


Reagents and conditions: a) $(Tf)_2O$, TEA, DCM, 95%; b) tri-*n*-butylsilane, $Pd(OAc)_2$, DPPP, CO (g) 17 bar, TEA, 70 °C, 69%; c) $NaBH_4$, MeOH, r.t., 100%; d) $SOCl_2$, r.t., 100 °C, 95%; e) R^1R^2NH, DIPEA, DMF, 140 °C, 74%; f) R^1NH_2, $NaBH(OAc)_3$, DCM-AcOH, 0 °C to r.t. g) R^2CHO, $NaBH(OAc)_3$, DCM-AcOH, 0 °C to r.t.; h) Li-I, 2,4,6-collidine, 130 °C, 30 minutes, 30–60%; i) R^3-OH, DTAD, TPP, THF, r.t., 30 minutes followed by TFA, 40–80%.

Scheme 35

The synthesis relied upon accessing sufficient quantities of the key intermediate 6-CHO-7-OCH_3. This was achieved by transformation of the 6-OH (**149**) (Scheme 35) to the corresponding triflate followed by Pd-catalyzed carbonylation in the presence of a hydride source.[54] Introduction of the amine moiety could be realized directly by reductive amination between aldehyde **150** and a range of amines or by alkylation on the resulting chloride, prepared in excellent yield by reduction aldehyde **150** to the alcohol and chlorination using an excess of thionyl chloride ($SOCl_2$). Deprotection of the aryl methyl ether at the 7 position of **151** was achieved under basic conditions using lithium iodide in 2,4,6-collidine to afford the phenol **152**. Final transformation of **152** to the desired final compounds (**153**) was achieved following standard Mitsunobu protocol.[55]

In order to increase the flexibility of the synthetic route, we managed to deprotect the aryl methyl ether in the presence of the aldehyde function of **150** by employing solid magnesium bromide ($MgBr_2$) in refluxing pyridine. The resulting 6-CHO-7-OH intermediate (**154**) proved to be a more versatile and functional group tolerant intermediate, allowing us to vary both positions efficiently and orthogonally to make diverse libraries of **153** (Scheme 36).



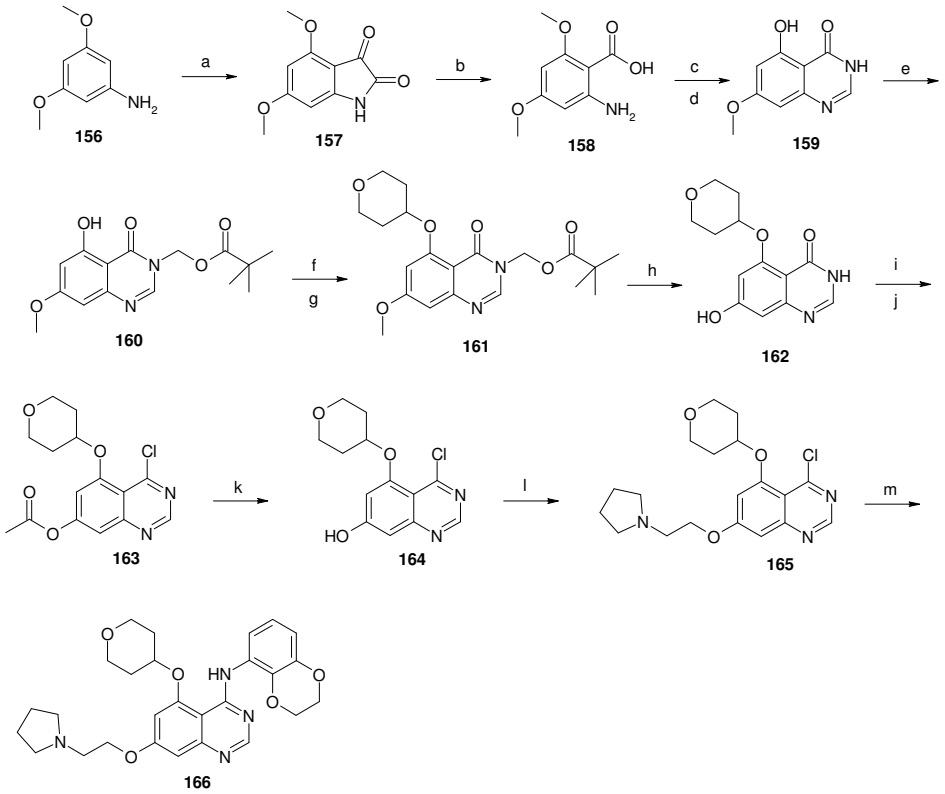
Reagents and conditions: a) $MgBr_2$, pyridine, 130 °C, 100%; b) R^1R^2NH, $NaBH(OAc)_3$, DCM-AcOH (10:1), r.t., 50–90%; c) R^3-OH, DTAD, TPP, THF, 50–80% or R^3-Cl/Br, K_2CO_3, DMF, r.t., 15–50%.

Scheme 36

2.5. 4,5,7-Trisubsubstituted quinazolines

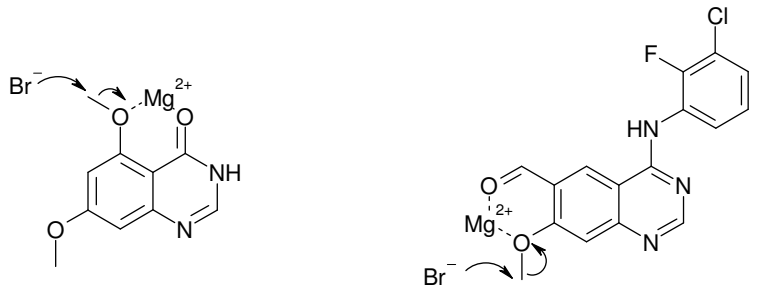
Quinazolines substituted at positions 4, 5 and 7, with only 1111 CAS Numbers and 87 patents, represent a much less significant sub-class than the 4,6,7-trisubstituted family. Indeed, the scaffold was first identified in our own laboratories as having potential for c-Src kinase inhibition. However, at the time, little was known about how to start to manipulate the two activated positions 5 and 7 of the quinazoline ring (Scheme 37). We decided to initially target a classical Niementowski synthesis, with a hope of differentiating between both positions *via* selective deprotection, thus targeted the synthesis of 3,5-dimethoxyanthranillic acid.[56] The synthesis started from 4,6-dimethoxyaniline (**156**). Cyclization with oxalyl chloride at 150 °C afforded 3,5-dimethoxyisatin (**157**) in excellent yield. Conversion to the anthranilic acid **158** was achieved using hydrogen peroxide (H_2O_2) in the presence of sodium hydroxide as the base at 105 °C. The resulting anthranilic acid **158** readily decarboxylated even at moderate temperatures. Therefore, all attempts to apply classical cyclization protocol (*e.g.*, formamide at >150 °C) failed due to competing

decarboxylation. In order to cyclize to the quinazolin-4(3*H*)-one **159**, **158** was first converted to its methyl ester using diazald and cyclized under milder conditions, using formamidine acetate in refluxing 2-methoxyethanol (Scheme 37). The resulting quinazolin-4(3*H*)-one **159** was selectively deprotected at the 5 position using magnesium dibromide in pyridine. The magnesium cation forms a stable 6-membered complex by coordinating to the carbonyl of the quinazolinone and the oxygen at the 5 position thus rendering the methyl group at position 5 much more susceptible to nucleophilic attack by the bromide anion (Scheme 38). This useful combination was also a key step used to deprotect an aryl methyl ether at the 7 position adjacent to a carbaldehyde moiety at the 6 position of **140** (Scheme 37).[55]



Reagents and conditions: a) oxalyl chloride, 150 °C, 86%; b) 30% H_2O_2(aq), NaOH, 105 °C, 55%; c) diazald, EtOH, NaOH, DCM, 0 °C, quant.; d) formamidine acetate, 2-methoxyethanol, reflux, 2 h, 94%; e) $MgBr_2$, pyridine, reflux, 98%; f) NaH, POM-Cl, 0 °C, DMF, 83%; g) Ph_3P, DTAD, tetrahydro-2H-pyran-4-ol, DCM, 88% then MeOH, NH_3, overnight, 94%; h) PhSH, K_2CO_3, NMP, 195 °C, 30 min., 91%; i) Ac_2O, catalytic pyridine, 80 °C, 30 min., 57%; j) Ph_3P, CCl_4, DCE, 70 °C, 2 h, 78%; k) MeOH, NH_3, r.t., 75% l) Ph_3P, DTAD, 2-pyrrolidin-1-ylethanol, DCM, 0°C to r.t., 88%; m) 2,3-dihydro-1,4-benzodioxin-5-amine, *i*-PrOH, reflux, 1.5 h, 60%

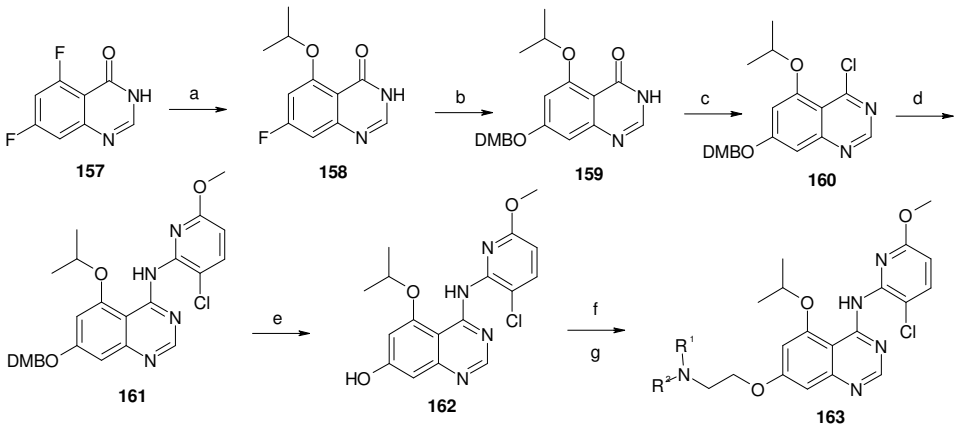
Scheme 37



Scheme 38

After installation of the POM group at N-3 affording **162**, the sequence was completed using standard functional group manipulation, relying on Mitsunobu alkylation steps to install the side chains at positions 5 and 7, with the exception of the chlorination step. In the presence of bulky substitution at the 5 position, the chlorination step was often slow under classical conditions (*e.g.*, an excess of chlorinating agent such as $POCl_3$ or $SOCl_2$ under reflux) and dimerization was a major problem. The employment of CCl_4 in the presence of triphenylphosphine proved to be vital in order to access sufficient quantities of 4-Cl-7-OAc quinazoline (**163**). Final transformation of **163** into the desired final structures (*e.g.*, **166**) was realized using standard functional group manipulation (Scheme 37).[57]

To ease further the diversification of this skeleton, we targeted the synthesis of the 5,7-difluoro-quinazolone (**1**) with the goal of carrying out two selective S_NAr reactions with alkoxides at the most activated 5 position followed by at the 7 position.[58,59] Indeed, displacement at the 5 position was achieved using a slight excess of sodium alkoxide at room temperature in DMF and the second displacement required a three-fold excess of potassium alkoxide in refluxing THF to complete the reaction to give **159**. The final finishing steps were achieved using standard chemistry to access the final compounds using a sequence that permits the exploitation of all 3 key positions. This flexible strategy reduced the number of steps compared to the process presented in Scheme 36 and avoided the hazardous preparation of 3,5-dimethoxy-anthranilic acid[54] was indeed adopted for the final manufacture of AZD0530 (Scheme 39).[13]



Reagents and conditions: a) *i*-PrOH, NaH, DMF, 5 C to r.t., 71%; b) 2,4-(MeO)BnOH (DMBOH) (3 equiv.), *t*-BuOK (6 equiv.), THF, reflux, 68%; c) $POCl_3$, Net-*i*-Pr_2, $ClCH_2CH_2Cl$, 75 C, 62%; d) NaHMDS (2 equiv.), 3-(chloromethyl)-6-methoxypyridin-2-amine (1 equiv.), THF, 0 C to r.t., 76%; (e) 20% TFA, CH_2Cl_2, quant.; (f) $Cl(CH_2)_3Br$, Cs_2CO_3, DMF, 60 °C, 55%; (g) $ClCH_2CH_2Cl$, K_2CO_3, DMF, 60 °C, 55%; (h) R^1R^2NH, KI, DMA, 90 C, 38–79%.

Scheme 39

3. Conclusions

From the results obtained by data mining using Sci-Finder®, it is clear that the interest in this scaffold is growing, reflecting our greater understanding as a whole of the reactivity of this heterocycle and its subsequent manipulation into pharmacologically attractive molecules from the milligram right up to the kilogram scale. While there has been some major advances in terms of the efficient library processing of these scaffolds all the way through to desired final products, there is still room to improve and innovate notably in developing more efficient cyclization protocols directly from readily-available aminoheterocycles.

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