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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. Dyestuff, electronic, and tanning structures, as well as life molecules frequently involve heterocyclic rings that play an important role in several chemical and biochemical processes.

Volume 16 (2012) keeps the international standard of TARGETS IN HETEROCYCLIC SYSTEMS – Chemistry and Properties (THS) series and contains eleven chapters, covering the synthesis, reactivity, and activity (including medicinal) of different heterorings. Authors from France, Germany, India, Italy, Poland, Russia, Slovakia, Sweden, and United Kingdom are present in this book.

As yet, THS Volumes 1-16 published 221 reviews by 626 authors from 29 different countries for a total of about 7.000 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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RECENT APPLICATIONS OF THE INTRAMOLECULAR DIELS ALDER FURAN (IMDAF) REACTION IN NATURAL PRODUCT SYNTHESIS

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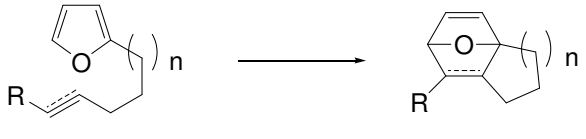
Abstract. *The intramolecular Diels-Alder furan (IMDAF) cycloaddition reaction is a versatile pericyclic reaction for the regio- and stereoselective synthesis of 6-membered carbocyclic and heterocyclic rings. In this chapter, recent applications of this reaction in organic synthesis are reviewed, with a particular emphasis on its utility as a key step in the total synthesis of complex natural products.*

Contents

1. Introduction

The Diels-Alder cycloaddition reaction is one of the most powerful and widely used methods for the synthesis of 6-membered ring systems. This pericyclic process allows the construction of 6-membered rings with a high degree of structural complexity in a single synthetic step, often with excellent regioselectivity and stereoselectivity. It is thus not surprising that Diels-Alder cycloadditions, particularly intramolecular Diels-Alder cycloadditions, have been so useful in the synthesis of natural products.[1] Within this class, the intramolecular Diels-Alder furan (IMDAF) cycloaddition reaction occupies a particular niche. In this reaction, a compound containing a furan moiety **1**, acting as the diene (4π-component), undergoes an intramolecular cycloaddition reaction with a tethered dienophile (2π-component), forming a tricyclic oxabicyclo[2.2.1] cycloadduct **2** (Scheme 1).



1 **2**

Scheme 1

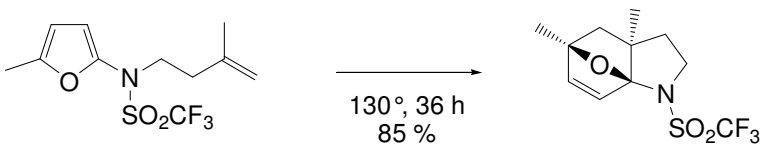
The synthetic versatility of the IMDAF reaction largely stems from the fact that the oxabicyclo[2.2.1] bridge of the initial cycloadduct **2** can be further manipulated or cleaved under a variety of conditions, giving rise to several useful functionalized 6-membered ring systems.

2. General aspects of the IMDAF reaction

The IMDAF reaction is quite general with respect to the diene component, the dienophile component, and the connecting tether between the two. A range of both electron-donating and electron-withdrawing substituents on the diene (furan) component is well tolerated, with different substitution patterns, while a wide variety of activated (electron-deficient) and unactivated dienophile components participate in the cycloaddition reaction, including alkenes, alkynes, allenes and benzynes. However, it should be noted that the IMDAF reaction is greatly accelerated by electron-withdrawing groups on the dienophile, as with all normal electron-demand Diels-Alder reactions. In addition, a range of reaction conditions has been developed to facilitate the IMDAF reaction, including the use of Lewis acids, microwave irradiation, high pressure and photochemical excitation. Several excellent reviews have covered in detail various aspects of the intramolecular Diels-Alder reactions of furans,[2] and thus these will only be mentioned very briefly here. In this chapter, we review the recent literature on the applications of the IMDAF reaction in organic synthesis, with a particular focus on its applications in the synthesis of complex natural products.

2.1. Regioselectivity and stereoselectivity

As with any intramolecular Diels-Alder cycloaddition reaction, the regioselectivity of the IMDAF reaction is necessarily controlled by the length of the tether connecting the reacting diene and dienophile components, and this can over-ride any electronic preferences in the reacting partners. Due to the susceptibility of IMDAF reactions to cycloreversion, thermal IMDAF reactions with short tethers usually give the thermodynamically more stable *exo*-cycloadducts where the tether sidearm connecting the dienophile to the furan ring is oriented *syn* to the oxygen bridge of the oxabicyclo[2.2.1] product. This is illustrated by the formation of *exo*-cycloadduct **4** as a single diastereomer in the thermal IMDAF reaction of 2-trifluoromethanesulfonamidofuran **3** (Scheme 2).[3] In certain cases the less favoured *endo*-cycloadducts can be isolated, particularly under conditions of kinetic control.



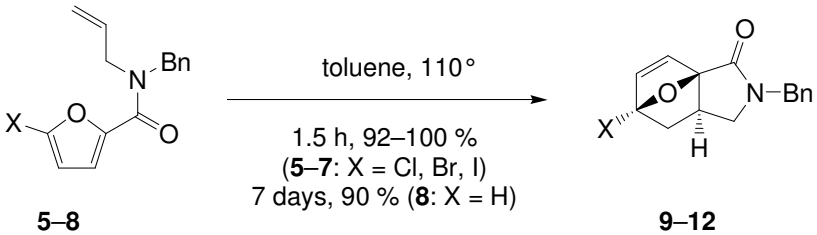
3 **4**

Scheme 2

2.2. Nature of the diene and dienophile

While IMDAF reactions are favoured when the dienophile is activated by electron-withdrawing groups, the origin of substituent effects on the furan diene component is less clear. In many cases, substituted furans react with faster rates than their unsubstituted analogues. Padwa discovered that a bromo-substituent in the 5-position of the furan ring had a significant effect on the rates of intramolecular Diels-Alder reactions of *N*-allyl-2-amidofurans.[4] While halo-substituted furans **5–7** (X = Cl, Br, I) underwent thermal IMDAF reaction to form cycloadducts **9–11** in high yields within 90 minutes, the reaction of the

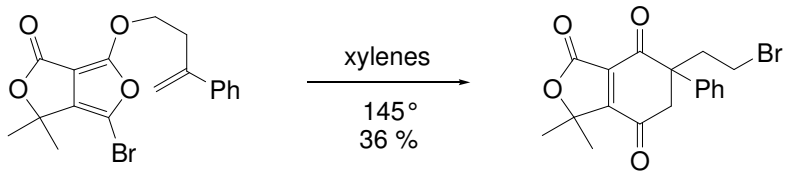
unsubstituted compound **8** (X = H) required 7 days to reach completion under the same conditions to form **12** (Scheme 3). The marked increase in reaction rate on incorporating a halogen substituent in the 5-position of the furan ring appeared to be general, and was attributed to an increase in the reaction exothermicity.



5–8 **9–12**

Scheme 3

In a related study, Padwa explored the IMDAF reaction of 5-bromofuran **13** that had been synthesized *via* a Rh(I)-catalyzed cyclization of a diazomalonate ester. Interestingly, thermal cycloaddition of **13** proceeded smoothly to afford bromide **14** (Scheme 4).[4a] This product is assumed to arise from fragmentation of the initial oxabicyclic cycloadduct giving a zwitterionic intermediate that expels bromide ion. The bromide ion then attacks the adjacent methylene position of the oxonium ion, giving **14**.



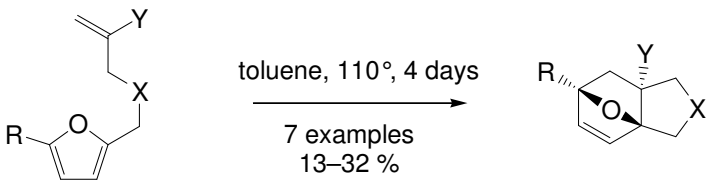
13 **14**

Scheme 4

2.3. Influence of the tether

The length of the tether can significantly affect the course of the IMDAF reaction. Reactions involving substrates with 3-atom and 4-atom tethers are usually successful, as they result in the formation of thermodynamically favoured 5- and 6-membered bridging rings, respectively. However, reactions of substrates with 2-atom and 5-atom tethers are rarely successful due to the formation of thermodynamically less stable 4-membered rings or kinetically unfavoured 7-membered rings, respectively. The presence of bulky substituents on the tether, particularly *gem*-dialkyl substituents, usually accelerates the rates of IMDAF reactions, most likely an illustration of the Thorpe-Ingold effect.

It is known that the presence of heteroatom groups in the tether can often facilitate IMDAF reactions that would otherwise not proceed with tethers composed only of carbon. A recent example is the intramolecular Diels-Alder cycloadditions of furans **15** bearing haloalkenes as the dienophile component (Scheme 5).[5]

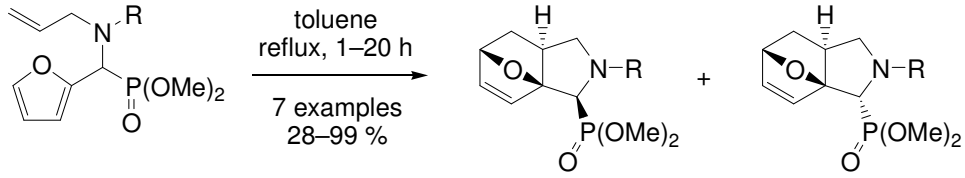


15 **16**

Scheme 5

These compounds undergo IMDAF reaction under thermal or microwave conditions generating tricyclic cycloadducts **16** containing halogen-functionalized quaternary stereocentres in moderate yields. The methodology is also successful with cyclic bromoalkenes as the dienophile component, which affords complex tetracyclic products.[6]

Although absolute stereocontrol of substituents on the diene or dienophile is usually observed in IMDAF reactions, this is often not the case for substituents attached to the tether connecting the two. In these cases isomeric mixtures are frequently obtained where the substituent on the tether adopts an equatorial position in the major isomer. A recent example of this is the thermal *exo*-selective IMDAF reaction of 1-acylamino(furan-2-yl)methyl phosphonates **17** which afforded mixtures of cycloadducts **18** and **19** differing only in the configuration of the phosphonate group (Scheme 6).[7] Under conditions of thermodynamic control, the major isomers **18** had the phosphonate group in the *endo*-orientation in each case.

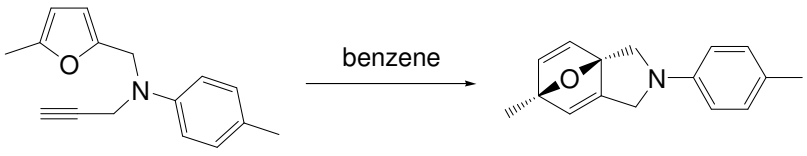


17 **18** **19**

Scheme 6

2.4. Activation of substrates toward IMDAF reaction

For the IMDAF reaction to be successful, two barriers must be overcome; the removal of the 6π-aromaticity of the furan ring, and the formation of a strained oxabicyclo[2.2.1]heptane ring system. Consequently, many methods have been studied to accelerate the IMDAF reactions of unactivated substrates, such as the use of Lewis acid catalysts, high pressure conditions and microwave acceleration. Microwave acceleration is particularly useful for facilitating IMDAF reactions of otherwise sluggish substrates. For example, Mance showed that IMDAF reaction of unactivated substrate **20** under microwave heating conditions gave higher yields of cycloadduct **21** in shorter reaction times compared to classical thermal conditions (Scheme 7).[8]

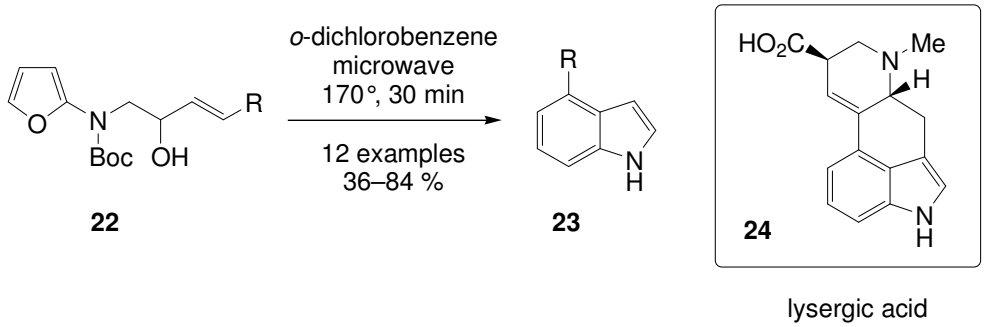


20 Conventional heating, 72 hrs: 12 % **21**
Microwave heating, 5 min: 46 %

Scheme 7

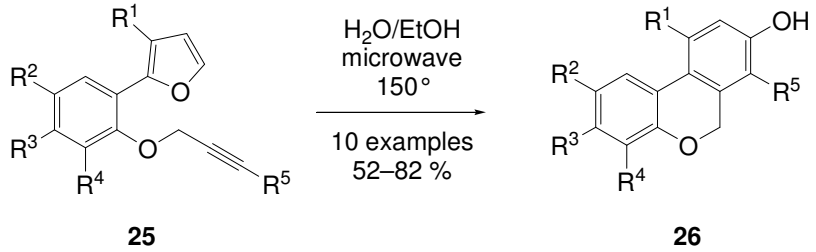
A concise approach to 4-substituted indoles involving an IMDAF reaction as the key step has been reported by Wipf. The intramolecular Diels-Alder furan reaction of a range of unsaturated *N*-(2-furanyl) amino alcohols **22** (prepared by the addition of lithiated alkylaminofurans to unsaturated aldehydes) afforded 4-substituted indoles **23** in good yields under microwave conditions (Scheme 8). The reaction proceeded by initial [4+2] cycloaddition, cleavage of the oxabicyclo[2.2.1] ring-system, double dehydration and subsequent aromatization to generate the indole ring system.[9] Interestingly, attempted cycloaddition reactions of **22** under thermal conditions (toluene, reflux, 48 hours) led to decomposition products. The

4-substituted indole moiety is a common structural motif found in many biologically important compounds, such as the Ergot alkaloid lysergic acid **24**.



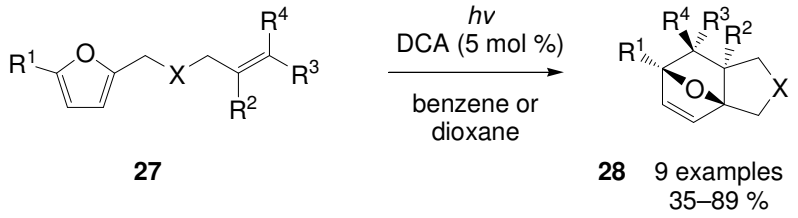
Scheme 8

In some cases Diels-Alder reactions can be accelerated in aqueous media compared to the analogous reactions carried out in organic solvents. For example, Zhang and Fan showed that a range of 6*H*-benzo [*c*]chromenes and 6*H*-benzo[*c*]chromen-8-ols could be synthesized by thermal IMDAF reactions of unactivated alkene and alkyne dienophiles in water.[10] Furthermore, the reaction could be accelerated significantly using microwave irradiation. Several 6*H*-benzo[*c*]chromen-8-ols **26** were readily synthesized by thermal IMDAF reaction of unactivated alkynes **25** in water at elevated temperature in a sealed vessel under microwave irradiation (Scheme 9).



Scheme 9

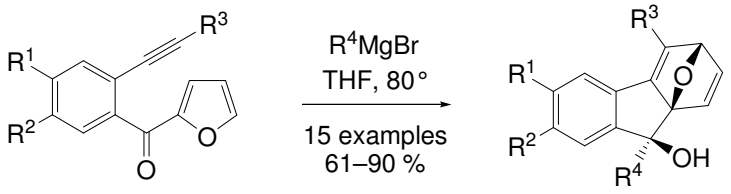
Frontier Orbital theory dictates that Diels-Alder furan reactions between electron-rich dienes and dienophiles proceed with difficulty and often require harsh reaction conditions. However, such reactions can be facilitated through radical ions or electronically excited states. Arai reported that intramolecular Diels-Alder furan reactions of a range of trisubstituted electron-rich dienophiles **27** proceeded in high yields in the presence of the photosensitizer 9,10-dicyanoanthracene (DCA) under UV irradiation (Scheme 10).[11] The expected cycloadducts **28** were obtained when the furan ring was substituted with an alkyl group. However, aryl-substituted furans cyclized in a completely different manner, affording spirocyclic and tricyclic products.



Scheme 10

Many IMDAF reactions can also be accelerated by chelation of the furan diene partner with a Lewis acid. A recent example is the cascade Grignard addition/Diels-Alder cycloaddition reactions of aryl furanyl

ketones **29** bearing unactivated alkyne dienophiles reported by Liu and Li.[12] Addition of Grignard reagents to ketones **29** gives a chelated magnesium species that undergoes rapid thermal IMDAF cycloaddition affording oxabicycles **30** in good to high yields (Scheme 11). The cycloadducts **30** were obtained as single diastereomers where the oxygen bridge and the hydroxyl group were oriented *syn*, most likely due to chelation control by the magnesium chelate formed in the initial Grignard addition step.

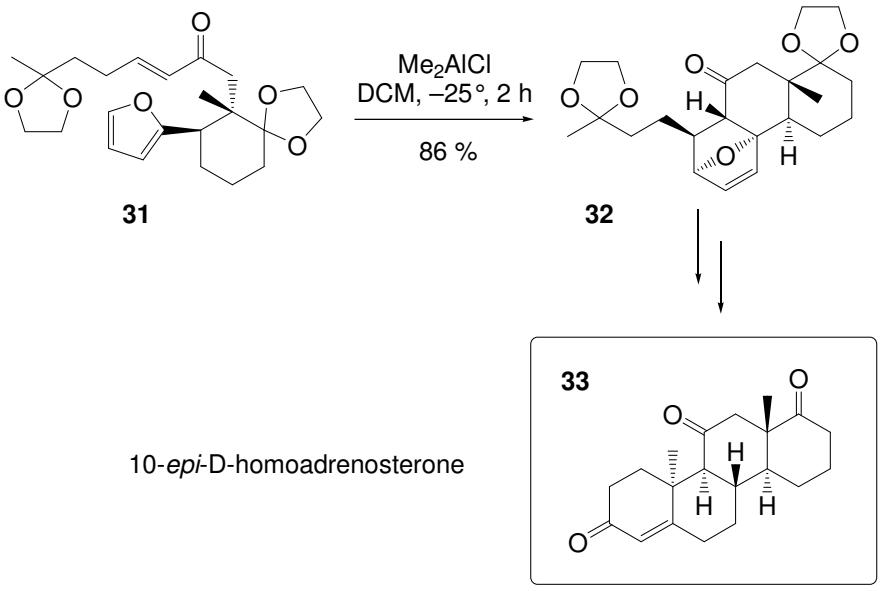


29 **30**

Scheme 11

3. Recent applications of the IMDAF reaction in total synthesis

De Clercq utilized an IMDAF reaction as a key step in the total synthesis of 10-*epi*-D-homo-adrenosterone **33** (Scheme 12).[13] Lewis acid-catalyzed IMDAF cycloaddition of precursor **31** under conditions of kinetic control (Me_2AlCl, DCM, –25 °C) afforded a high yield of *exo*-cycloadduct **32** as a single diastereomer. In contrast, IMDAF cycloaddition of **31** under thermal conditions (25 °C, 24 h) generated a mixture of **32** and predominantly a second, more stable *exo*-diastereomer. Cleavage of the oxabicyclo[2.2.1] bridge of **32** and further synthetic elaboration generated the tetracyclic ring system of 10-*epi*-D-homoadrenosterone **33**.

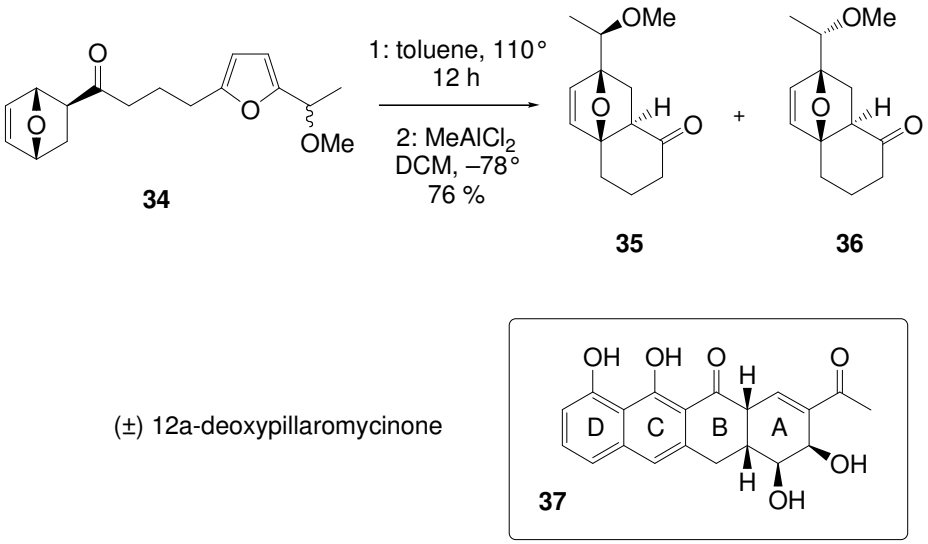


31 **32**

Scheme 12

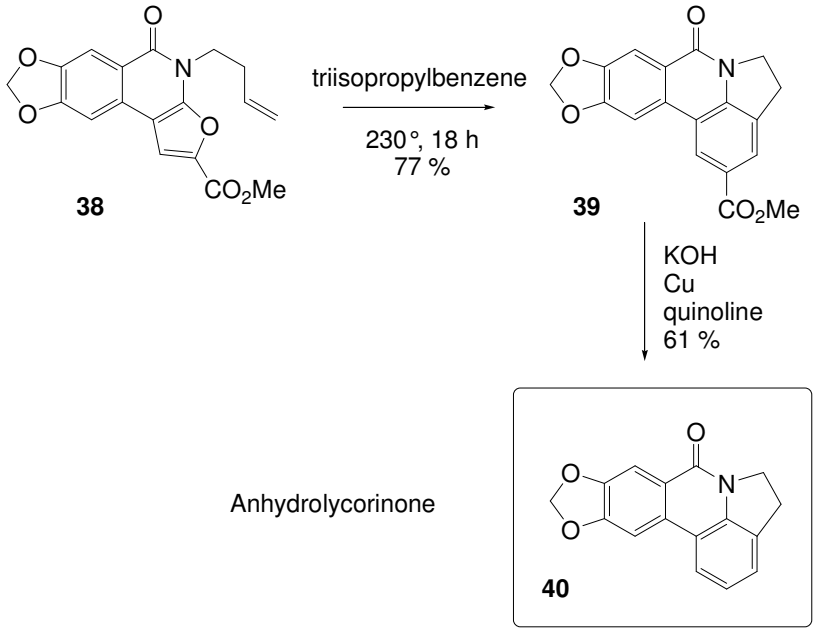
Rodrigo employed the cycloadduct of an intermolecular Diels-Alder furan reaction between an acrylamide and furan as a masked acryloyl ketone during the synthesis of the ABCD ring system of (±)-12a-deoxypillaromycinone **37**. Retro-Diels-Alder reaction of racemic **34** under thermal conditions generated the unsaturated acryloyl ketone dienophile that subsequently underwent IMDAF cycloaddition under kinetic conditions affording a 1:1 separable mixture of diastereomeric cycloadducts **35** and **36** (Scheme 13).[14] Although the diastereomeric cycloadducts **35** and **36** were separated, the absolute

configuration of the methoxy-group in these compounds was immaterial as both cycloadducts were further manipulated to generate advanced tetracyclic intermediates containing the ABCD rings of (±)-12a-deoxy-pillaromycinone **37** and related natural products.



Scheme 13

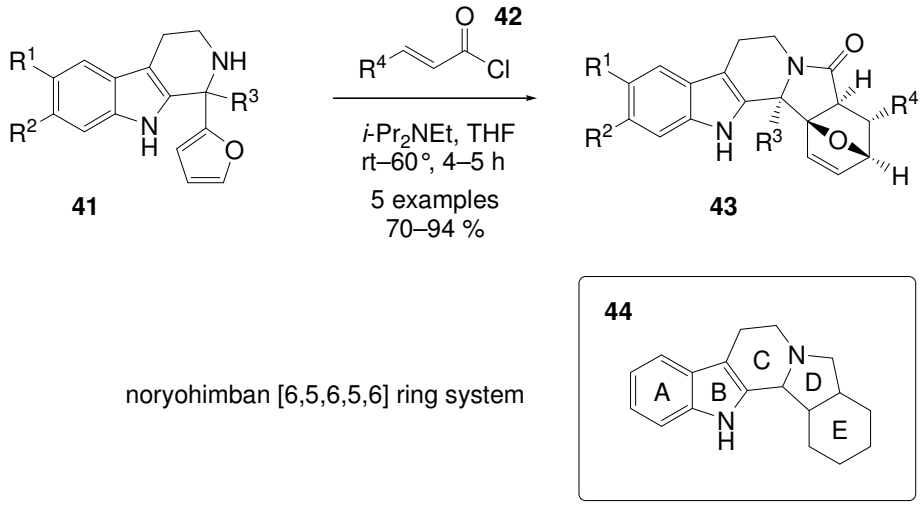
In an elegant and concise approach to the total synthesis of the *Amaryllidaceae* plant metabolite anhydrolycorinone **40**, Boger employed a late-stage tandem intramolecular Diels-Alder reaction of a 1,3,4-oxadiazole with an alkene, followed by an IMDAF reaction of the resulting furan with a vinyl ether dienophile (Scheme 14) as the key step.[15] Initial intramolecular Diels-Alder reaction of an *N*-(1,3,4-oxa-diazolyl)-2-vinylbenzamide with the 1,3,4-oxadiazole moiety at 165 ^{o}C generated furan cycloadduct **38** that underwent a second intramolecular Diels-Alder reaction of the furan moiety at 230 ^{o}C with subsequent aromatization to furnish **39**. This sequence of cycloadditions was also conveniently performed in one-pot (230 ^{o}C, 24 h, 72%). Subsequent removal of the ester group afforded the natural product **40**.



Scheme 14

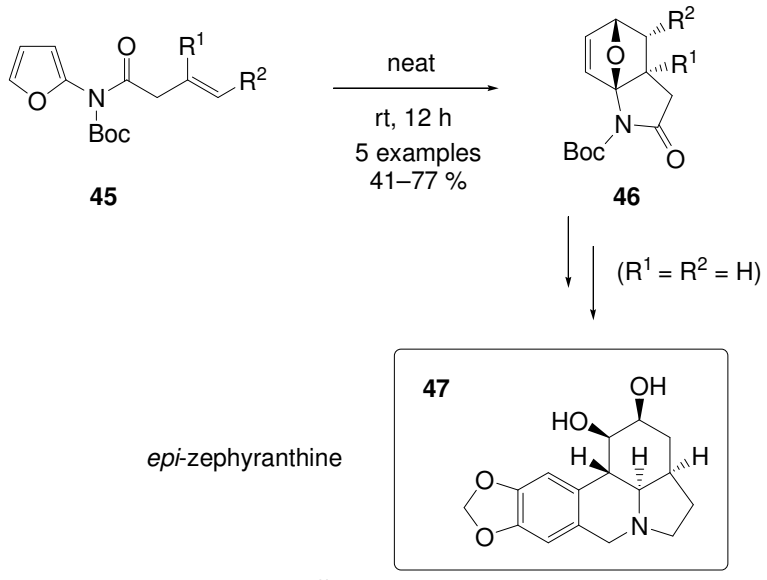
A rapid approach to the pentacyclic [6,5,6,5,6] ring system of the indole alkaloid noryohimbane was developed by Fokas, involving tandem *N*-acylation/ IMDAF reaction of 1-(2-furyl)-β-tetrahydrocarbolines.[16]

Several 1-(2-furyl)-β-tetrahydrocarbolines **41** were prepared by Pictet-Spengler reactions of various tryptamines with a 2-furyl-α-ketoester. Subsequent *N*-acylation of these compounds with acryloyl chlorides **42**, or with maleic anhydride, and subsequent IMDAF cycloaddition of the resulting adducts furnished functionalized *exo*-cycloadducts **43** containing the ABCDE ring system of the noryohimbane skeleton **44** (Scheme 15).



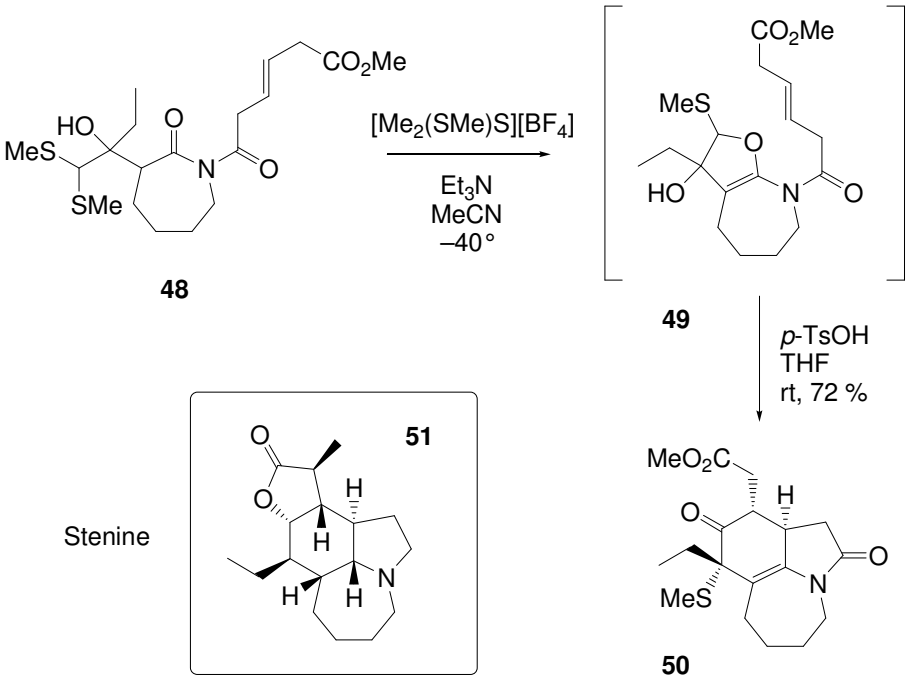
Scheme 15

The synthetic versatility of the oxabicyclo[2.2.1] bridge of IMDAF cycloadducts was illustrated by Padwa during the total synthesis of (±)-epi-zephyranthine **47**, a member of the *Amaryllidaceae* family of alkaloids. The synthesis comprised a facile IMDAF reaction of a 2-amidofuran **45**, followed by a Rh(I)-catalyzed ring opening of the oxabicyclo[2.2.1] bridge of the resulting cycloadducts **46** as key steps.[17] The IMDAF cycloaddition reaction of **45** was extraordinarily facile, and generated cycloadducts **46** under mild conditions (Scheme 16). The isolation of cycloadducts **46** under mild conditions was attributed to the electron-withdrawing effect of the carbonyl groups, which prevented the anticipated ring-cleavage/rearrangement reactions encountered in related systems. Rh(I)-catalyzed nucleophilic ring opening of cycloadduct **46** ($R^1 = R^2 = H$) established the *cis*-1,2-diol stereochemistry and further manipulation furnished (±)-*epi*-zephyranthine **47**.



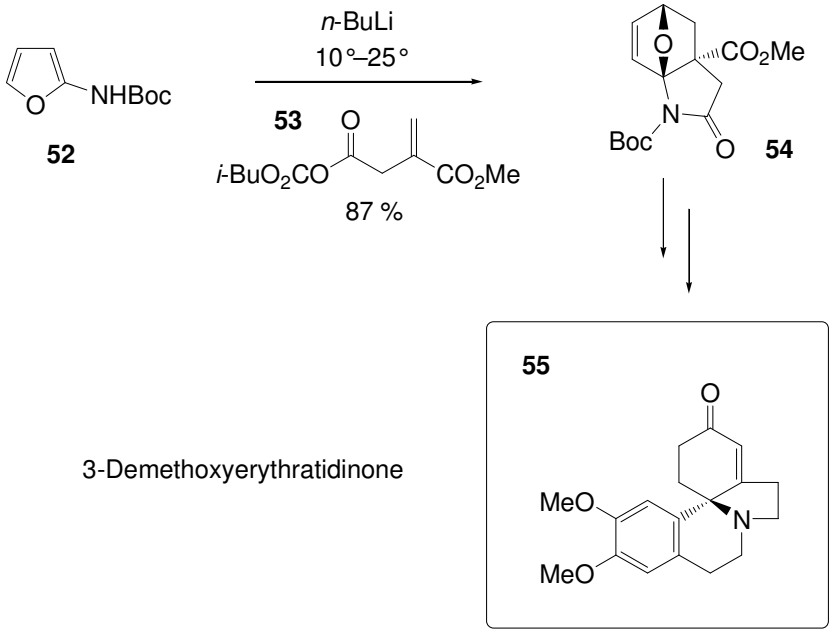
Scheme 16

Padwa employed an intramolecular Diels-Alder reaction of a 2-methylthiofuran as the key step in his elegant total synthesis of the stemona alkaloid stenine **51**. In a first generation approach, the furan cycloaddition precursor **49** was generate *in situ* by a dimethyl(methylthio)sulfonium tetrafluoroborate-mediated cyclization of imidodithioacetal **48** (Scheme 17).[18] Treatment of **49** with acid generated the furan ring *in situ* and subsequent IMDAF cycloaddition generated cycloadduct **50** as a single diastereomer. However, difficulties with the subsequent reduction of the keto group of the cycloadduct **50** led to a slightly modified and ultimately successful approach to (±)-stenine **51**.[19]



Scheme 17

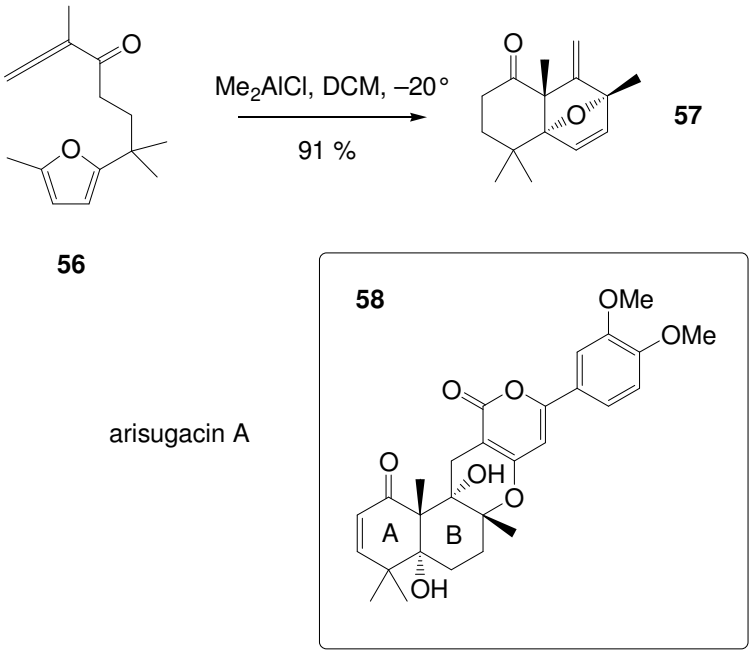
The facile IMDAF reactions of 2-amidofurans were exploited by Padwa during the total synthesis of the *Erythrina* alkaloid 3-demethoxyerythratidinone **55** (Scheme 18).



Scheme 18

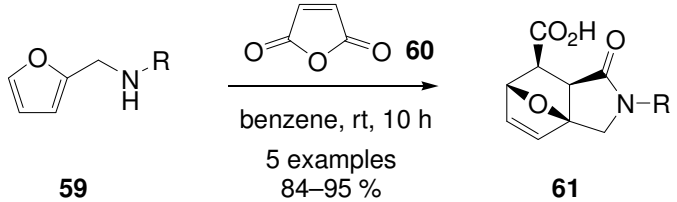
Deprotonation of protected 2-aminofuran **52** and trapping with mixed anhydride **53** was followed by a rapid IMDAF reaction generating *exo*-cycloadduct **54** in high yield.[20] Rh(I)-catalyzed ring opening of the oxabicyclo[2.2.1]heptene of **54** and further synthetic transformations (*N*-alkylation, Pictet-Spengler cyclization, Barton decarboxylation and amide reduction) generated the natural product **55**.

A stereoselective approach to the A and B rings of the acetylcholine esterase inhibitor arisugacin A **58** has been reported by Jung. The key step was a Lewis acid-catalyzed IMDAF reaction of the allenyl ketone **56** in the presence of dimethylaluminium chloride which led to the formation of cycloadduct **57** as a single diastereomer in 91% yield (Scheme 19).[21] Analogous IMDAF reactions of similar precursors having alkene dienophiles gave the expected cycloadducts in significantly lower yields, presumably due to facile retro Diels-Alder reactions.



Scheme 19

The isoindolone ring system is a key structural feature of several natural products of biological significance, such as the alkaloid lennoxamine. A rapid entry to the isoindolone system using an IMDAF reaction was reported recently.[22] The reaction of 2-furylamines **59** with maleic anhydride **60** afforded the *exo*-cycloadducts **61** in one-pot (Scheme 20). The reaction proceeded by initial *N*-acylation followed by stereoselective intramolecular Diels-Alder cycloaddition. Opening of the oxygen bridge of the cycloadducts **61** and subsequent aromatization afforded the desired isoindolones.

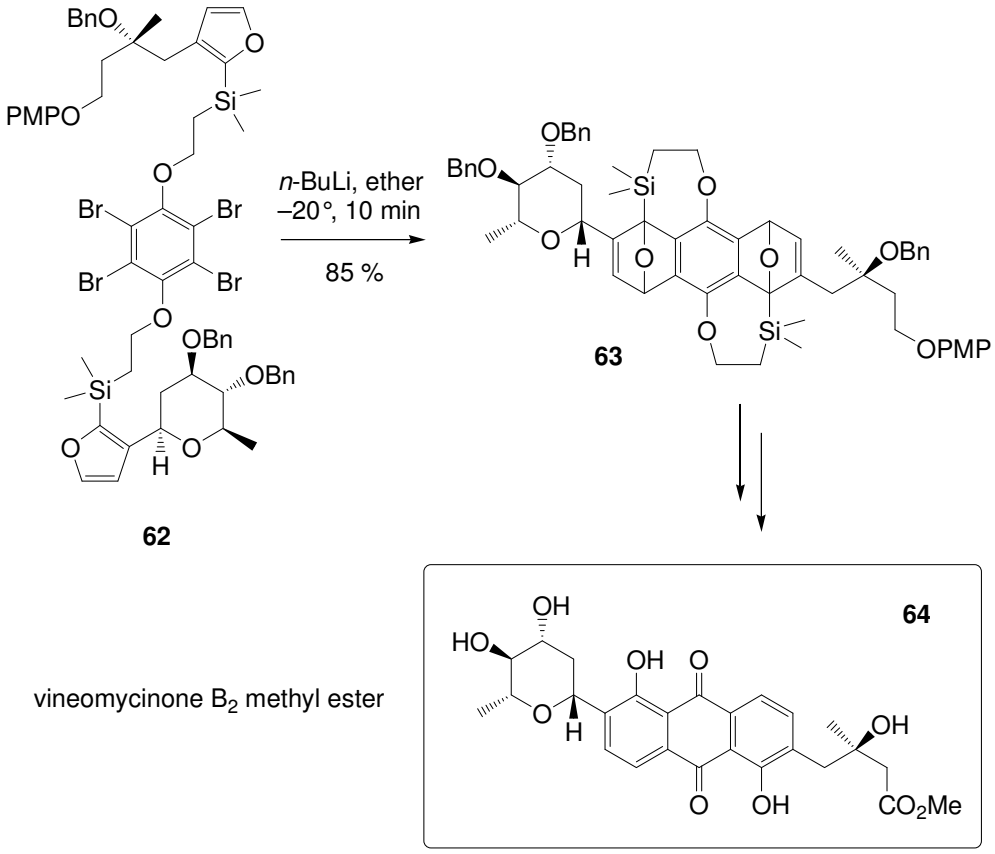


59 **61**

Scheme 20

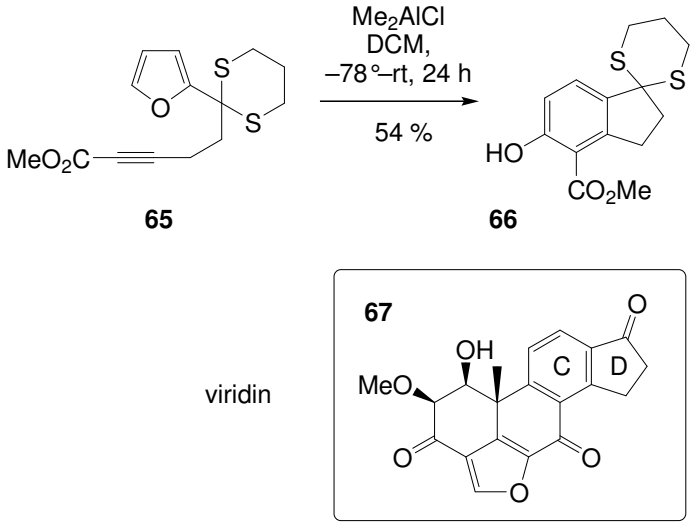
Tandem intramolecular benzyne-furan Diels-Alder cycloaddition reactions have been developed by Martin during synthetic studies towards the vineomycin family of antibiotics. After successful synthetic

studies on model compounds, the methodology was applied to the total synthesis of vineomycinone B_2 methyl ester **64** (Scheme 21).[23] The key cycloaddition precursor **62** was treated with *n*-BuLi generating a benzyne intermediate that was subsequently trapped by cycloaddition with the tethered furan moieties generating, after a second iteration, cycloadduct **63**. Further transformations resulted in a highly convergent total synthesis of vineomycinone B_2 methyl ester **64**. A notable feature of this methodology is the use of temporary silicon tethers to control the regiochemical outcome of the key iterative IMDAF steps.



Scheme 21

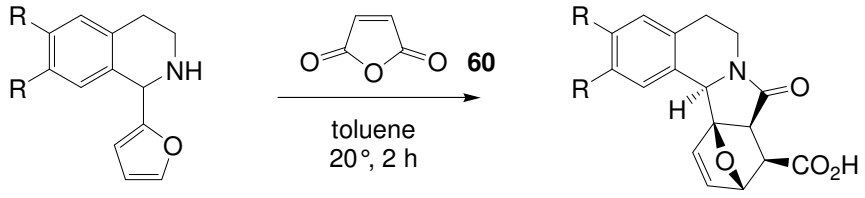
An eight-step regiospecific synthesis of the C and D rings of the furanosteroid antibiotic viridin **67** was achieved by Keay using an IMDAF reaction as the key step.[24]



Scheme 22

Starting from 2-furaldehyde, cycloaddition precursor **65** was synthesized and subjected to IMDAF reaction conditions. Although thermal conditions were not successful, **65** underwent [4 + 2] cycloaddition under Lewis acid catalysis (Me_2AlCl) at low temperature to generate the aromatized cycloadduct **66** in 54% yield (Scheme 22). Protected indanone **66** maps well onto the C and D rings of viridin **67**.

Elegant and concise syntheses of the isoindolo[1,2-*a*]isoquinoline cores of the nuevamine, jamtine and hirsutine alkaloids were recently reported by Zubkov.[25] The reactions of 1-furyl-1,2,3,4-tetrahydroisoquinolines **68** and **69** (which were obtained by a three step procedure) with unsaturated carboxylic acid derivatives (acryloyl chlorides, crotonyl chloride and maleic anhydride **60**) afforded intermediates that underwent subsequent IMDAF reaction in one-pot under mild reaction conditions to generate exclusively the *exo*-cycloadducts (*e.g.*: **70** and **71**) in high yield (Scheme 23). Interestingly, in the presence of activated alkynes (*e.g.*: DMAD), only the corresponding Michael addition products were obtained. In a subsequent report,[26] aromatization of cycloadducts **70** and **71** to the nuevamine ring system was successfully accomplished by exposure of **70** and **71** to hot aqueous sodium hydroxide.

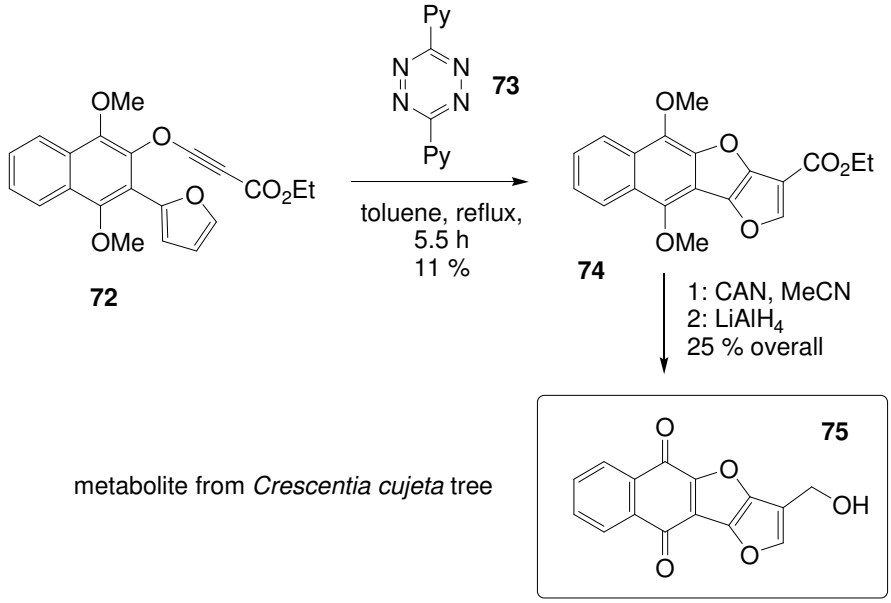


68–69

70: R = H: 90 %
71: R = OMe: 97 %

Scheme 23

The total synthesis of a metabolite isolated from the tropical American tree *Crescentia cujeta* has been reported by Wege.[27] This natural product contains the unusual and structurally rare furo[3,2-*b*]furan bicyclic ring system. Following successful studies on simpler model compounds, the key cycloaddition intermediate **72** was synthesized. Thermal IMDAF reaction of **72** in refluxing toluene afforded an oxabicyclo[2.2.1]heptadiene intermediate that was trapped by Diels-Alder reaction with 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **73**.



72

74

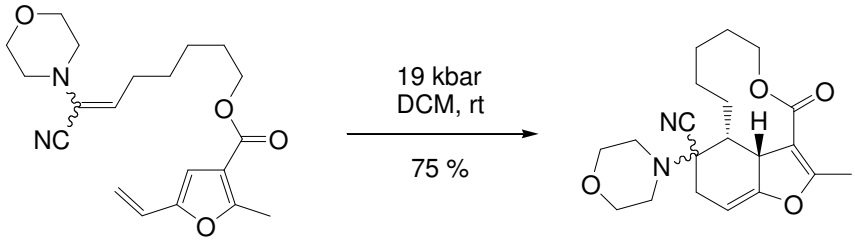
75

metabolite from *Crescentia cujeta* tree

Scheme 24

Subsequent extrusion of nitrogen and retro-Diels-Alder cycloaddition afforded the tetracyclic ester **74** in 11% yield (Scheme 24). Oxidative aromatization with ceric ammonium nitrate followed by reduction of the ester group completed the synthesis and gave the natural metabolite **75**.

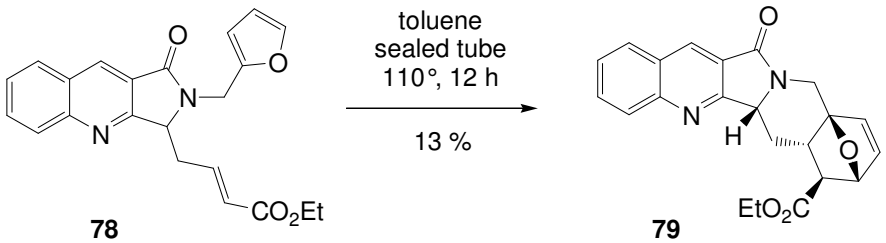
It has been shown that 2-vinylfurans undergo Diels-Alder cycloaddition with doubly activated dienophiles under ultra-high-pressure conditions *via* the diene comprising the exocyclic vinyl group as opposed to the furan diene.[28] Realizing the potential of this methodology to access the colletofragarones (fungal germination self-inhibitors), Harwood reported a concise approach to the macrocyclic core of these fungal metabolites. In the key step, cycloaddition precursor **76**, which was synthesized in 6 steps, underwent ultra-high pressure-mediated intramolecular Diels-Alder reaction in an extra-annular fashion affording the advanced intermediate **77** in 75% yield (Scheme 25).[29]



76 **77**

Scheme 25

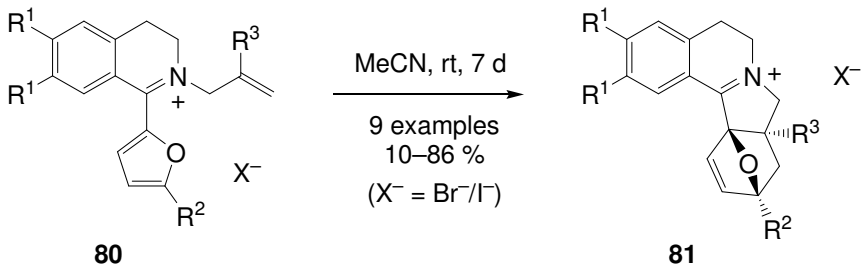
Daïch recently reported a concise approach to the pentacyclic ring system of the aromathecin alkaloids which employed an *exo*-selective IMDAF reaction as the key step.[30] The key cycloaddition intermediate **78** was synthesized in 6 steps from aniline, and then underwent an *exo*-selective IMDAF reaction in refluxing toluene in a sealed tube to generate the cycloadduct **79** as a single stereoisomer, albeit in an optimized yield of only 13% (Scheme 26). The methodology was also successful with the corresponding isoindolinone.



78 **79**

Scheme 26

An unusual example of an IMDAF reaction involving a cationic iminium species was reported by Zubkov.

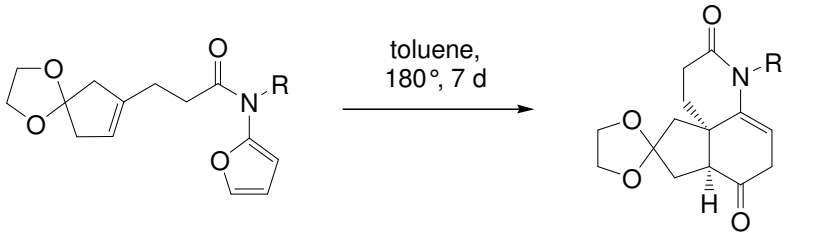


80 **81**

Scheme 27

The authors found that *N*-allylation reactions of a range of 1-furyl-3,4-dihydroisoquinolines (easily synthesized from readily available phenethylamines) afforded iminium salts **80** that underwent spontaneous IMDAF reaction to generate only the *exo*-cycloadducts **81** in a one-pot reaction (Scheme 27).[31] The adducts contain the basic structural element of the isoindolo[1,2-*a*]isoquinoline alkaloids jamtine and hirsutine, and the methodology could thus permit facile access to these natural products in the future.

During synthetic studies towards the synthesis of the lycopodium alkaloid (±)-fawcettidine, Padwa reported the efficient construction of the BCD ring core of this natural product *via* an intramolecular Diels-Alder furan/rearrangement cascade sequence of a 2-amidofuran.[32] Following model studies which supported the feasibility of this approach, cycloaddition precursors **82** and **83** were synthesized and subjected to thermolysis at 180 °C in toluene, affording Diels-Alder cycloadducts which underwent rearrangement under the reaction conditions to generate the desired tricyclic products **84** and **85** (Scheme 28). Unfortunately, further manipulations aimed at closing the A-ring and completing the synthesis of (±)-fawcettidine were unsuccessful.

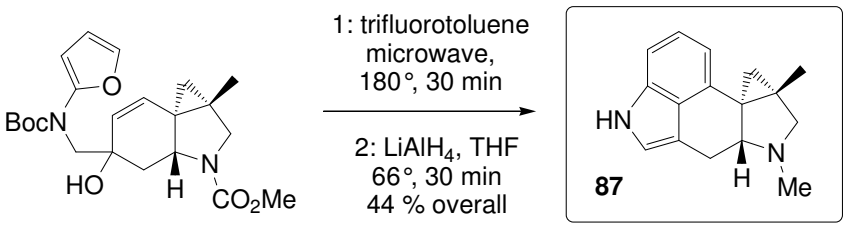


82–**83**

84: R = $CH_2CH{=}CH_2$: 67 %
85: R = $CH_2CH_2CH_2OTBS$: 88 %

Scheme 28

Wipf has recently disclosed novel routes to the naturally occurring indole alkaloid (±)-cycloclavine **87** and its unnatural C(5)-epimer which employed a late stage IMDAF reaction as a key step.[33] A first generation approach afforded the unnatural C(5)-epimer of (±)-cycloclavine **87** which contained the *cis*-configuration at the C(5)–C(10) ring junction. Subsequently, a second generation approach employed an intramolecular Diels-Alder reaction of a methylenecyclopropane to install the correct relative stereochemistry at the C(5)–C(10) ring junction, giving rise to intermediate **86**. IMDAF reaction of **86** occurred under microwave conditions with subsequent dehydration and aromatization to afford (±)-cyclo-clavine **87** in two steps in 44% overall yield (Scheme 29).



86

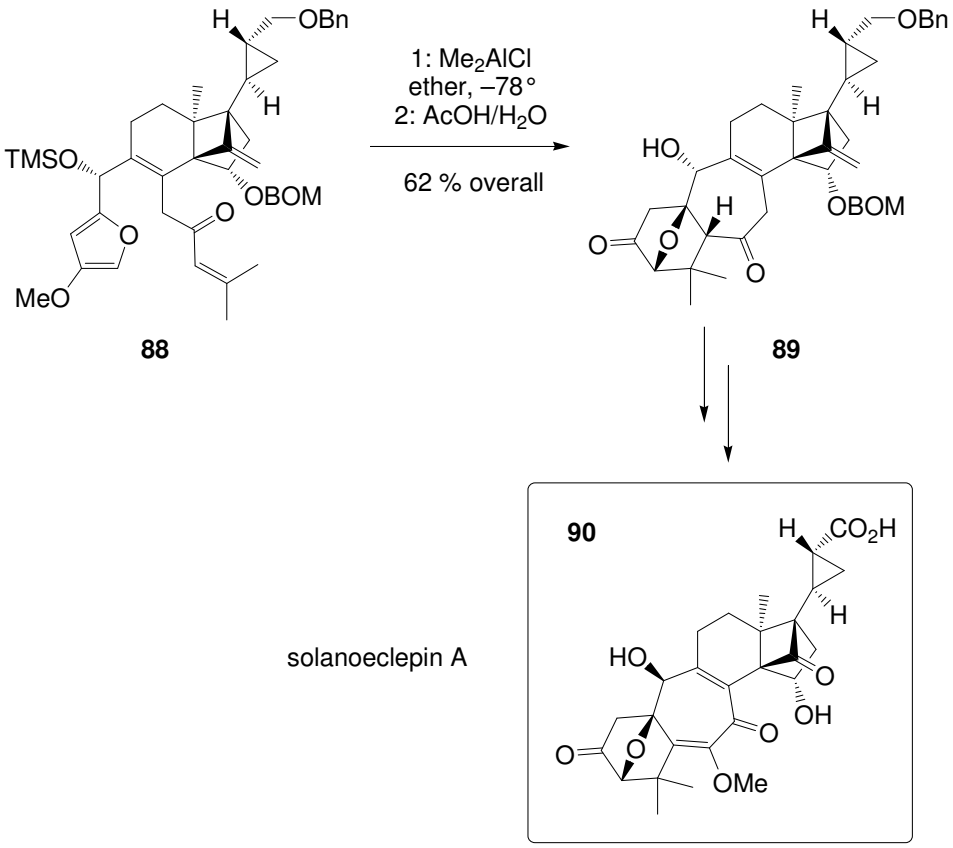
87

cycloclavine

Scheme 29

The first total synthesis of solanoeclepin A, the hatch-stimulating substance of the potato cyst nematode, was reported by Tanino and Miyashita.[34] One of the key steps in the synthesis was the

construction of the oxabicyclo[2.2.1]heptan-2-one ring system of solanoeclepin A **90** *via* a stereoselective intramolecular Diels-Alder furan reaction. A sequence of linear steps afforded the optically active cycloaddition precursor **88**. The crucial IMDAF reaction occurred when **88** was treated with dimethylaluminum chloride in ether at low temperature which gave rise to cycloadduct **89** in 62% yield in a stereoselective manner following treatment of the cycloadduct with aqueous acetic acid (Scheme 30). Further manipulations gave access to solanoeclepin A **90**.

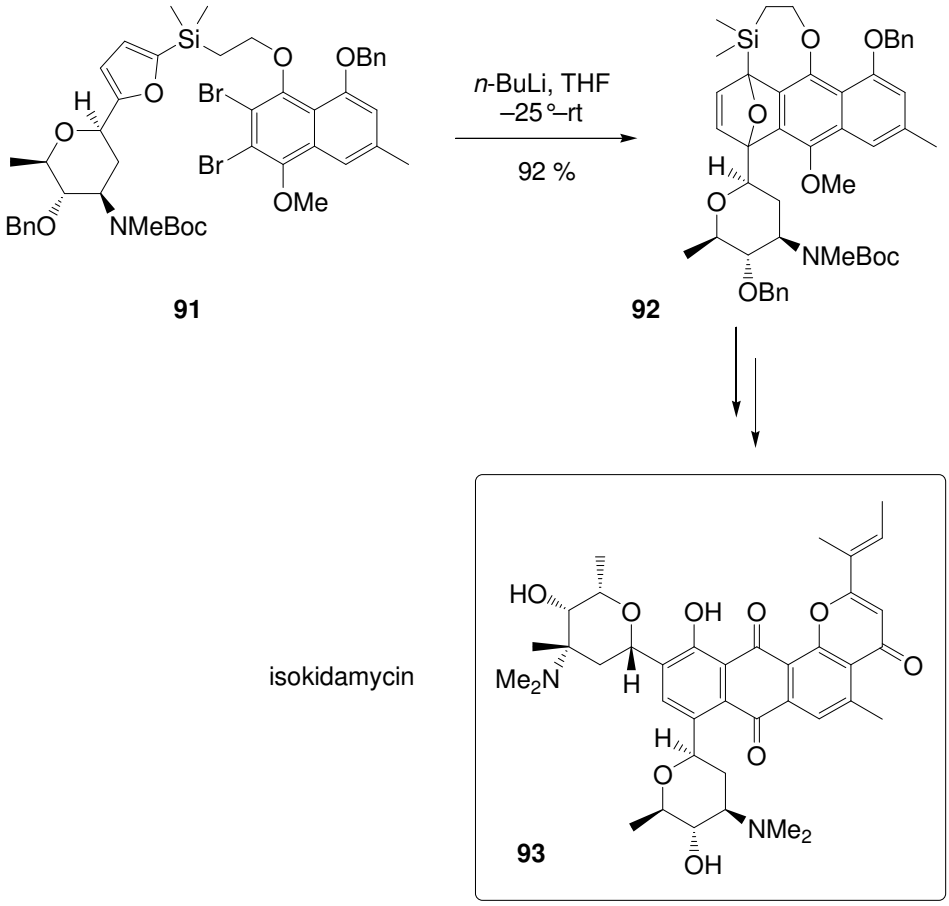


Scheme 30

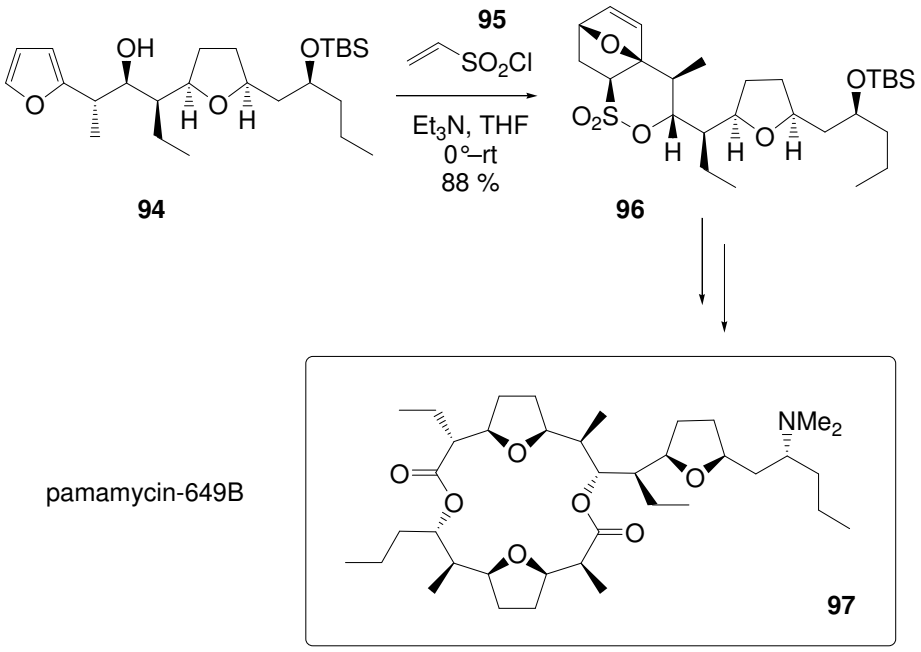
Kidamycin and isokidamycin are members of the pluramycin class of antibiotics isolated from *Streptomyces phaeoverticillatus* and the first total synthesis of isokidamycin **93** was recently reported by Martin.[35] The approach featured a highly efficient intramolecular Diels-Alder reaction between a substituted naphthyne and a glycosylated furan to form the tricyclic anthracene core. A notable feature of the synthesis was the use of a temporary silicon tether to control the regiochemistry of the key IMDAF reaction. Linear construction of **91** set the stage for the key IMDAF step. Treatment of **91** with *n*-butyllithium generated a benzyne intermediate that underwent intramolecular Diels-Alder reaction generating the cycloadduct **92** in 92% yield. Removal of the silicon tether with TBAF and further elaboration led to isokidamycin **93** (Scheme 31).

The first total synthesis of the macrolide antibiotic pamamycin-649B **97** isolated from various *Streptomyces* species was reported recently by Metz. A key step in the synthesis was the intramolecular Diels-Alder reaction of the furan ring of **94** with a vinyl sulfonate ester formed *in situ* from the reaction of **94** with vinylsulfonyl chloride **95** (Scheme 32).[36] This reaction gave cycloadduct **96** as a single diastereomer in high yield, and established two of the stereogenic centres in one of the tetrahydrofuran rings of **97**. Subsequent cleavage of the oxabicyclo[2.2.1] bridge with ethyllithium and further steps generated an

advanced intermediate that was united with a smaller fragment in a double Yamaguchi esterification protocol affording pamamycin-649B **97**.



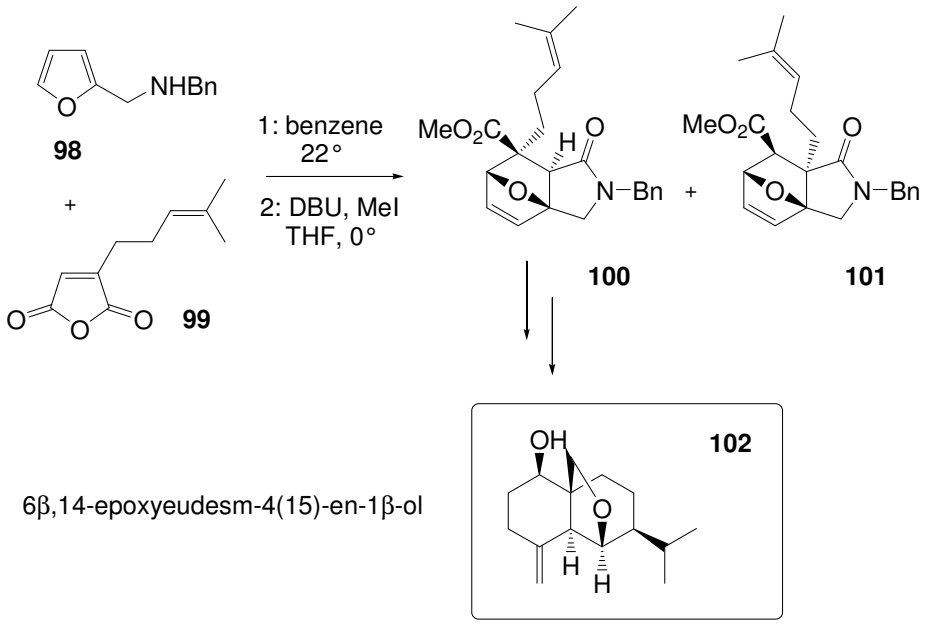
Scheme 31



Scheme 32

An early-stage intramolecular Diels-Alder furan cycloaddition reaction was employed by Li during the total synthesis of (±)-6β,14-epoxyeudesm-4(15)-en-1β-ol **102**, a member of the eudesmane sesquiterpenoid family of natural products. Acylation of furanyl amine **98** with homoprenylmaleic anhydride **99**, subsequent

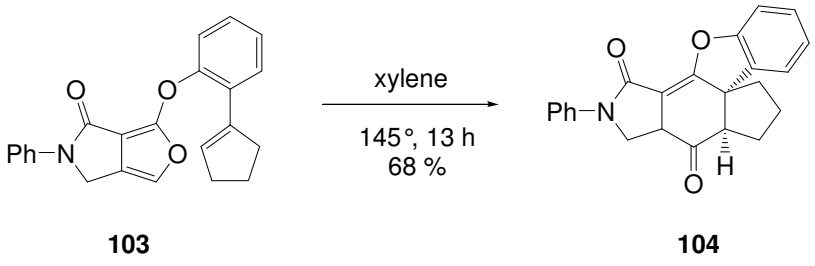
intramolecular Diels-Alder cycloaddition and methylation of the carboxylic acid products afforded a mixture of **100** and its regioisomer **101** with complete stereoselectivity (Scheme 33).[37] The cycloaddition reaction installed the correct relative stereochemistry of three of the stereogenic centres of **102**. Hydrogenation of the cyclic double bond of **100** and further synthetic steps generated the natural product **102**.



Scheme 33

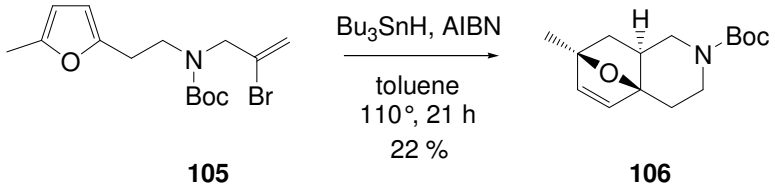
4. New synthetic methodology involving the IMDAF reaction

An efficient method for the synthesis of structurally complex polycyclic ring systems was reported by Padwa involving a Rh(II)-catalyzed cyclization/IMDAF sequence. The Rh(II)-catalyzed cyclization of diazo malonate esters and related compounds with pendant propargyl groups generated furo[3,4-*c*]furans. Subsequent IMDAF reactions of these compounds generated complex pentacyclic products that could be useful precursors for the synthesis of natural products. For example, Rh(II)-catalyzed cyclization of a diazo β-amido ester generated **103** that underwent thermal IMDAF cycloaddition with subsequent cleavage of the oxabicyclo[2.2.1]heptane affording pentacyclic lactam **104** in 68% yield (Scheme 34).[38]



Scheme 34

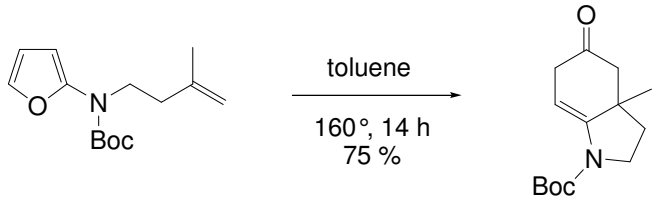
A rare example of an IMDAF reaction under free radical conditions was reported by Parsons. Treatment of unsaturated furan **105** with tributyltin hydride/AIBN under thermal conditions afforded cycloadduct **106** in 22% yield (Scheme 35).[39] No other products were detected arising from the anticipated cyclization of the alkenyl radical onto the furan ring. Presumably, the reaction proceeds through radical dehalogenation of **105** and subsequent thermal IMDAF cycloaddition of the resulting alkenyl species.



105 **106**

Scheme 35

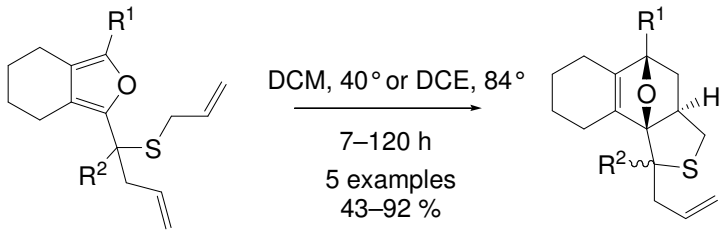
Many IMDAF reactions require high pressures or Lewis acid catalysts to give satisfactory yields of the cycloadducts.[40,41] In contrast, furans containing heteroatoms in the tether directly attached to the furan ring react more rapidly under milder conditions than those containing only carbon atoms in the tether. For example, Diels-Alder cycloaddition of the sterically demanding dienophile of **107** generated enaminoketone **108** in good yield (Scheme 36).[42] The initially formed oxabicyclo[2.2.1]heptane was spontaneously cleaved, generating an iminium oxyanion species that underwent a subsequent 1,2-hydride shift to generate the final product **108**.



107 **108**

Scheme 36

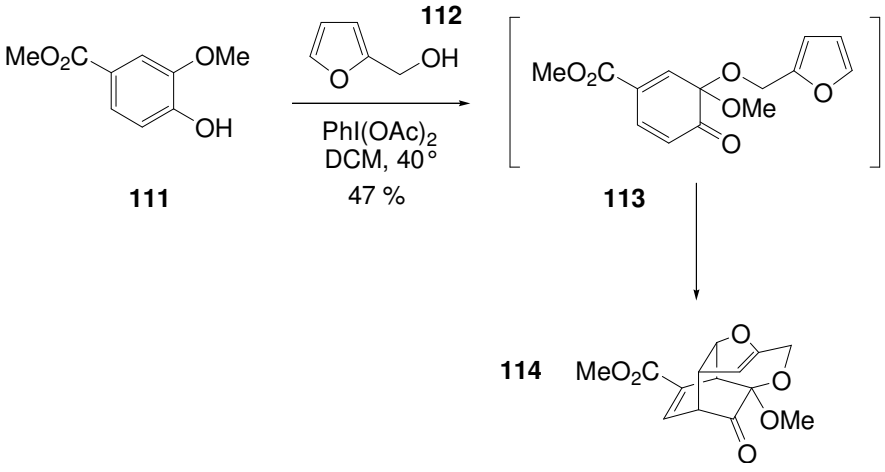
Uemura showed that (2-furyl)carbenoids generated by the Rh_2OAc_4-catalyzed cyclization of enyne carbonyl compounds can be trapped using allylic sulfides to generate furanyl sulfides. In some cases, IMDAF reactions are also observed depending on the steric properties of the substrate. In the case of enynals, trapping of the (2-furyl)carbenoids with diallylsulfide afforded compounds **109** that subsequently underwent thermal IMDAF cycloadditions to give tetracyclic cycloadducts **110** as mixtures of epimers (Scheme 37).[43]



109 **110**

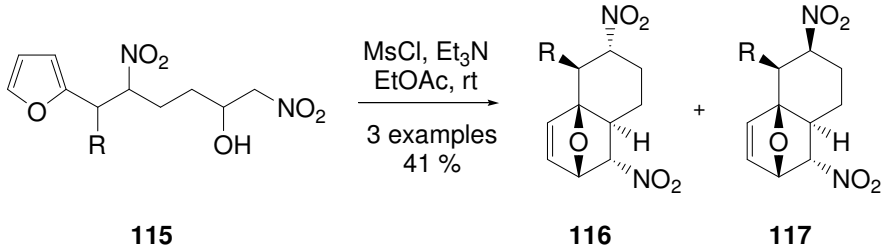
Scheme 37

An unusual example of an IMDAF cycloaddition reaction involving a furan as the dienophile component was reported by Plumet.[44] Reaction of methyl vanillate **111** with furfuryl alcohol **112** in the presence of $PhI(OAc)_2$ afforded the masked orthoquinone monoketal intermediate **113**. Compounds such as **113** act as masked orthobenzoquinone intermediates and react as dienes in Diels-Alder cycloaddition reactions. In the present case, intermediate **113** underwent rapid thermal IMDAF cycloaddition to generate tricyclic compound **114** as the sole product (Scheme 38), which arises *via* cycloaddition of the unsubstituted double bond of the furan ring onto the cyclohexa-1,3-diene component of **113**.



Scheme 38

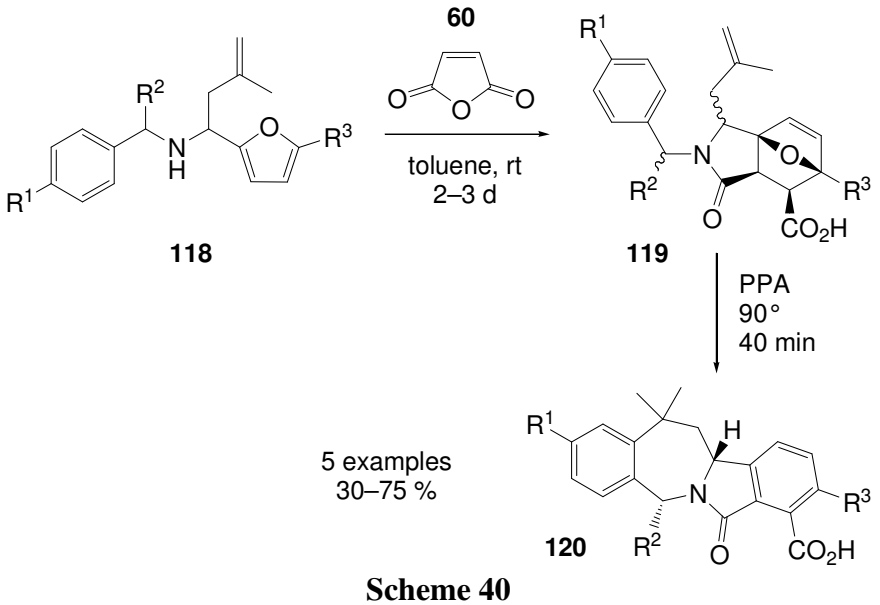
A versatile method for the synthesis of the carbocyclic scaffolds of the Ergot alkaloids was described by Lallemand and Tillequin. The key step involved a facile thermal IMDAF reaction of a furanyl nitroalkene generated *in situ* by dehydration of compounds **115** (Scheme 39).[45] This reaction proceeded with complete *exo*-selectivity, and afforded mixtures of diastereomers **116** and **117** (15:1 ratio of **116**:**117**) differing only in the configuration of the nitro-group at C-2 of the tether.



115 **116** **117**

Scheme 39

A rapid and efficient synthesis of a range of biologically interesting isoindolo[2,1-*b*][2]benzazepines was reported by Zubkov. Reactions of amines **118** (which were readily obtained from 2-furaldehydes) with maleic anhydride **60** proceeded smoothly to afford the epimeric IMDAF cycloadducts **119** (Scheme 40).[46]

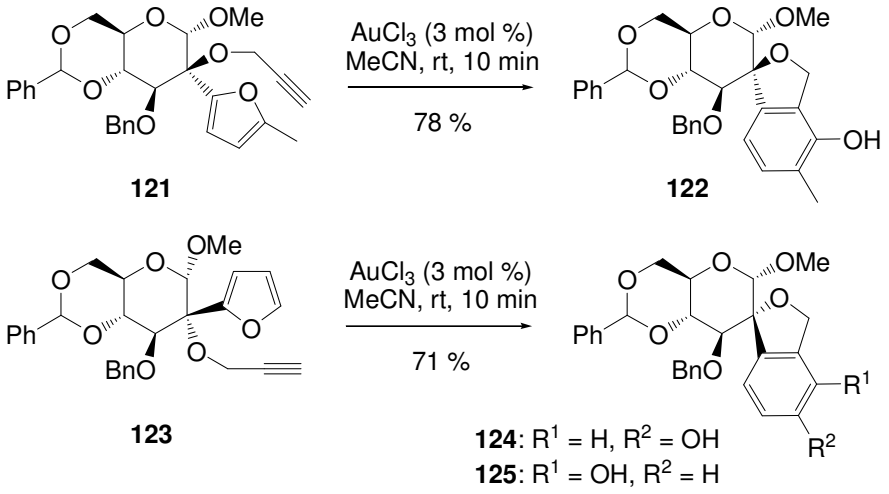


118 **119** **120**

Scheme 40

The reaction proceeds by initial *N*-acylation of amines **118** and subsequent *exo*-selective IMDAF cycloaddition of the resulting amides. Further treatment of the cycloadducts **119** with polyphosphoric acid led to cleavage and aromatization of the oxabicyclo[2.2.1]heptane and electrophilic cyclization of the alkenyl group onto the aromatic ring, to generate a range of functionalized isoindolo[2,1-*b*][2]benzazepine products **120**.

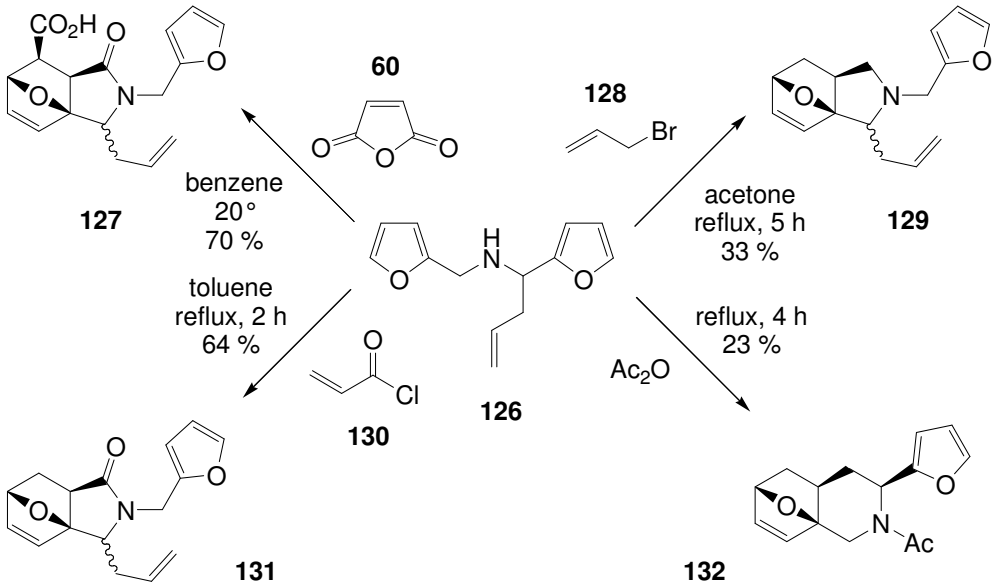
As part of their studies on the synthesis of protein kinase inhibitors, Hotha *et al.* synthesized a range of spiroannulated dihydroisobenzofurans *via* gold-catalyzed intramolecular Diels-Alder cycloadditions of carbohydrate-derived furanyl propargyl ethers. Addition of 2-furyllithiums to carbohydrate-derived ketones and subsequent propargylation generated cycloaddition precursors such as **121** and **123** (Scheme 41). Cycloaddition of **121** and **123** and *in situ* aromatization of the cycloadducts was effected using catalytic gold(III) chloride in acetonitrile, and gave cycloadducts **122**, **124** and **125** in high yields under very mild conditions.[47] The methodology was general for a range of carbohydrate-derived substrates, and furnished spirocyclic cycloadducts otherwise difficult to synthesize.



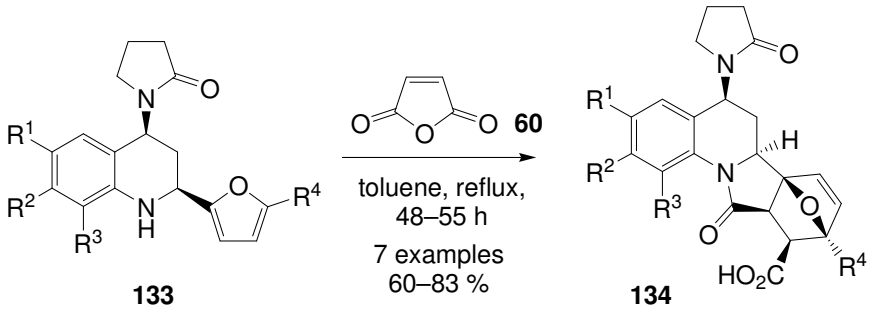
Scheme 41

The sequence of *N*-allylation/acylation of secondary furfurylamines, followed by intramolecular Diels-Alder furan reaction constitutes a convenient method for the rapid synthesis of potentially biologically active polycyclic amines. This is illustrated by the thermal IMDAF reactions of amine **126** that occur when **126** is treated with acryloyl chloride **130**, maleic anhydride **60**, allyl bromide **128** or acetic anhydride (Scheme 42).[48] Interestingly, difuryl derivative **126** reacted in a completely regioselective way so as to form the most substituted five-membered ring as illustrated by the exclusive formation of **127** (with maleic anhydride **60**), **131** (with acryloyl chloride **130**), **129** (with allyl bromide **128**) and **132** (with acetic anhydride).

Building on this methodology, a versatile entry to a range of densely functionalized, pharmacologically useful isoindolo[2,1-*a*]quinolines was reported by Zubkov.[49] In this approach, 2-furyl-tetrahydroquinolines **133** (which were obtained by a three-component Povarov reaction) were reacted with acryloyl chloride **130** or with maleic anhydride **60** affording intermediates that underwent thermal intramolecular Diels-Alder reaction generating polycyclic isoindolo[2,1-*a*]quinolines such as **134** in good yields (Scheme 43). It was also shown that the newly-formed oxabicyclo[2.2.1]heptene ring could be aromatized on exposure of the cycloadducts to phosphoric acid at 70 ^{o}C.

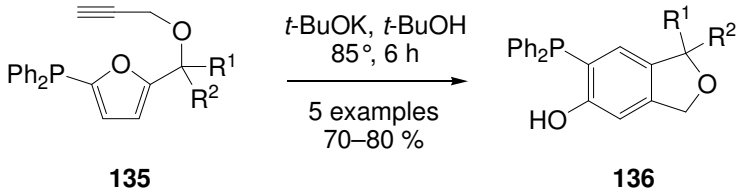


Scheme 42



Scheme 43

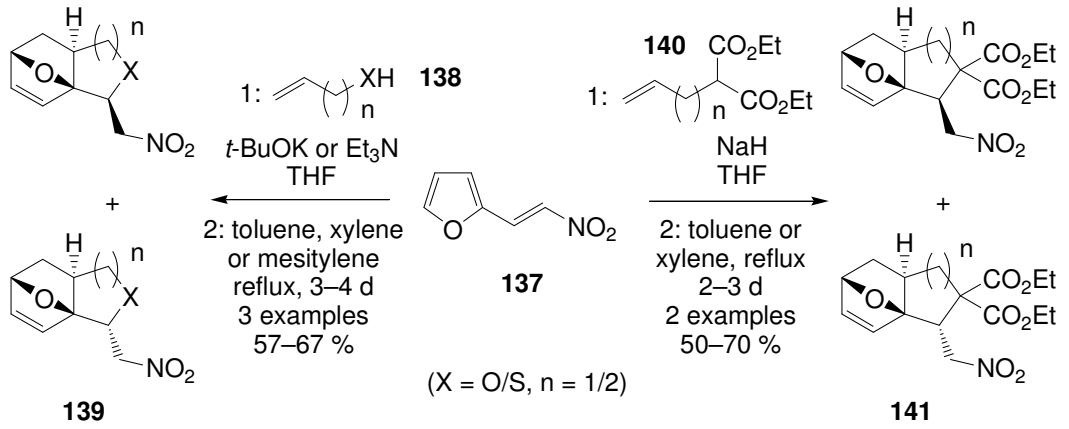
An unusual entry to a potentially useful class of *o*-diphenylphosphinophenol ligands using the IMDAF reaction was reported by Wu.[50] According to the proposed mechanism, the base-catalyzed intramolecular Diels-Alder reactions of furans **135** bearing propargyl ether dienophiles proceeded *via* the corresponding allenyl ethers to generate cycloadducts that underwent cleavage of the oxanorbornene ring. Subsequent nucleophilic 1,2-rearrangement of the diphenylphosphino-group in the resulting zwitterion and tautomerization furnished the aromatized products **136** (Scheme 44).



Scheme 44

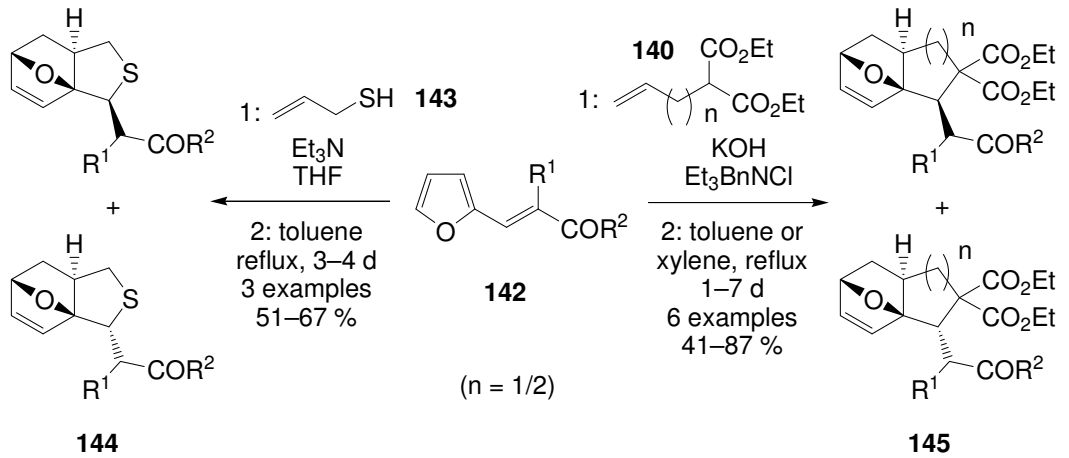
A rapid entry to complex tricyclic oxanorbornenes employing the IMDAF reaction has been reported. The conjugate addition of various unsaturated carbon and heteroatom nucleophiles to β-furanylnitroalkenes **137** generates Michael addition products. These compounds undergo subsequent thermal IMDAF reactions generating a range of tricyclic oxanorbornenes **139** (with heteroatom nucleophiles **138**) and **141** (with malonate nucleophiles **140**) as separable diastereomeric mixtures (Scheme 45).[51] The cycloaddition reactions were highly selective for the epimers where the nitromethyl groups and oxygen bridges were oriented *syn*.

The methodology is general for a range of nucleophiles, and allows the rapid synthesis of densely functionalized tricyclic targets containing 5- and 6-membered carbocyclic and heterocyclic rings.



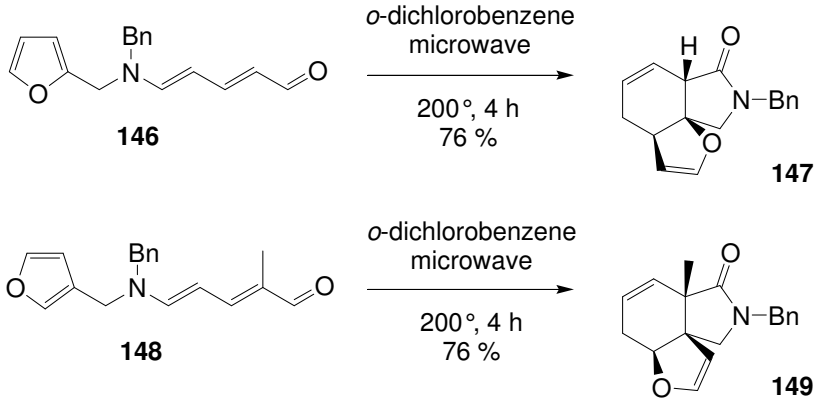
Scheme 45

Similarly, this tandem Michael addition/IMDAF cycloaddition sequence was employed on other Michael acceptors. The conjugate addition of various unsaturated carbon and heteroatom nucleophiles to β-furanylenones and β-furanylacrylates **142** provided Michael addition products that underwent facile intramolecular Diels-Alder cycloaddition between the furan diene and the unsaturated tether to generate only the *exo*-cycloadducts such as **144** (with allylmercaptan **143** as the nucleophile) and **145** (with malonates **140** as the nucleophiles) on heating in toluene or xylene (Scheme 46).[52] Once again, the products were obtained as separable mixtures of diastereomers epimeric at the β-carbon of the Michael acceptor **142**.



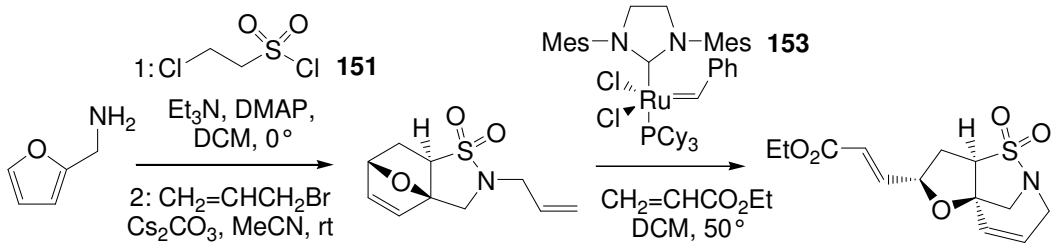
Scheme 46

A rare example of the participation of a furan moiety as the dienophile component in an intramolecular Diels-Alder reaction was disclosed by Vanderwal.[53] Thermal treatment of 5-amino-2,4-pentadienals (Zincke aldehydes) generated zwitterionic intermediates that underwent a pericyclic reaction cascade to afford unsaturated amides. However, with *N*-allyl-5-amino-2,4-pentadienals, trapping of one of the intermediates in this cascade took place to afford bicyclic lactams as single diastereomers. Two such examples are shown in Scheme 47 involving 2- and 3-furanyl-substituted starting materials **146** and **148** that afforded tricyclic lactams **147** and **149**, respectively, on microwave heating. The methodology constitutes a promising strategy for the synthesis of complex, alkaloid-like scaffolds from simple starting materials.



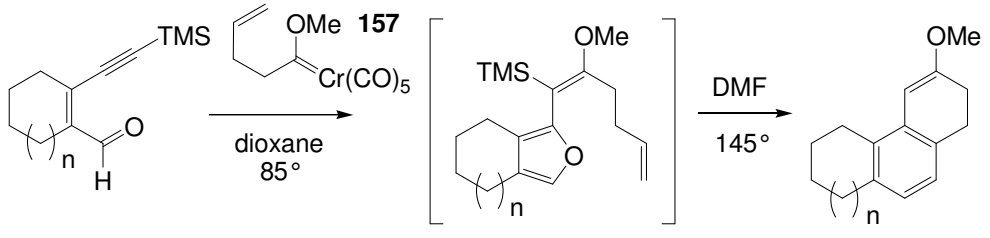
Scheme 47

Hanson recently showed that the sequence of IMDAF reactions followed by cascade olefin metathesis reactions is a powerful method to generate structurally complex small molecules in drug discovery and diversity-oriented synthesis (DOS).[54] A range of tricyclic sultams such as **152** were easily synthesized from furfurylamine **150** *via* sulfonamide formation (using **151**) followed by IMDAF reaction (Scheme 48). The strained internal double bond of the cycloadducts then reacted in a ring-opening metathesis/ring-closing metathesis/cross-metathesis cascade sequence of reactions in the presence of Grubbs 2nd generation catalyst **153**, affording a range of skeletally diverse bi- and tricyclic sultams (as exemplified by the conversion of **152** to **154**, Scheme 48).



Scheme 48

An unusual entry to hydronaphthalenes was reported by Herndon. The coupling of enynals **155** and **156** with γ,δ-unsaturated Fischer carbene complexes **157** generated bicyclic furans **158** and **159** bearing pendant alkene groups. Subsequent thermal intramolecular Diels-Alder furan cycloaddition reaction afforded cycloadducts that underwent ring-opening and subsequent dehydration, resulting in tricyclic hydronaphthalene ring systems **160** and **161** (Scheme 49).[55] The same methodology was successfully implemented using 2-alkynylbenzaldehydes to generate hydrophenanthrenes *via* IMDAF reactions of isobenzofuran intermediates.[56]

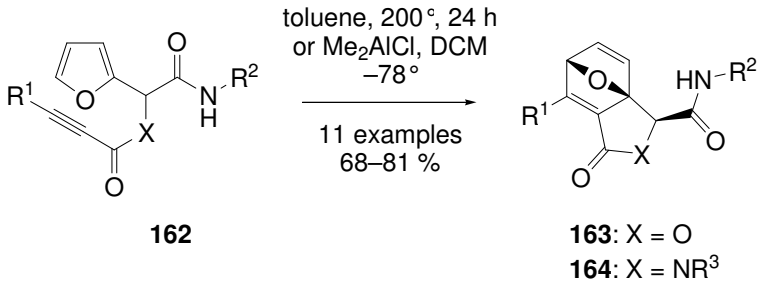


155–156 **158–159**

160: n = 0: 64 %
161: n = 1: 60 %

Scheme 49

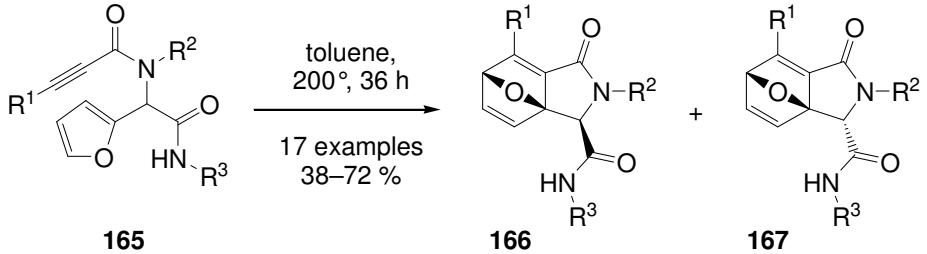
A tandem multicomponent reaction/IMDAF sequence was reported by Wright for the rapid synthesis of a range of fungal steroid precursors. Cycloaddition precursors **162** were assembled either by an Ugi or Passerini multi-component condensation reaction. Thermal IMDAF cycloaddition of compounds **162** generated tricyclic lactones **163** and lactams **164** in high yields and with high diastereoselectivity (Scheme 50).[57] Interestingly, the use of thermal conditions was successful and the use of Lewis acid conditions was unsuccessful for the synthesis of lactams **164**. However, the reverse was true for the synthesis of the lactones **163**, which were prone to retro-IMDAF reactions at elevated temperatures or in the presence of acid.



162 **163**: X = O
164: X = NR^3

Scheme 50

Similarly, McCluskey disclosed an efficient entry to a family of substituted tricyclic lactams using the IMDAF reaction as the pivotal step. The four component Ugi reaction of 2-furaldehyde, an isonitrile, an alkynoic acid and a primary amine afforded furanyl alkyne derivatives **165** that underwent thermal intramolecular Diels-Alder cycloaddition reactions in one-pot on heating.[58] The products were isolated as separable mixtures of *syn*- and *anti*-diastereomers **166** and **167**, respectively (Scheme 51). The methodology was tolerant of a wide range of different amines and isonitriles.



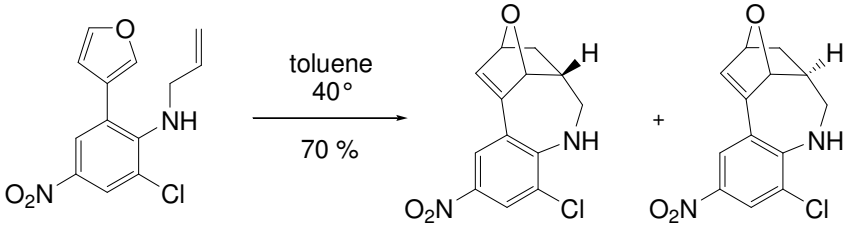
165 **166** **167**

Scheme 51

A detailed study into the reactivity and stereoselectivity of the IMDAF reactions of a range of allylamino- and allyloxy-(2-furyl)arenes was carried out by Gundersen. These compounds, containing a 2-furyl group bound to an aromatic ring, reacted with tethered allyl-groups at elevated temperatures (xylene, 150 ^{o}C or toluene, 100 ^{o}C) to give tetracyclic products with high or complete *exo*-selectivity.[59] Interestingly, a rare example of an IMDAF reaction of a 3-furyl-tethered compound was also reported (Scheme 52). Diels-Alder cycloaddition of **168** proceeded under mild conditions to afford a mixture of cycloadducts **169** and **170** containing 7-membered rings. In this case, the *endo*-cycloadduct **169** was the major product while the *N*-diallyl analogue of **168** cyclized with complete *endo*-selectivity.

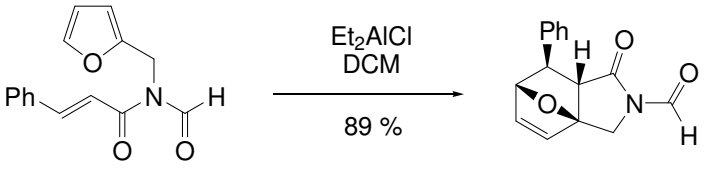
A versatile and useful extension of the intramolecular Diels-Alder reaction to *N*-formylacrylamides was recently reported by Danishefsky. These dienophiles were readily synthesized by the reactions of isonitriles with acrylic acids under microwave irradiation, and were found to be more reactive towards

intramolecular Diels-Alder cycloadditions than other acyl-activated dienophiles typically studied to date. An example is the conversion of **171** to cycloadduct **172** under Lewis-acid conditions (Scheme 53).[60] The *N*-formyl group was found to be essential for cycloaddition, as the corresponding deformylated acrylamides did not react at all under the same conditions. The enhanced reactivity of imides such as **171** towards cycloaddition was attributed to efficient bidentate chelation of the carbonyl-groups of the substrates with the Lewis acid.



168 **169** **170**

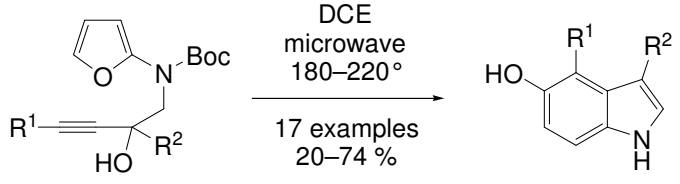
Scheme 52



171 **172**

Scheme 53

A convergent approach to a series of biologically important 3,4-disubstituted 5-hydroxyindoles has been described by Wipf. Alkynylfurans **173** were synthesized by the addition of lithiated *N*-Boc-2-methyl-aminofurans to alkynones, and then subjected to microwave irradiation at elevated temperatures. The initial IMDAF cycloadducts underwent cleavage of the oxabicyclo[2.2.1] bridge, dehydration, aromatization and *N*-Boc deprotection in a cascade reaction sequence to give 3,4-disubstituted 5-hydroxyindoles **174** in moderate to good yields (Scheme 54).[61] The methodology represents a convergent and unusual entry to both benzene and pyrrole rings of the indole ring system.



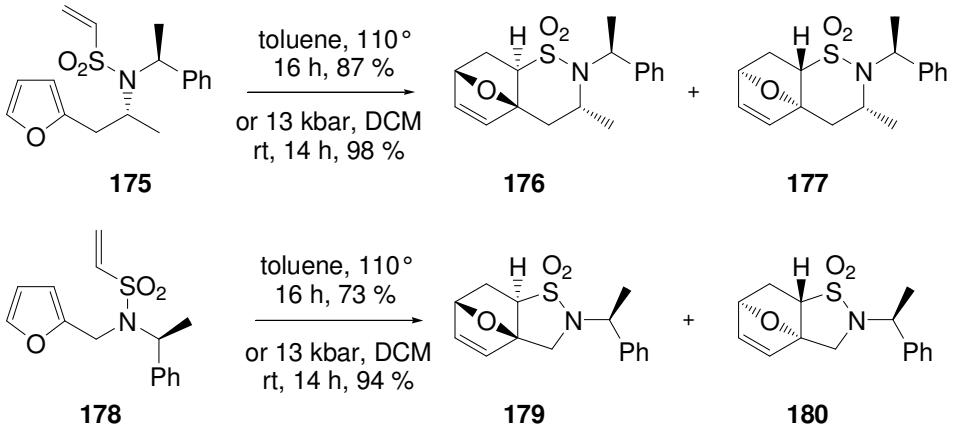
173 **174**

Scheme 54

5. Asymmetric approaches

One of the most efficient strategies for the asymmetric synthesis of IMDAF cycloadducts and their derivatives has been the use of chiral auxiliaries. In one such approach, a range of γ- and δ-sultams was prepared by Metz using diastereoselective IMDAF cycloadditions of chiral amine-derived vinylsulfonamides. IMDAF cycloaddition of enantiomerically pure sulfonamide **175** with two stereogenic

centres under thermal conditions generated a 79:21 mixture of δ-sultam cycloadducts **176** and **177**. Under high-pressure conditions (13 kbar, DCM) the diastereoselectivity was higher, and a 93:7 mixture of cycloadducts **176** and **177** was obtained (Scheme 55).[62] In the case of sulfonamide **178** with a single stereogenic centre, lower diastereoselectivities were observed in the formation of γ-sultams **179** and **180** under both thermal (58:42 mixture of **179** and **180**) and high-pressure (66:34 mixture of **179** and **180**) conditions.

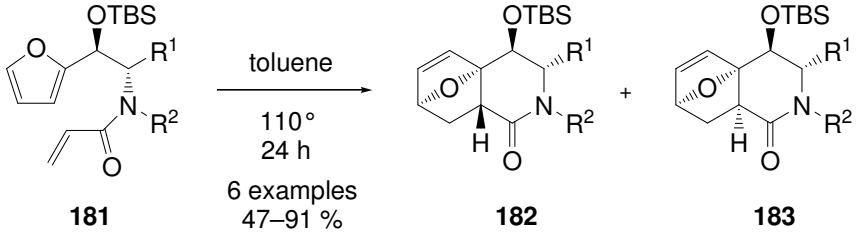


175 **176** **177**

178 **179** **180**

Scheme 55

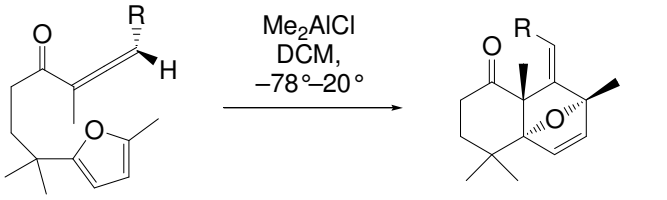
In a similar study, Brussee investigated the diastereoselectivity of IMDAF cycloaddition of some chiral acrylamides bearing two asymmetric centres. Thermal Diels-Alder cycloaddition of chiral acrylamides **181** afforded diastereomeric cycloadducts **182** and **183**, with the *exo*, *anti*-cycloadduct **182** being the major product, or even the only product in some cases (Scheme 56).[63] However, the degree of stereoselectivity was dependent on the steric nature of the substituent R^1, with the more bulky substituents (R^1 = Et, Ph) switching the selectivity in favour of the *endo*, *anti* cycloadducts **183**. In most cases, the silyloxy-group and the oxo-bridge resided on opposite sides of the bicyclic ring system.



181 **182** **183**

Scheme 56

Activated terminal allenes are known to be effective dienophiles in intramolecular Diels-Alder furan cycloadditions. Jung found that chiral racemic allenyl ketone **184** with a terminal methyl group underwent IMDAF reaction with complete *exo*-selectivity and complete chirality transfer, affording cycloadduct **186** as a single diastereomer in high yield (Scheme 57).[64] Realizing the potential of this methodology to access optically active cycloadducts, the analogous enantiomerically pure precursor **185** was synthesized. IMDAF cycloaddition of **185** in the presence of a Lewis acid generated in high yield a single stereoisomer of the tricyclic ketone **187**, which can be considered a useful building block for the asymmetric synthesis of the potent acetylcholine esterase inhibitor arisugacin A.

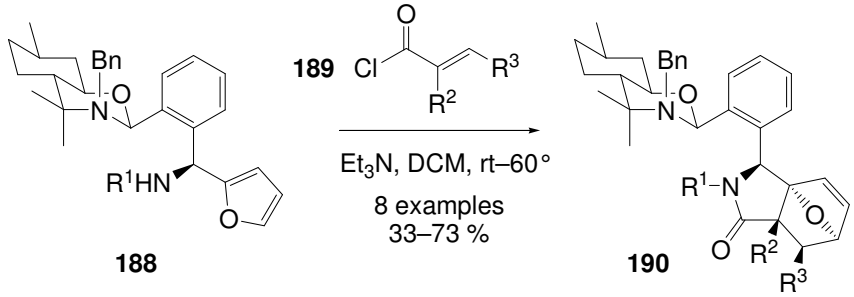


184–185

186: R = Me: 80 %
187: R = C_7H_{15}: 88 %

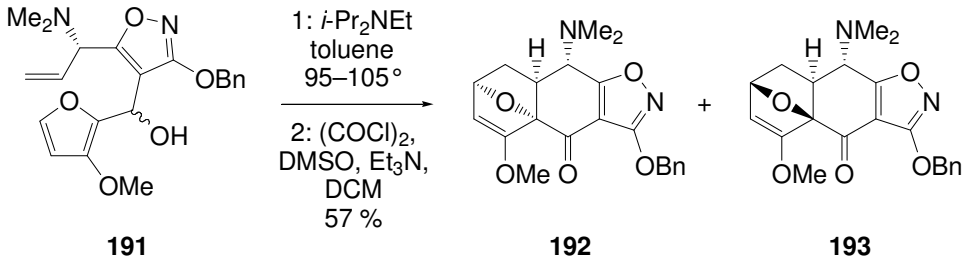
Scheme 57

An efficient asymmetric synthesis of enantiomerically pure perhydroepoxyisoindolones using a chiral auxiliary approach has been described by Pedrosa. Chiral furanyl amines **188** were synthesized as single diastereomers from (–)-8-aminomenthol. Acylation of these amines with acryloyl chlorides **189** and subsequent thermal IMDAF reaction *in situ* furnished a range of cycloadducts **190** in moderate to good yields as single diastereomers (Scheme 58).[65] The cycloadditions proceeded with complete facial selectivity and *exo*-stereoselectivity with the creation of up to 5 new stereogenic centres in a single step. Subsequent hydrogenation of **190** and hydrolytic cleavage (ethanolic HCl at reflux) of the auxiliary generated the enantiopure perhydroepoxyisoindolones.



Scheme 58

A practical, large scale (40 g) enantioselective synthesis of a key precursor to the tetracycline class of antibiotics was developed by Myers. The addition of an enantiomerically enriched (93% ee), lithiated isoxazole to 3-methoxy-2-furaldehyde afforded a 1.3:1 mixture of epimeric alcohols **191**. Subsequent thermal IMDAF cycloaddition of **191** proceeded with complete facial selectivity onto a single π-face of the dienophile, giving a mixture of cycloadducts **192** and **193** following Swern oxidation of the intermediate alcohols (Scheme 59).[66] Notably, the cycloaddition was also *endo*-selective, with the desired *endo*-cycloadduct **192** predominating. Lewis acid-mediated cleavage of the oxabicyclo-bridge of **192** generated the desired precursor in 93% ee.

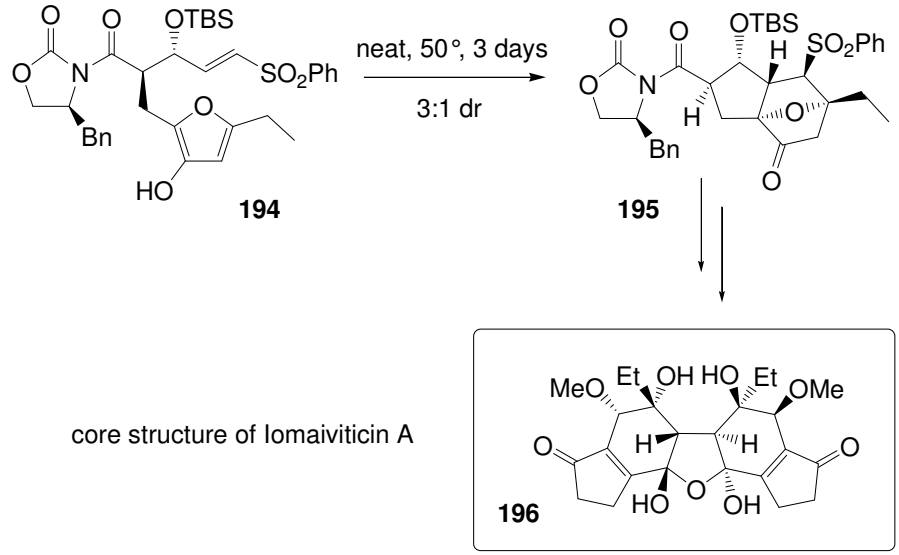


191 **192** **193**

Scheme 59

An enantioselective approach to the C_2-symmetric central ring system of the potent antibiotic lomaiviticin A was recently reported by Shair. The strategy relied on the stereoselective oxidative enolate

dimerization of two identical fragments that were formed by an IMDAF reaction of a furanylsulfone bound to an Evan's chiral auxiliary.[67] Enantioselective construction of furanylsulfone **194** was followed by an *endo*-selective intramolecular Diels-Alder reaction of the vinyl sulfone with the furan moiety (as its enol tautomer) to generate cycloadduct **195** after enol tautomerization (Scheme 60). Removal of the chiral auxiliary and further steps afforded a ketone that was oxidatively dimerized [LiHMDS, then $(Cp_2Fe)PF_6$] and further manipulated to generate the core structure of lomaiviticin A **196**.



Scheme 60

6. Conclusions

It is clear from the recent literature that the intramolecular Diels-Alder cycloaddition reaction of furans continues to play a central role in the construction of annulated carbocyclic and heterocyclic compounds. The synthetic utility of this reaction stems not only from the excellent regio- and stereoselectivity of the cycloaddition step, but also from the many methods available for additional synthetic manipulation of the oxabicyclic products. Further advances are anticipated in the applications of this important reaction in the future.

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ASYMMETRIC CATALYTIC SYNTHESIS OF CORYNANTHE AND IPECAC ALKALOIDS

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Abstract. *Corynanthe and ipecac alkaloids constitute a large group of natural occurring alkaloids that demonstrate a vast variety of bioactivity and have a long history of usage as herbal drugs. Both the corynanthe and ipecac alkaloids share a common structural unit with a quinolizidine ring fused with a benzo- or indolo-group and three stereocentres wherein one is a ring-junction stereocentre. From synthetic point of view, these natural products represent an intriguing challenge and over the years several strategies toward the asymmetric total synthesis of corynanthe and ipecac alkaloids have been devised and the majority of these are target specific natural-pool based strategies. However, during the last few years, several efficient and diverse strategies based on asymmetric catalysis and one-pot cascade protocols as the key-steps have emerged. In this mini-review the attention is to give an overview of these strategies.*

Contents

1. Introduction

The indolo[2,3-a]quinolizidine and benzo[a]quinolizidine substructure build up the basic skeleton of a vast number of structurally related natural products that belongs to the *corynanthe* and *ipecac* alkaloid families (Figure 1).

The *corynanthe* alkaloids are found mainly in eight plant families, of which *Apocynaceae*, *Loganiaceae* and *Rubiaceae* provide the best sources.[1] These plants have a long tradition as herbal drugs in traditional folk medicine treating symptoms as inflammations, rheumatism, gastric ulcers, tumours, dysentery, and birth control as well as promote wound healing. More modern studies of the indole alkaloids of the *corynanthe* group reveals activity against hypertension and cerebrovascular disorders[2] as well as antiparasitic, antiviral and analgesic activity.[3] Over the years, there have been several studies on the individual alkaloids pharmacological property and new interesting biological activities have been discovered. One example is the alkaloid *Hirsutine* that exhibits antihypertensive effects and further studies also found that it is displaying highly potent anti-influenza (subtype H3N2) activity that is 10–20 times more active than the clinically used ribavirin.[4] Further, the epimeric compound *dihydrocorynantheine* and the analog *corynantheine* operate through inhibition of multiple ion channels.[5] The *ipecac* alkaloids, which are based on the benzoquinolizidine substructure, mainly occur in three plant families: *Alangiaceae*, *Icacinaceae* and

Rubiaceae where *Psychotria ipecacuanha* (*Rubiaceae*) is one of the main sources for these alkaloids.[1] The main components of ipecac alkaloids, *emetine, cephaeline* and *tubulosine* are all potent inhibitors of protein synthesis and they display antitumour and antiviral as well as antiamoebic activity,[6] but they have found limited use as therapeutics due to the high toxicity. *Tubulosine* is a remarkably active agent against several cancer cell lines[7] and it has been studied for various other biological activities, such as inhibition of protein biosynthesis[6] and HIV reverse transcriptase inhibitory activities.[8]

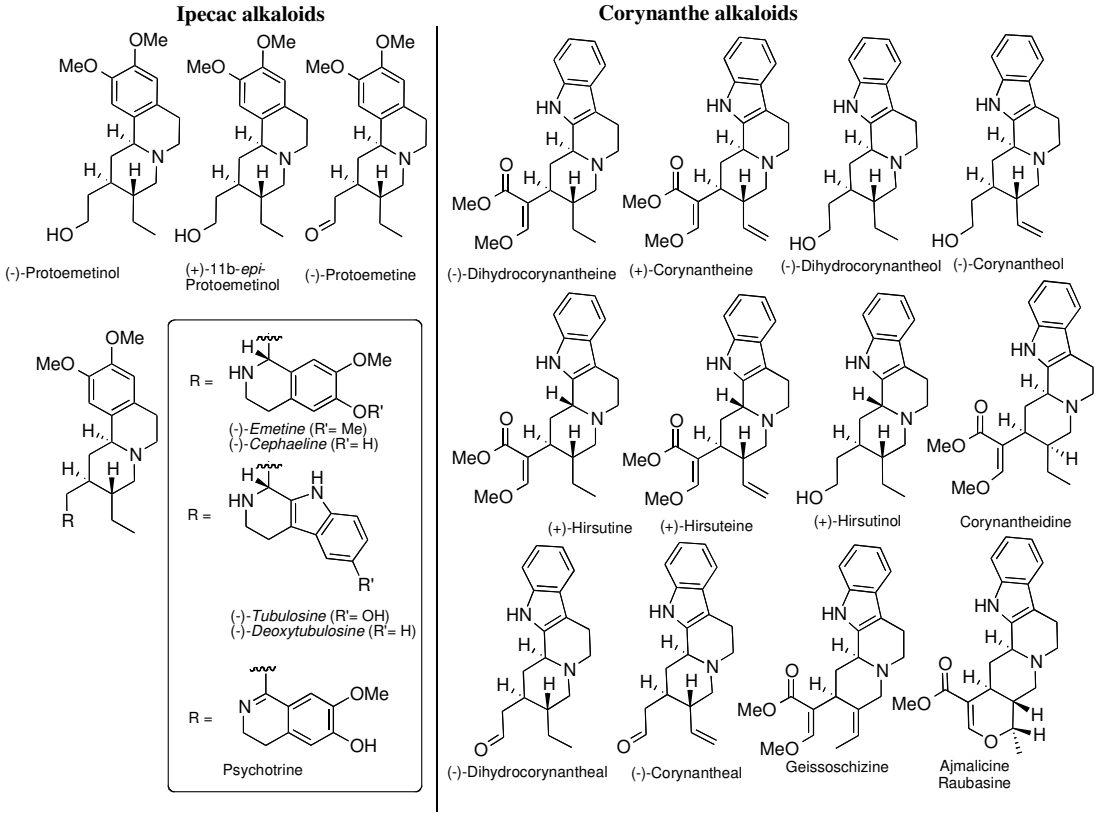
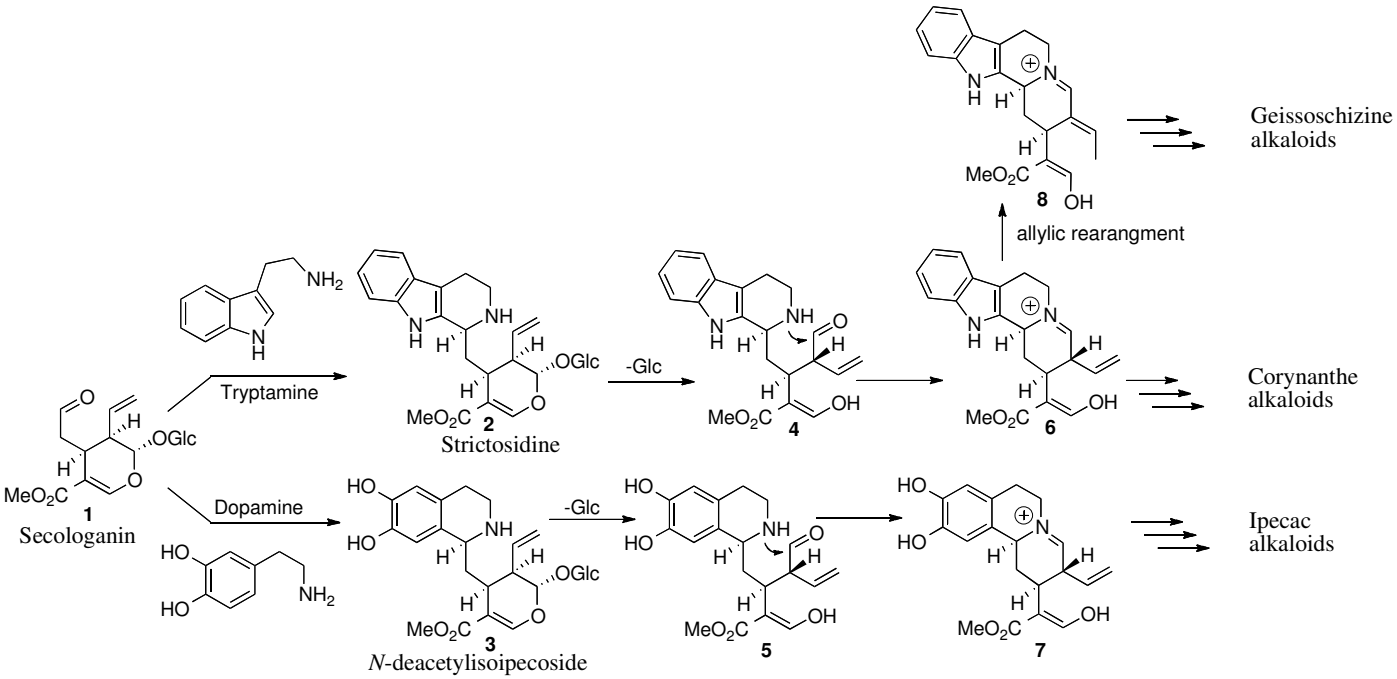


Figure 1. Naturally occurring alkaloids from the *corynanthe* and *ipecac* families.



Scheme 1. Biosynthesis of *corynanthe* and *ipecac* alkaloids.

In nature, *corynanthe* and *ipecac* alkaloids share a similar biogenesis pathway that begins with enzymatic decarboxylation of the corresponding amino acid to give tryptamine and dopamine. The biogenic amines condense with *secologanin* **1** to form the tetrahydro-β-carboline alkaloid *strictosidine* **2** and tetrahydroisoquinoline *N-deacetylisoipecoside* **3**, respectively, in a Pictet-Spengler cyclization (Scheme 1).[1] The *secologanin* fragment contains an acetal function that will be converted to aldehydes **4** and **5** by hydrolysis of the glucoside moiety. The liberated aldehydes condense with the secondary amine to give the quaternary Schiff bases **6** and **7** that are the key intermediates to the *corynanthe* and *ipecac* group of alkaloids. Furthermore, allylic rearrangement of Schiff base **6** gives **8** that is the indoloquinolizidine precursor of *geissoschizine* and its analogues (Scheme 1). Compound **8** has also been identified as the key intermediate in the biosynthesis of several higher complexity alkaloids such as *catharanthine*, *strychnine*, *quinine*, *reserpine* and *vinblastine* among others.

The common structural unit for the *corynanthe* and *ipecac* alkaloids is the quinolizidine ring fused with an indolo- or benzo-group that contains three stereocentres of which one is a ring-junction stereocentre. The ring junction stereocentre has a great impact on the conformation of the alkaloid as can be seen through comparison of the two naturally occurring ring junction epimers, *dihydrocorynantheine* and *hirsutine,* where the configuration of this stereocentre will lead to a distinguish difference in the conformation that these molecules adapt. *Dihydrocorynantheine* is the thermodynamically most stable form and has all groups on the quinolizidine substructure in equatorial position (Figure 2).[9] On the other hand, *hirsutine* has the aromatic group in an axial position that forces the molecule to adapt a V-shaped form. Interestingly, *dihydrocorynantheine* and *hirsutine* have been found to have different biological activities. Biological studies show that *dihydrocorynantheine*, but not *hirsutine*, has a potent α-adrenoceptor blocking activity and revealed that the planarity in the molecular structure is necessary for their affinity to α-adrenoceptors.[10] In the study of *corynanthe* group alkaloids as anti-influenza A drug candidates, *hirsutine* exhibited potent inhibition of the replication of the strains of influenza A while its epimer *dihydrocorynantheine* lacked of that activity.[4a]

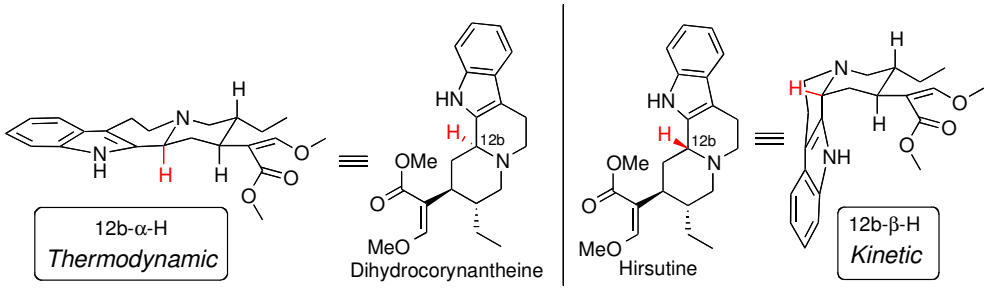


Figure 2. Conformations of the epimeric natural products 12b-α-H-*dihydrocorynantheine* and 12b-β-H-*hirsutine*.

From a synthetic point of view, these natural products are deceptively simple targets; however, construction of the fused ring system of the *corynanthe* and *ipecac* alkaloids with high control of the relative and absolute stereochemistry on the quinolizidine core structure represents a significant challenge[11] and considerable research focus has been placed on their laboratory preparation. In fact, the total synthesis of aromatic quinolizidine alkaloids has an over 50 years long history, and several of the strategies developed have been towards the synthesis of the racemic alkaloids.[12] During the years, extensive focus has been put on the asymmetric synthesis of *corynanthe* and *ipecac* alkaloids and the majority of these works has the

target to the specific multi-step synthesis that relies on starting materials from the chiral pool.[13] However, chiral pool strategies are often encumbered with imperfections that require additional operations to remove unnecessary chiral elements in the starting materials and they often include several functional group transformations and protection/deprotection steps to assemble the desired molecule and each of these operations usually involves tedious isolation and purification processes of synthetic intermediates. This makes the total syntheses of *Corynanthe* and *ipecac* alkaloids and analogues thereof highly demanding with respect to resources and time. Furthermore, the loss of material in each transformation and purification step of a multi-step sequence dramatically decreases chemical efficiency, making larger scale preparation of the target molecule almost impossible. Consequently, new approaches are required to overcome many of the bottlenecks associated with conventional organic synthesis. The key to circumvent this problem is through implementation of asymmetric catalytic one-pot multiple reactions or asymmetric catalytic cascade/tandem reactions in a synthetic sequence.[14] Such strategies will have the advantage of avoiding traditional stop-and-go synthesis,[15] thus avoiding tedious isolation and purification of synthetic intermediates and steps involving the protection and deprotection of functional groups, thereby allowing for processes with high efficiency and atom economy.

Lately, there have been several reports on efficient synthesis of optically active *corynanthe* and *ipecac* alkaloids and different analogs based on asymmetric catalysis. Moreover, cascade reactions, domino reactions and one-pot processes have been implemented in these strategies enhancing efficiency and economy of the whole process.[16] In this review, we intend to provide an account on the research that has appeared in the recent years concerning the asymmetric synthesis of *corynanthe* and *ipecac* alkaloids. The focus is especially put on those based on asymmetric catalysis and cascade/one-pot protocols in one or several of the key steps.

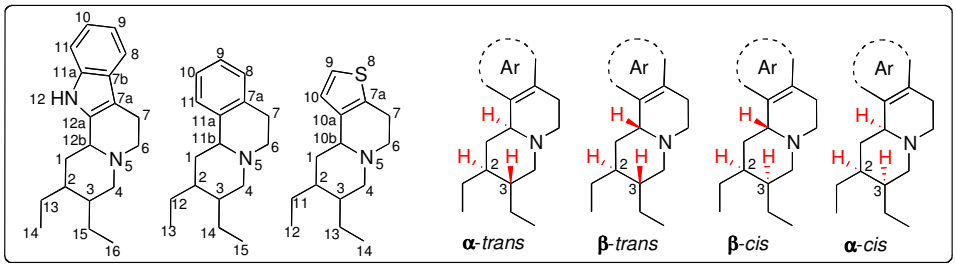


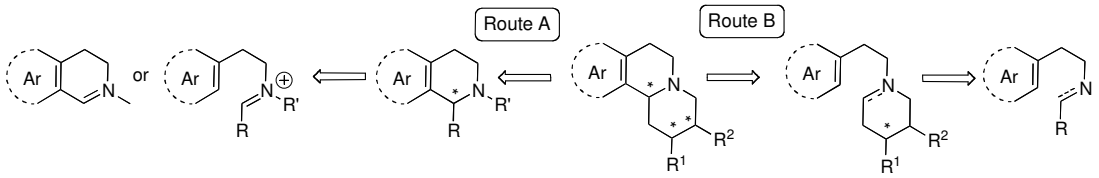
Figure 3. Nomenclature used through this review (α and β refers to the ring junction configuration, *trans* and *cis* refers to the relative relationship between C^2 and C^3).

2. Synthetic strategies for the synthesis of *corynanthe* and *ipecac* alkaloids

The synthetic strategies that have evolved during the last years can generally be summarized in two general approaches (Scheme 2):

Route A: asymmetric catalytic construction of the ring-junction stereocentre followed by diastereoselective formation of the C^2/C^3 stereocentres. The protocols based on this strategy almost all commence from the synthesis of chiral tetrahydro-β-carboline or tetrahydroisoquinoline derivatives which are the practical forerunner for the synthesis of aromatic quinolizidine compounds.

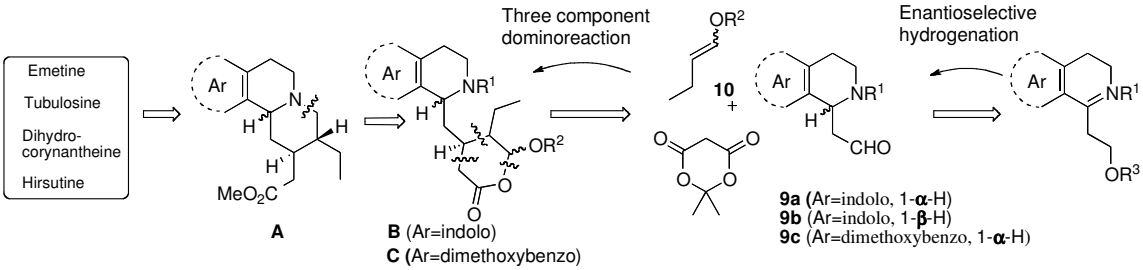
Route B: asymmetric catalytic formation of the C^2 and/or the C^3 stereocentre followed by diastereoselective formation of the of the ring-junction stereocentre.



Scheme 2. General strategies for asymmetric catalytic synthesis of aromatic quinolizidine natural products.

2.1. Route A: early enantioselective formation of the ring-junction stereocentre

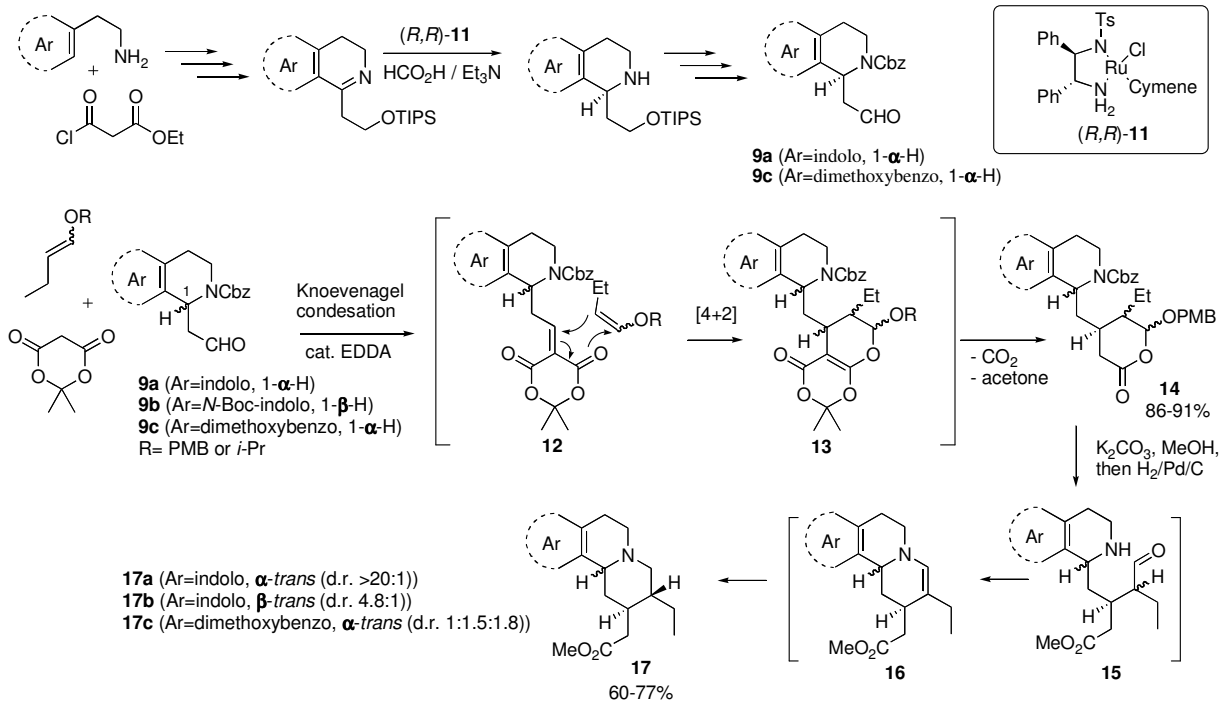
Two early examples of the total syntheses of both *dihydrocorynantheine* and *ipecac* alkaloids based on asymmetric catalysis and domino-reactions were reported by Tietze and coworkers in a series of papers.[17] Their retrosynthetic analysis leads back to ester **A** having both the α- and β-configuration on the ring junction stereocentre. Further disconnections leads back to *strictosidine* or *deacetylisoipecoside* analogues **B** and **C** that can be obtained through optically active tetrahydro-β-carboline **9a,b** or tetrahydroisoquinoline **9c**, Meldrums's acid and enol ether **10**.



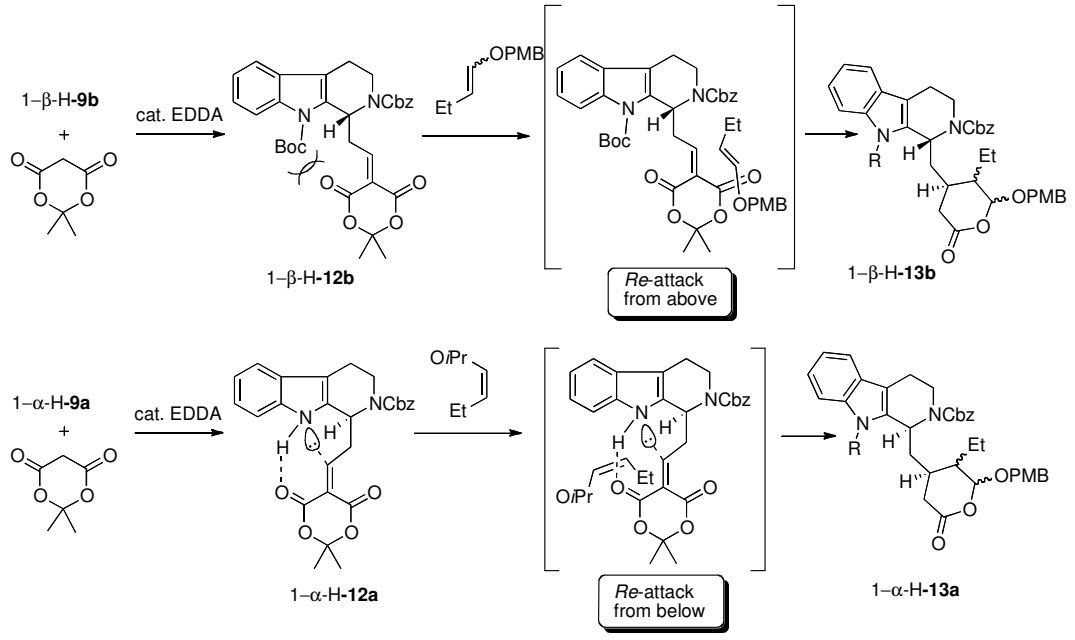
Scheme 3. Tietze's retrosynthesis of *Corynanthe* and *Ipecac* alkaloids.

The optically active 1-α-H-tetrahydro-β-carboline **9a** and 1-α-H-tetrahydroisoquinoline **9c** were accessible through enantioselective transfer-hydrogenation of the corresponding imine using triethyl ammonium formate in the presence of Noyori's ruthenium catalyst (*R*,*R*)-**11**(Scheme 4).[18] 1-β-H-Tetrahydro-β-carboline **9b** was obtained through chiral resolution.[17a] To construct the quinolizidine ring, aldehydes **9a–c** were treated with a mixture of Meldrum's acid and enol ether **10** in a three-component Knoevenagel/hetero-Diels-Alder cascade catalyzed by ethylenediammonium diacetate (EDDA). At first Meldrum's acid reacted with aldehydes **9** to give the Knoevenagel adducts **12**. These latter underwent a hetero-Diels-Alder reaction with inverse electron demand to give **13** that, under the reaction conditions, lost acetone and CO_2 forming *strictosidine* and *deacetylisoipecoside* analogues **14**. Treatment of the latter with K_2CO_3/MeOH and catalytic amount of Pd/C under hydrogen atmosphere revealed the latent aldehyde moiety and deprotected the piperidine nitrogen (**15**, Scheme 4). Subsequent reductive amination gave the methyl esters **16**. It is interesting to point out the facial selectivity in the hetero-Diels-Alder reaction that favours *Re*-addition starting from both 1-α-H-tetrahydro-β-carboline **9a** and 1-β-H-tetrahydro-β-carboline **9b** (Scheme **9**). This was explained by the authors to be an effect of the different conformations of the two Knoevenagel adducts 1-α-H-**12a** and 1-β-H-**12b**. For the 1-α-H-**12a** with the free indole-NH, a possible interaction of the nonbonding electrons at the indole nitrogen with the π*-orbital of the alkylidene-1,3-dicarbonyl group, accompanied by the formation of a hydrogen bond between the N–H and one of the carbonyl groups might stabilize the conformation of intermediate **12a** and render the *Re*-face more accessible to approach of the enol ether. In contrast, using the *N*-indol-protected aldehyde 1-β-H-tetrahydro-β-carboline **9b**, the *Re*-face of the alkylidene **12b** is blocked by the Cbz-group leading to high *Re*-facial

selectivity. In addition, the indolo-derivated enamines **16a** and **16b** were hydrogenated in a highly stereocontrolled reaction to give esters **17a** and **17b** with good to excellent diastereoselectivity. In contradiction, the 1-α-H-tetrahydroisoquinoline **16c** showed poor selectivity in the Knoevenagel/hetero-Diels-Alder cascade and the subsequent hydrogenation and a mixture of diastereomers were isolated as the products where the desired stereoisomer **17c** unfortunately was the minor one.

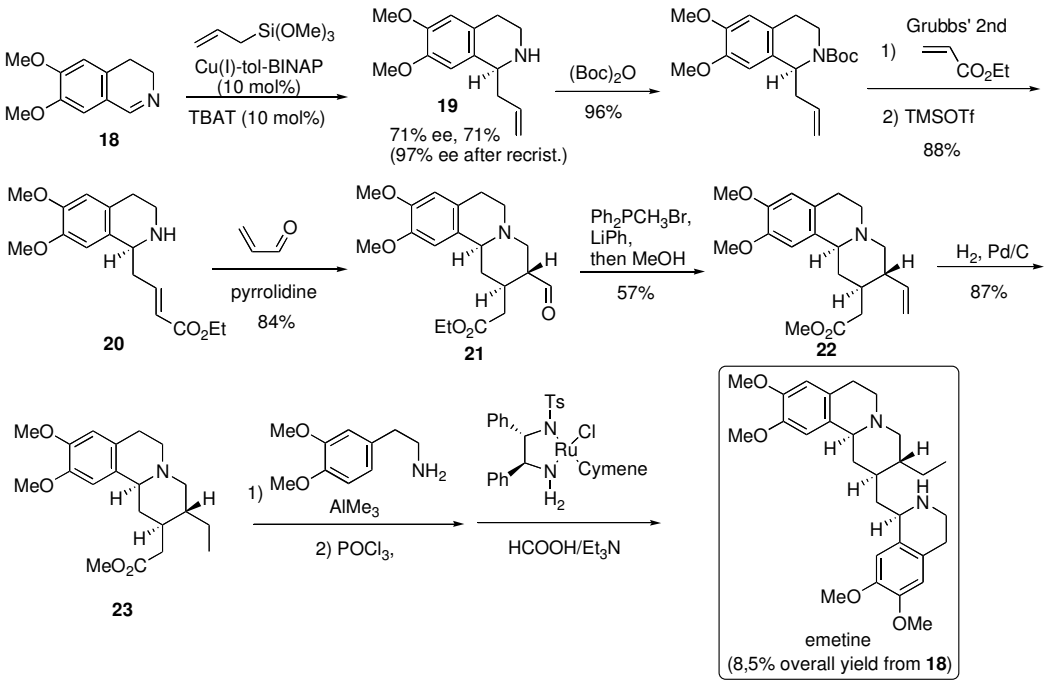


Scheme 4. Schematic overview of Tietze's three-component Knoevenagel/hetero-Diels-Alder domino-reaction of *corynanthe* and *ipecac* alkaloids (EDDA: ethylenediammonium diacetate).



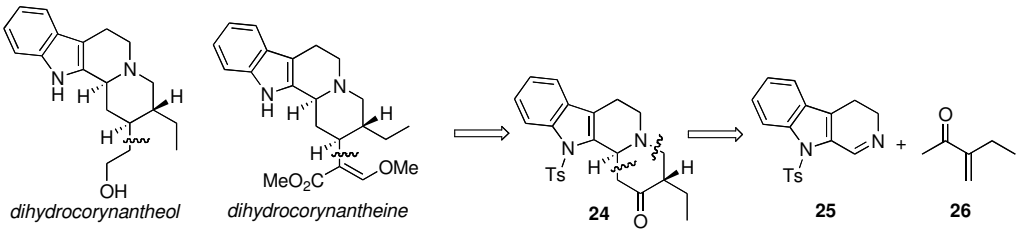
Scheme 5. Origin of selectivity in the Knoevenagel/hetero-Diels-Alder cascade.

Through the implementation of this Knoevenagel/hetero-Diels-Alder cascade, Tietze and co-workers successfully performed the concise synthesis of *hirsutine*, *dihydrocorynantheine*, *emetine* and *tubulosine* as well as a small library of their analogues in order to investigate their potential pharmaceutical applications.



Scheme 6. Itoh's *emetine* synthesis.

In a work related to Tietze's *corynanthe* and *ipecac* alkaloid synthesis (*vide supra)*, Itoh *et al.* developed a catalytic asymmetric allylation reaction[19] as the key step for the formal total synthesis of *emetine* (Scheme 6).[20] Cu(I)-tol-BINAP was used as the chiral catalyst for the allylation of cyclic imine **18** with allyl trimethoxysilane to give the 1-allyl-tetrahydroisoquinoline **19** in high yield and moderate enantioselectivity (71% ee). However, the optical purity was improved to 97% by recrystallization with dibenzoyl tartaric acid. The allylic double bond was further converted to the unsaturated ester **20** by a cross-metathesis with ethyl acrylate. After removed the Cbz-protection group on the nitrogen, an elegant double Michael annulation sequence was performed between the unsaturated ester **20** and acrolein that gave the benzoquinolizidine core unit **21** in high yield. The high α-*trans* stereochemistry observed in the annulation, which correlate with the stereochemistry of *emetine* is proposed to originate from the thermodynamic stability of the all-equatorial transition state. Subsequent Wittig olefination gave compound **22** followed by hydrogenation of the 3-vinyl group to give **23** that was transformed into naturally occurring *emetine* by the method developed by Tietze[17] in 8.5 % overall yield starting from **18**.

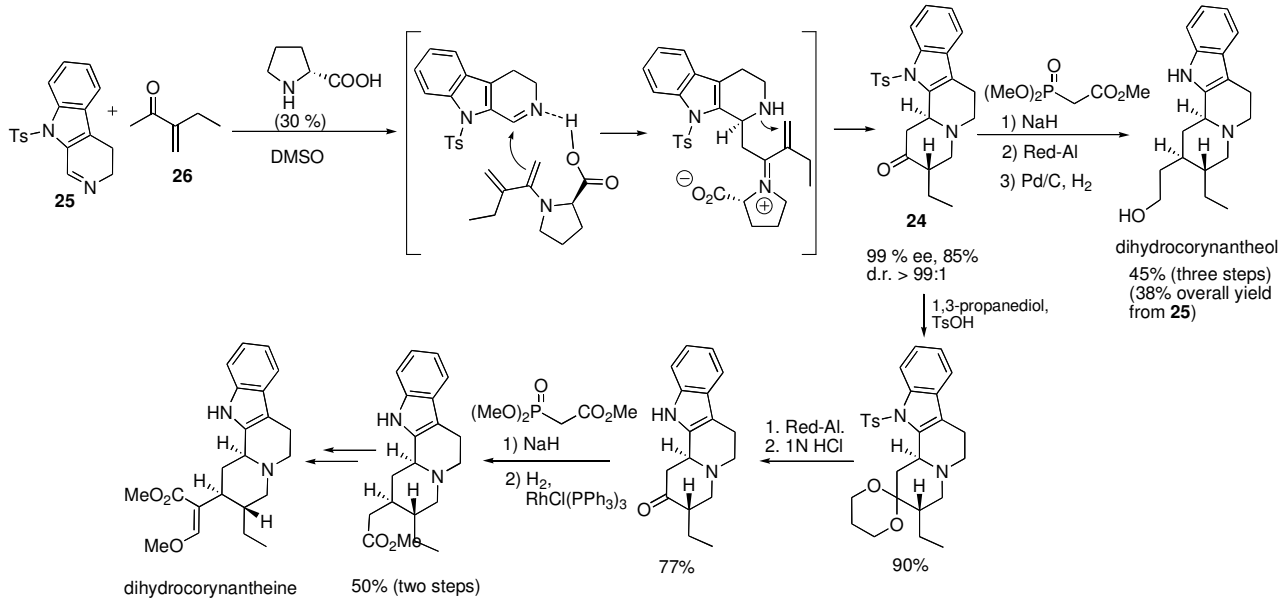


Scheme 7. Itoh's retrosynthetic analysis of *dihydrocorynantheol* and *dihydrocorynantheine*.

Organocatalytic reactions have been found to be powerful participants in asymmetric one-pot and domino reactions for total synthesis of natural products.[21,22] This can mainly be accounted for by the robustness of the catalysts, insensitivity towards air and moisture and extensive functional group tolerance.

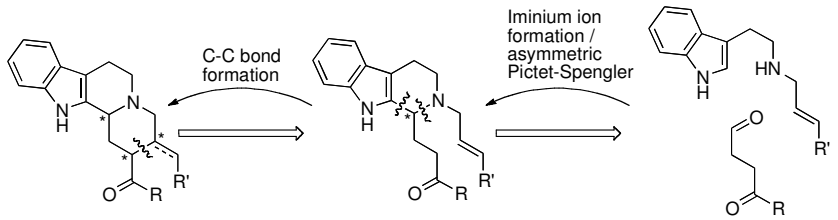
This was nicely illustrated by Itoh's approach to the synthesis of *dihydrocorynantheol* and *dihydrocorynantheine*.[23]

There retrosynthetic analysis leads back to ketone **24** that can be accessed through the annulation of dihydro-β-carboline **25** with 3-ethyl-3-buten-2-one **26**.



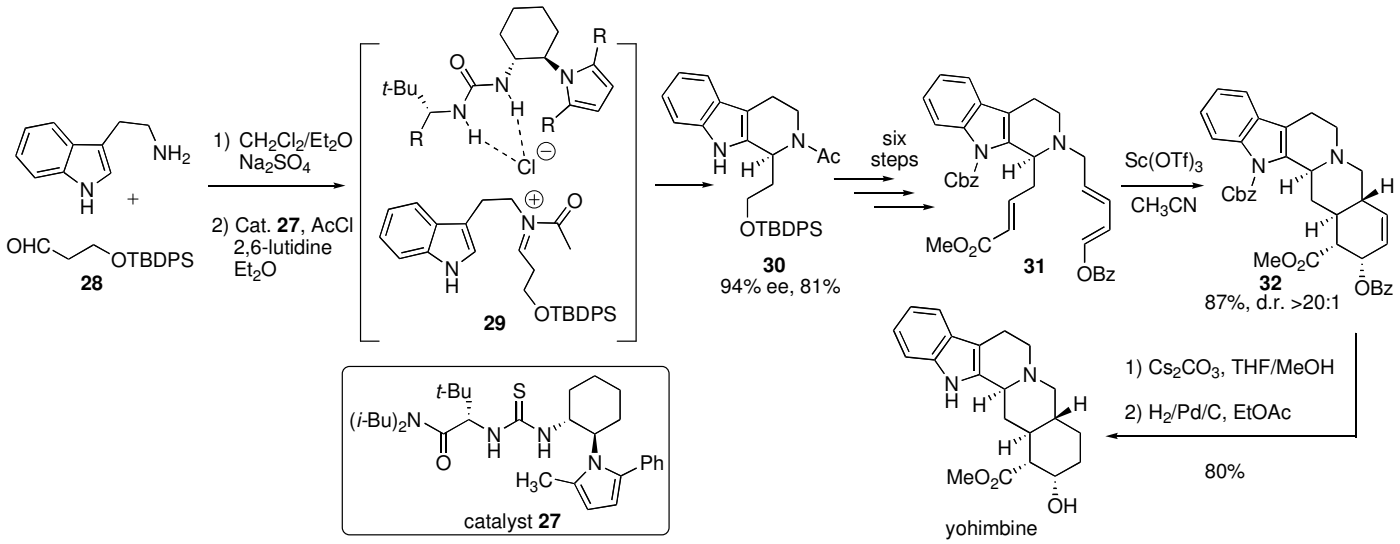
Scheme 8. Itoh's total synthesis of *dihydrocoryantheol* and *dihydrocorynantheine*.

Their approach starts from the reaction between 3-ethyl-3-buten-2-one **26** and *N*-tosyl-dihydro-β-carboline **25** in the presence of 30 mol% (*R*)-proline. This cyclization was believed going through a Mannich-Michael cascade sequence *via* a typical enamine-iminium cascade activation mode to give the key intermediate **24** in 85% yield (Scheme 8).[21] Extremely high enantioselectivity (99% ee) and almost complete diastereomeric control was observed. The ketone functionality of **24** was next converted to the α,β unsaturated ester through a Horner-Wadsworth-Emmons olefination. Reduction of the ester group and tosyl deprotection by Red-Al followed by double bond hydrogenation upon Pd/C gave *dihydrocoryantheol* as a single isomer with the correct α-*trans* stereochemistry in only 4 steps and 38% overall yield from *N*-tosyl-dihydro-β-carboline **25**. The analog strategy was also implemented for the formal synthesis of *dihydrocorynantheine* (Scheme 8).[24]



Scheme 9. Synthetic strategy of *Corynanthe* alkaloids based on asymmetric Pictet-Spengler cyclization.

The Pictet-Spengler reaction is a classical transformation frequently used in organic synthesis as well as by various organisms to synthesize tetrahydro-β-carbolines or tetrahydroisoquinolines from carbonyl compounds and tryptamines and phenyl ethylamine, respectively.[25] A general retrosynthetic analysis of quinolizidine alkaloids based on an asymmetric Pictet-Spengler reactionis outlined in Scheme 9. Jacobsen *et al.* have extensively studied the thiourea-catalyzed enantioselective acyl-Pictet-Spengler reaction and they discovered that pyrrole-containing thiourea **27** was able to promote the intramolecular addition of indoles to *N*-acyl-iminium ions generated *in situ* from imines and acetyl chloride to afford the chiral tetrahydro-β-carbolines.[26]

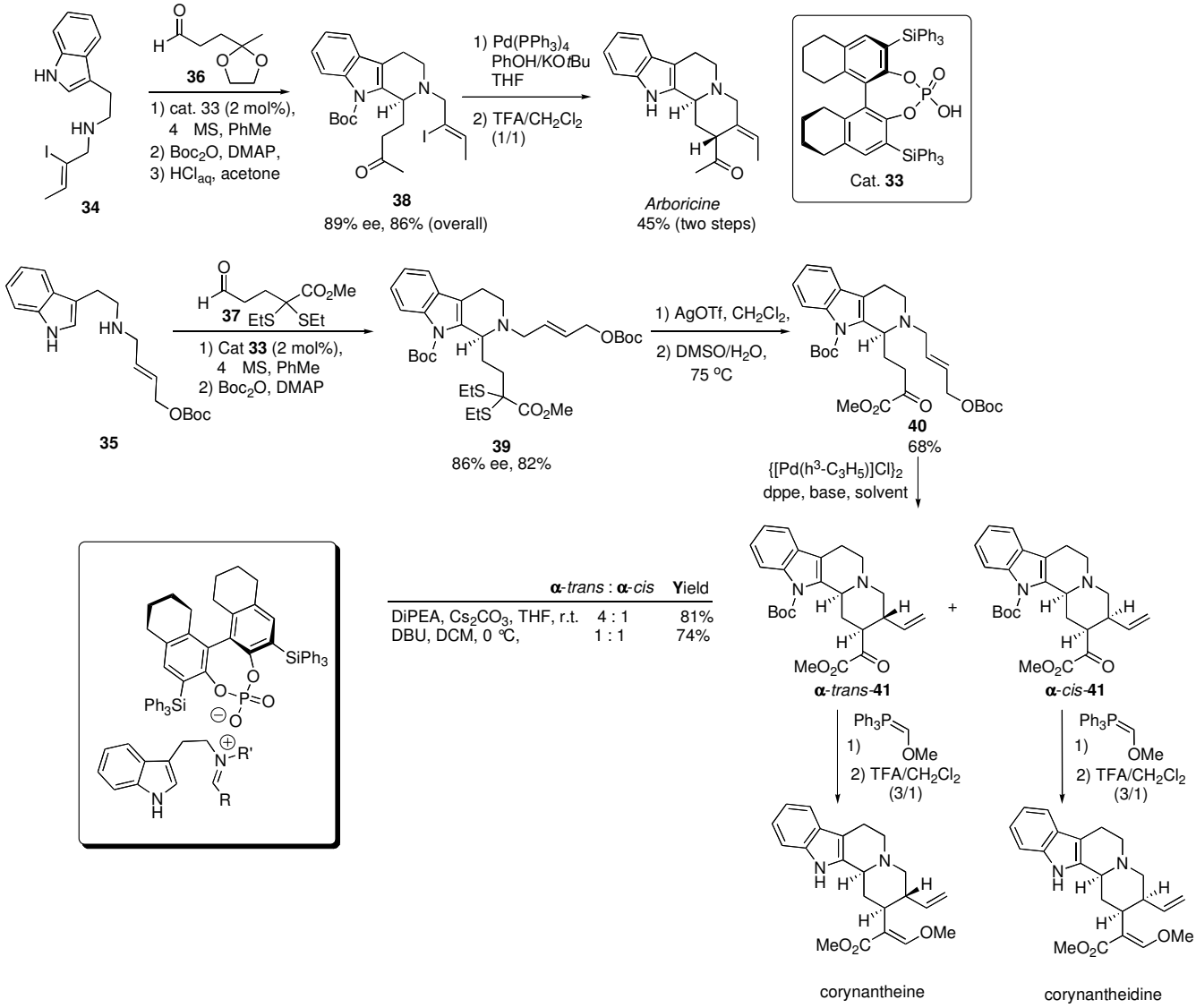


Scheme 10. Jacobsen's total synthesis of *Yohimbine* based on an asymmetric catalytic Pictet-Spengler cyclization and an intramolecular Diels-Alder reaction.

This reaction was applied by the same group as an early key step in their enantioselective total synthesis of (+)-*yohimbine*.[27] The synthesis started by the condensation of tryptamine and the protected hydroxyaldehyde **28** to generate the corresponding imine (Scheme 10). Subsequent treatment of the latter with acetyl chloride in the presences of thiourea catalyst **27** gave the intermediate chiral tight ion pair complex **29**, with the thiourea catalyst H-bonded to the chloride counterion, that was proposed to account for the high enantioselectivity in the formation of **30**. The tetrahydro-β-carboline **30** was further functionalized to **31** in six steps to install the functional groups required for the following Diels-Alder annulation that would build up the final two fused rings of the *yohimbine* skeleton. When compound **31** was treated with an excess amount of $Sc(OTf)_3$, the intramolecular Diels-Alder annulation proceeded smoothly with excellent diastereoselectivity and yielded the protected *yohimbine* analog **32** as a single observed diastereoisomer with the correct relative stereochemistry. Finally, the protecting group was removed and the olefin was hydrogenated in two additional steps to give (+)-*yohimbine*.

Shortly after Jacobsen, Hiemstra and co-workers implemented a similar strategy for the total synthesis of the indole alkaloids, *arboricine*,[28] *corynantheine, corynantheidine*[29] and *yohimbine*.[30] Alternatively to Jacobsens chiral thioureas, Hiemstra *et al*. applied chiral phosphoric acids as the catalysts for the asymmetric Pictet-Spengler reaction.[26d] The phosphoric acid **33** catalyzed iminium ion formation of *N*-substituted tryptamines **34** and **35** and functionalized aldehydes **36** and **37** to form a tight chiral ion pair. The chiral counterion controls the stereoselectivity of the Pictet-Spengler reaction giving optically active tetrahydro-β-carboline **38** and **39** in moderate enantioselectivity (see Scheme 11). Thus, bearing the appropriate functionalized side chains for further transformations, tetrahydro-β-carboline **38** was reacted in a highly stereoselective intramolecular Pd(0)-catalyzed α-vinylation, according to the method developed by Bonjoch and co-workers.[31] Subsequent deprotection and recrystallization gave enantiomerically pure (−)-*arboricine* as a single diastereomer in 33% overall yield in six steps starting from tryptamine.[32] Alternatively, in the total synthesis of *corynantheine* and *corynantheidine*, an intramolecular Pd(0)-catalyzed allylic alkylation of **39** to **40** was used as the key step to build up the carbon skeleton of the target molecule. However, this reaction showed moderate to no diastereoselectivity and a mixture of epimers with the opposite configuration at C^3 was obtained in a 1:1 to 1:4 ratio, depending on the base used in the allylic alkylation

(Scheme 11). However, after separation of α-*trans*-**41** and α-*cis*-**41**, *corynantheine* and *corynantheidine* could be accessed in a few additional steps, according to Scheme 11.



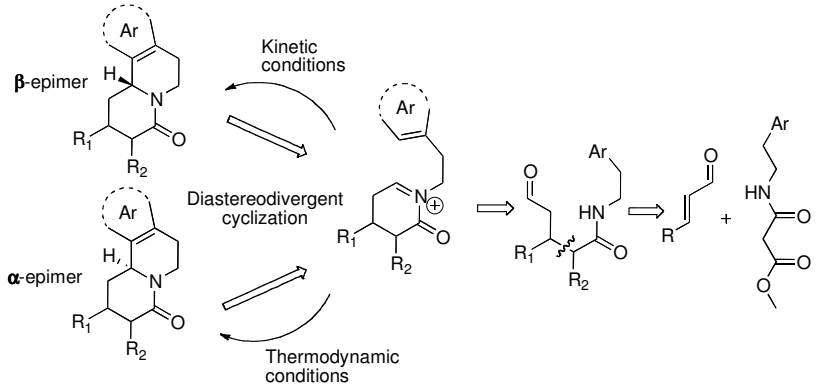
Scheme 11. Hiemstra's synthesis of *arboricine*, *dihydrocorynantheine*, *corynantheine* and *corynantheidine* based on a Pictet-Spengler cyclization.

2.2. Route B: late diastereoselective formation of the ring-junction stereocentre

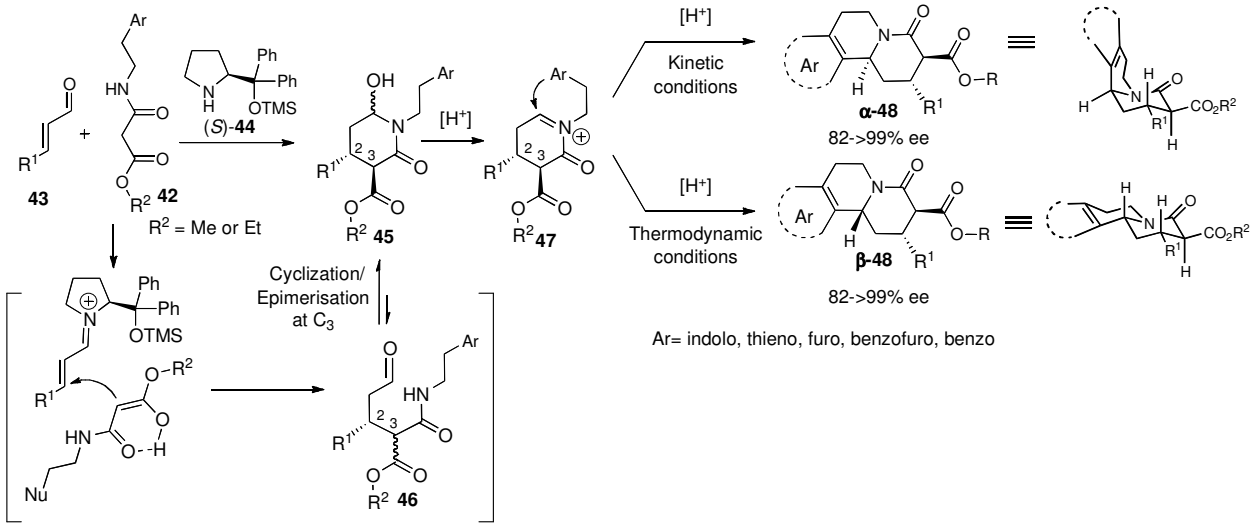
In addition to the strategy of constructing optically active aromatic quinolizidine compounds through early installation of the ring junction stereocentre (*vide supra*), early construction of the C^2 or C^3-stereocentre has also be used as an efficient pathway to guide the relative formation of the remaining stereocentres. Several novel approaches based on this strategy have successively emerged since 2009 when we first reported our initial study on asymmetric catalytic one-pot synthesis of chiral quinolizidine derivatives. It is also worth pointing out that all of these approaches exploited organocatalysis and cascade/one-pot reactions as the key step to assemble the aromatic quinolizidine skeleton. In general, such approaches allow for fast access to molecular complexity and provide high levels of atom and step economy.

Our strategy for the asymmetric synthesis of aromatic quinolizidine derivatives is based on a two-step one-pot process.[33] From the retrosynthetic analysis, we envisioned that the ring-junction stereocentre could be constructed through an acyl-Pictet-Spengler cyclization (Scheme 12).[34] Taking into account the higher

thermodynamic stability of the flat α-epimer compared to the V-shaped β-epimer (*cf.* 12b-α-H *dihydrocorynantheine* and 12b-β-H *hirsutine*, Figure 2) and the fact that acyl-Pictet-Spengler cyclization are known to be under kinetic control,[34a] we envisioned that it could be possible to find stereodivergent one-pot reaction conditions that could selectively favour the formation of either the β-epimer (kinetic reaction conditions) or the α-epimer (thermodynamic reaction conditions) (Scheme 12). Such a diastereomeric switch will provide an efficient protocol for the enantio- and diastereoselective synthesis of both the ring-junction epimers of the quinolizidine skeleton. Furthermore, we wanted to broaden the scope of the one-pot sequence to access different fused aromatic and heteroatom aromatic quinolizidine ring systems.



Scheme 12. Retrosynthetic analysis of both ring-junction isomers through a diastereodivergent cyclization.



Scheme 13. Asymmetric catalytic one-pot reaction for the formation of aromatic quinolizidine compounds.

We found that conjugate addition[35] of indole-substituted amide **42** to cinnamaldehyde derivatives **43**, catalyzed by prolinol derivative (*S*)-**44**, smoothly gave the hemiaminal intermediate **45** with the *trans* stereochemistry between C^2 and C^3 (Scheme 13).[36] The absolute configuration at C^2 was controlled by the catalyst through the iminium ion activation conjugate addition. The C^3-stereocentre would spontaneously epimerize to the thermodynamically most stable *trans*-configuration (**46**→**45**). After full conversion of amide **42**, TFA was added to the reaction mixture inducing loss of water to give the *N*-acyl iminium ion **47**. This compound reacted in an acyl-Pictet-Spengler cyclization to give the α- and β-epimer **48** as a 1:1 mixture in high yield and good enantioselectivity. However, the tuning of the acid and temperature of the second step of the one-pot procedure (catalytic HCl, in Et_2O, −78 °C) revealed that the kinetically favoured α-epimer α-**48** could be obtained as the major isomer in moderate to good diastereoselectivity. After further

tuning of the acid conditions, we found that the thermodynamically favoured product β-**48** could be obtained by using excess amounts of TFA at elevated temperatures. The scope of the reaction was further investigated with respect to aromatic group and acidic conditions and we were able to identify three major modes of diastereocontrol in the acyl-Pictet-Spengler cyclization that was dependent on the character of the aromatic moiety, kinetic, thermodynamic and chelation control. A plausible mechanistic rationalization of the diastereoselection is outlined in Figure 4.

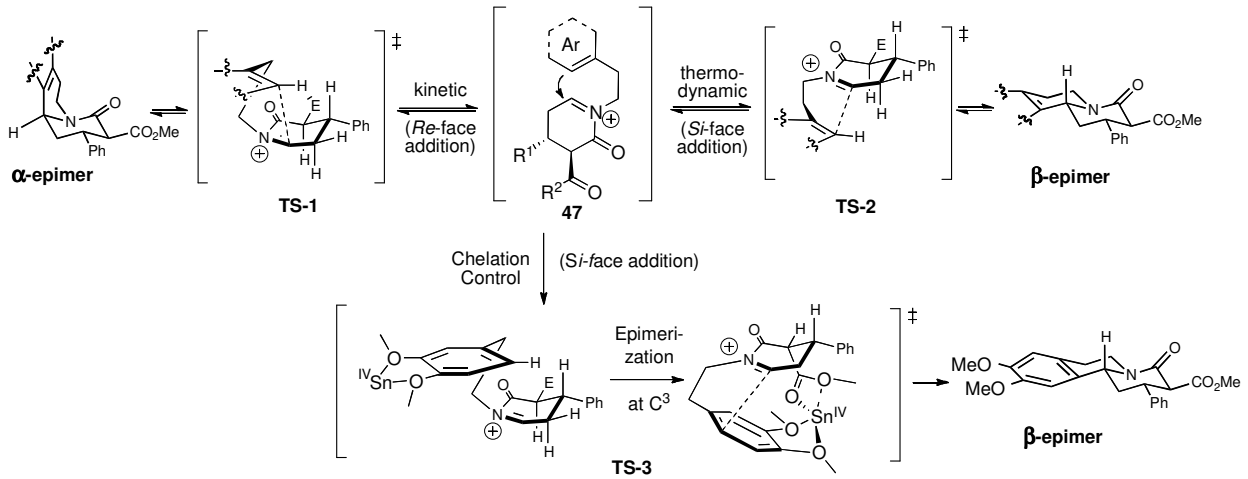


Figure 4. Origin of selectivity in the acid-promoted second step of the one-pot sequence.

The approach of the aromatic ring to the *N*-acyl iminium ion **47** from the *Re*-face to give the kinetic α-isomer is believed to be faster due to the favoured axial attack in the transition state (TS-1). This is to be compared to the equatorial *Si*-face attack that gives the higher energy transition state TS-2 leading to the thermodynamically more stable all-equatorial β-epimer.[37] However, we found that for indolo- and the 3,5-dimethoxybenzo-derivatives, the *N*-acyl-Pictet-Spengler cyclization was reversible under acidic conditions at elevated temperatures and the equilibrium lies toward the thermodynamically favoured epimer. Thus, applying these conditions in the one-pot sequence, the thermodynamically favoured products could be isolated in moderate diastereoselectivity. In contrast, the 3,4-dimethoxylphenyl and thionyl substrates were not under kinetic and thermodynamic control and only the kinetically favoured epimers were observed as the major product with low d.r. even under thermodynamic conditions.

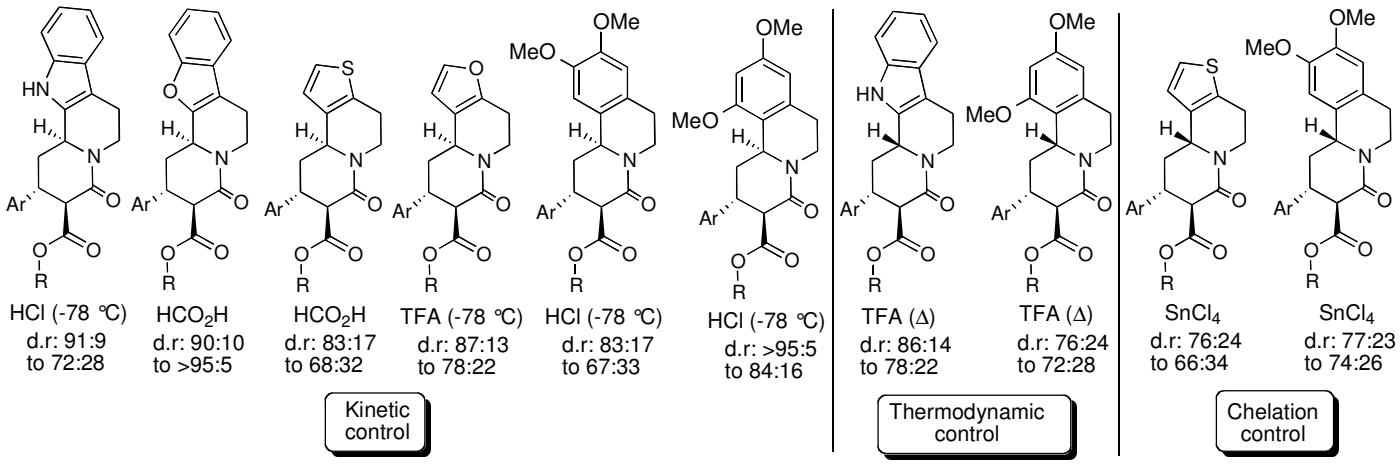
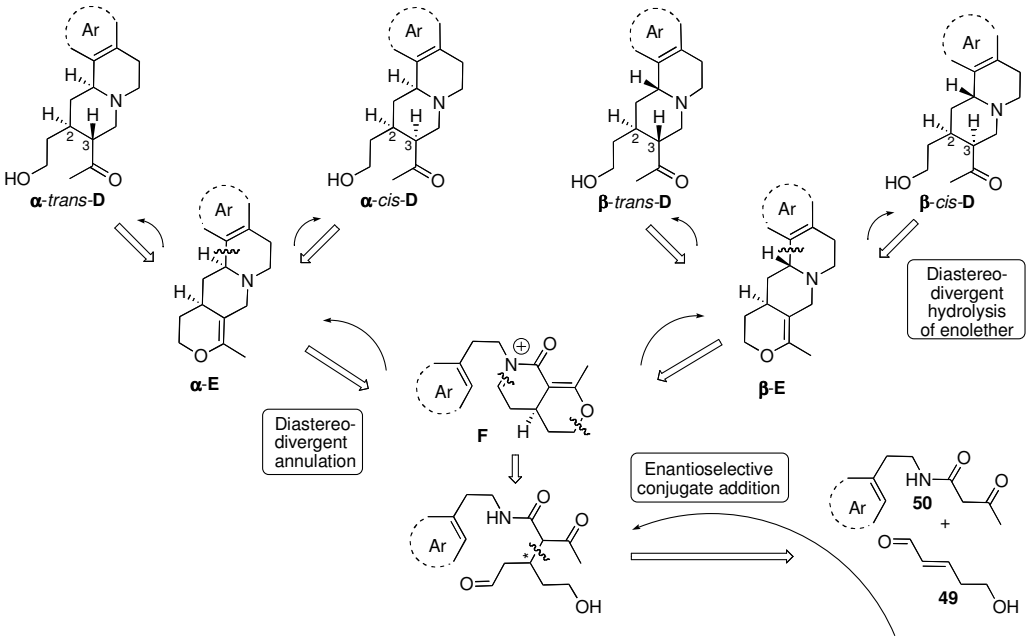


Figure 5. Scope of the diastereodivergent asymmetric catalytic one-pot reaction.

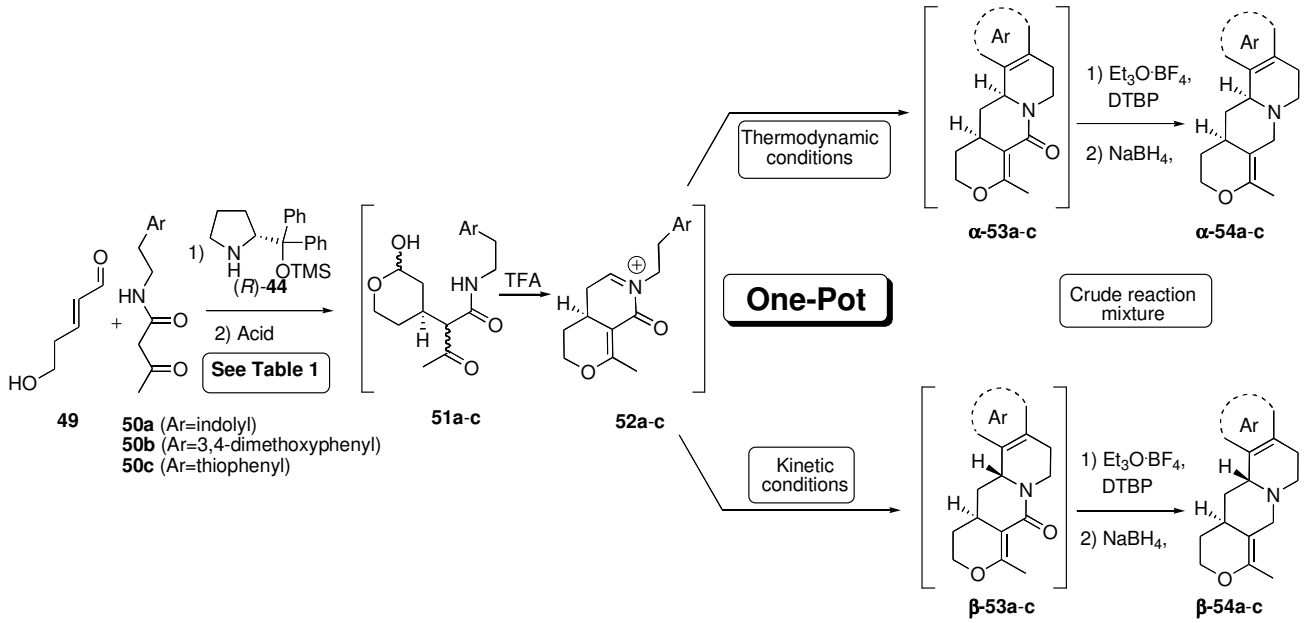
Alternatively, $SnCl_4$ was found optimal to generate the thermodynamic favoured product that probably cyclized through a chelation pathway (TS-3), rather than the thermodynamically controlled pathway. Figure 5 displays the structural and stereochemical diversity of aromatic quinolizidine derivatives that are accessible through this methodology.

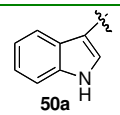
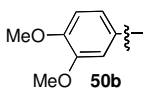
Next we turned our attention towards the development of this diverse one-pot sequence into a synthetic strategy of *corynanthe* and *ipecac* alkaloids as well as their non-natural analogs and epimers.[38] Keeping in mind the structural similarity of the quinolizidine alkaloids, where the only difference is variation on the ring-junction stereocentre, the substituents on C^2 and C^3 and the fused aromatic group (see Figure 1), we anticipated that an array of naturally occurring quinolizidine alkaloids, their epimers and analogs, could be prepared *via* a single and general strategy. Our plan was to develop a common synthetic route to a series of functionalized quinolizidine intermediates with skeletal and stereochemical variation. These epimeric structurally different intermediates are to be designed in such a way that they can be rapidly modified, in a few synthetic operations, to the desired alkaloids with correct absolute and relative stereochemistry. We were also determined to put a considerable focus on the over all efficiency of the synthetic strategy through the implementation of asymmetric one-pot and cascade/tandem reactions. We came to the conclusion that the four different epimers of quinolizidine derivatives **D** would be prominent precursors for a broad series of *corynanthe* and *ipecac* alkaloids, their epimers and different analogs (Scheme 14). The strategy should be based on asymmetric catalysis and we also envisioned a stereodivergent introduction of the following stereocentres by taking advantage of thermodynamic and kinetic reaction conditions. This will allow for fast construction of different epimeric intermediates from common starting materials. We anticipated that it would be possible to hydrolyzed the enol ether moiety of compound **E** in a diastereodivergent manner, thus achieving the C^2–C^3 *cis*- or *trans*-configuration. From compound **E**, the first C–C bond disconnection leads back to the *N*-acyliminium ion **F**. Based on our previous developments in stereoselective *N*-acyliminium ion cyclizations (*vide supra*), we proposed that the annulation could be controlled to give either the α- or β-epimer in a second diasterodivergent reaction. Further disconnections leads back to the α,β-unsaturated aldehyde **49** and β-ketoamide **50** (Scheme 14).



Scheme 14. Stereodivergent retrosynthetic analysis of quinolizidine alkaloids.

Following our outlined synthetic strategy, we found that β-keto amide **50a–c** smoothly reacted with 5-hydroxyl pentenal **49** in the presence of catalyst (*R*)-**44**, giving a diastereomeric mixture of lactols **51a–c** (Scheme 15). The mechanism for this reaction is proposed to proceed through iminium ion activation and conjugate addition, generating the C^2-stereocentre with the desired absolute configuration. Subsequent addition of TFA to the reaction mixture containing lactol **51** triggers an acid-catalyzed cascade reaction consisting of: lactol ring opening, enol ether formation, hemiaminal formation and acid-catalyzed loss of water to give *N*-acyliminium ion **52**. Subsequent *N*-acyl-Pictet-Spengler cyclization gives a 1:1 mixture of α-**53a–c** and β-**53a–c** in good yields and high enantioselectivity in a two-step one-pot process. After extensive acid screening, we found a series of conditions that allowed for a diastereomeric switch (see Table in Scheme 15). Thus, quenching the reaction of indole substituted β-ketoamide **50a** with acetyl chloride, the thermodynamically favoured indolo[2,3-*a*]quinolizidine α-**53a** as the only observable isomer was formed. Interestingly, when using benzoyl chloride, we observed a switch in diastereoselectivity and the kinetically favoured product β-**53a** was obtained as the major isomer in 82:18 diastereoselectivity.

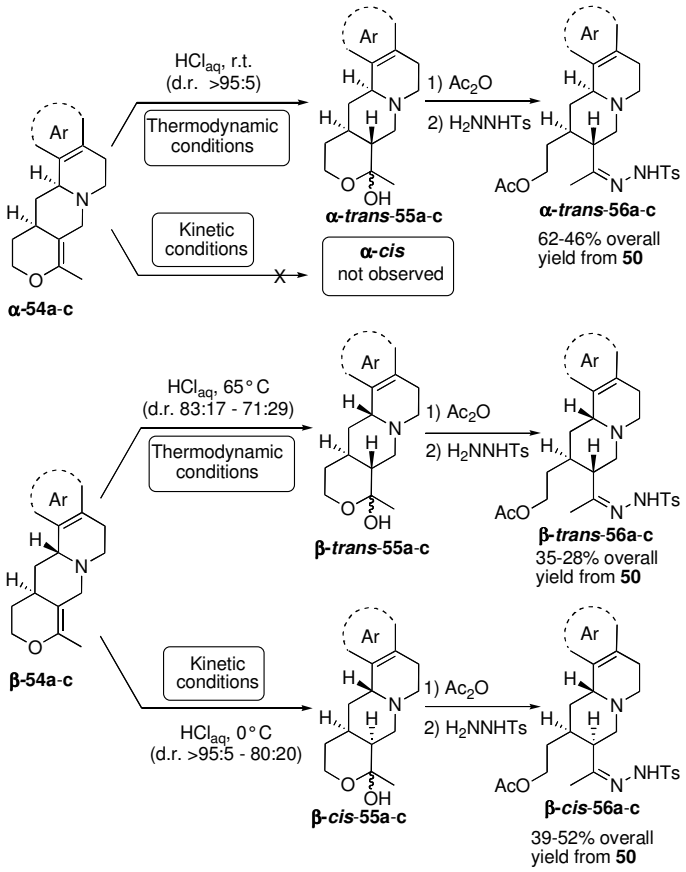


Ar	Conditions	[Acid]	D.r. [T/K]	e.e. [%]	Major Product	Overall Yield (from **50**)[%]
 **50a**	T	AcCl	>95/5	99	α-**54a**	81
	K	BzCl	18/82	95	β-**54a**	54
 **50b**	T	$Et_3O·BF_4$	70/30	92	α-**54b**	63
	K	$SnCl_4$	22/78	92	β-**54b**	66
 **50c**	T	$Et_3O·BF_4$	67:33	95	α-**54c**	65
	K	BzCl	33:67	94	β-**54c**	57

Scheme 15. Enantioselective and diastereodivergent one-pot synthesis of the quinolizidine skeleton.

Unfortunately, the optimized acid conditions for the indole-compound could not be directly applied for selective ring junction formation of the benzo[*a*]- or the thieno[3,2-*a*]quinolizidines **53b,c**. Eventually, we found that triethyloxonium tetrafluoroborate promoted formation of the thermodynamically favoured ring junction stereocentre α-**53b,c** with moderate selectivity. One-pot conditions favouring the kinetic epimers

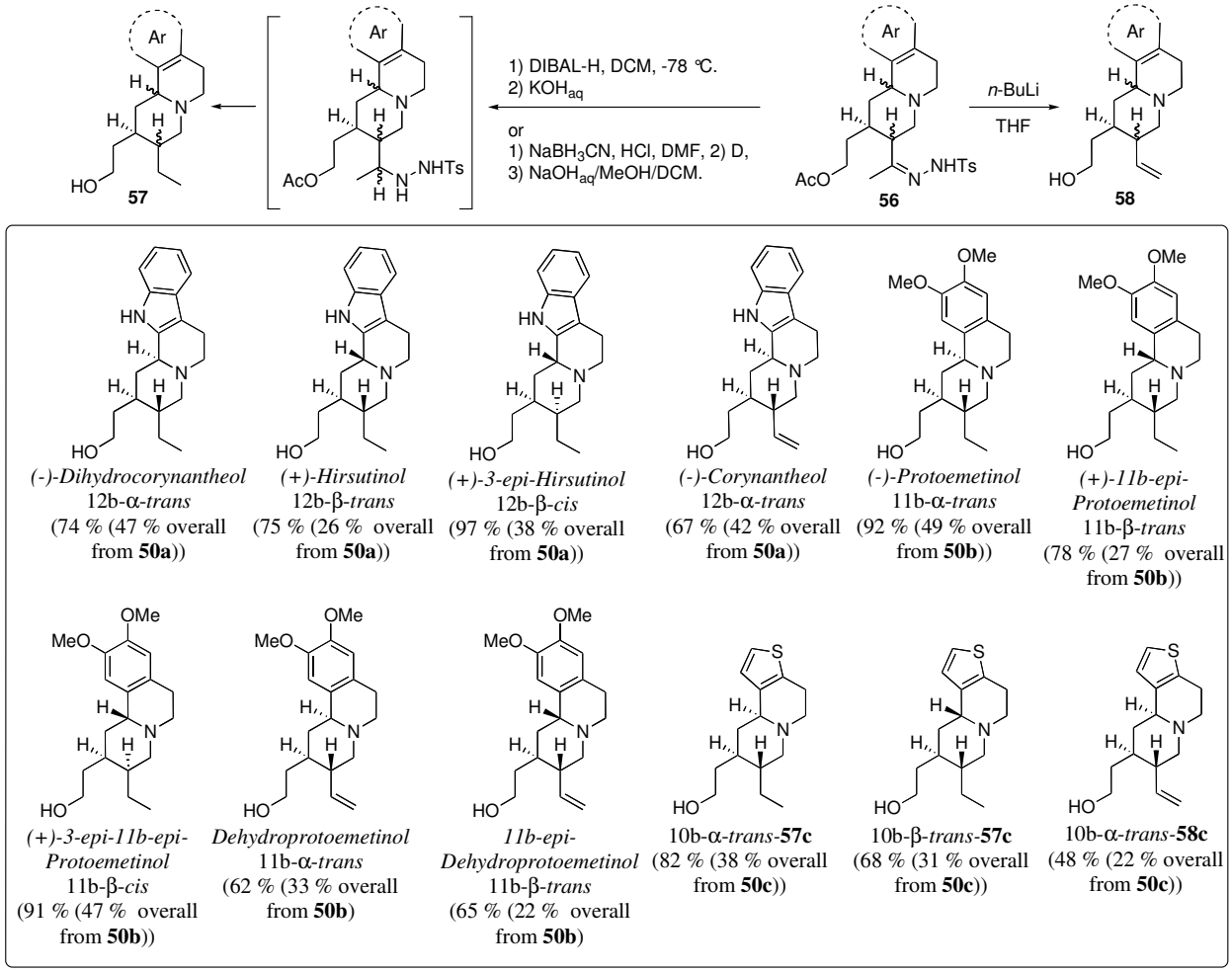
benzo[*a*]- and thieno[3,2-*a*]quinolizidines β-**53b,c** with moderate selectivity were identified to be tin(IV)chloride and benzoyl chloride, respectively. The exact role of the acid with respect to selectivity in the formation of the ring junction stereocentre is not clear and we have not been able to detect any obvious trends between different acids during the screening. Direct reduction of the crude reaction mixture of amides **53** from the one-pot-cascade was accomplished by initial alkylation with triethyloxonium tetrafluoroborate, followed by $NaBH_4$ reduction to give the corresponding amines **54a–c** in high to moderate overall yields from their corresponding β-ketoamides **50** (Scheme 15). At this stage, the α- and β-epimers of amines **54a–c** could be easily separated by flash column.



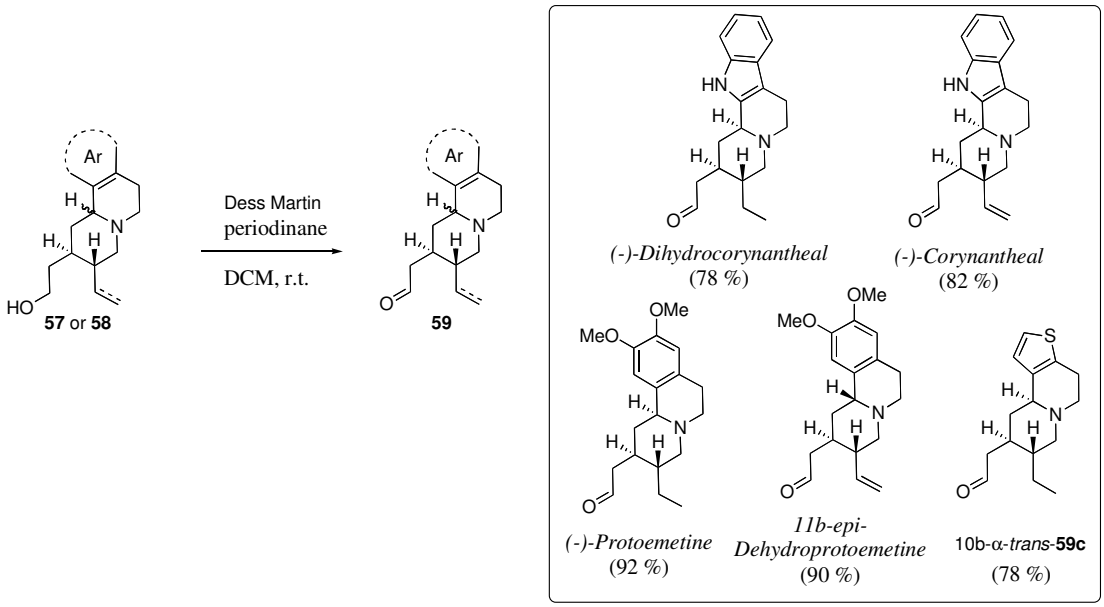
Scheme 16. Diastereodivergent hydration of enol ether **54a–c**.

The lactols **55** were isolated by extraction and subsequently treated with acetic anhydride and tosyl hydrazide to give the corresponding hydrazones **56** (Scheme 16). Any undesired epimer from the previous hydration of enol ether **55** was separated by flash column and the α-*trans*, β-*trans* and β-*cis* epimers of hydrazones **56a–c** were isolated as single isomers in good to excellent overall yields from amines without purification of the synthetic intermediates. We decided to proceed through the hydrazone intermediate because from here we have a choice between full reduction to the saturated C^3 alkyl **57** chain or partial reduction under Shapiro conditions to give the C^3 vinyl-group **58**. The full reduction of hydrazones **56** to the ethyl group (**57**) gave the natural product (−)-*protoemetinol* in 92 % and 49 % overall yield from β-ketoamide **50b** (Scheme 17). In the same manner, the natural products (−)-*dihydrocorynantheol* and (+)-*hirsutinol* together with a series of non-natural analogs were prepared in high yields. Partially reduction of the hydrazone moiety under Shapiro conditions gave the terminal vinyl-group at the C^3 position (**58**) providing access to the natural product (−)-*corynantheol* and several non-natural analogs in moderate to

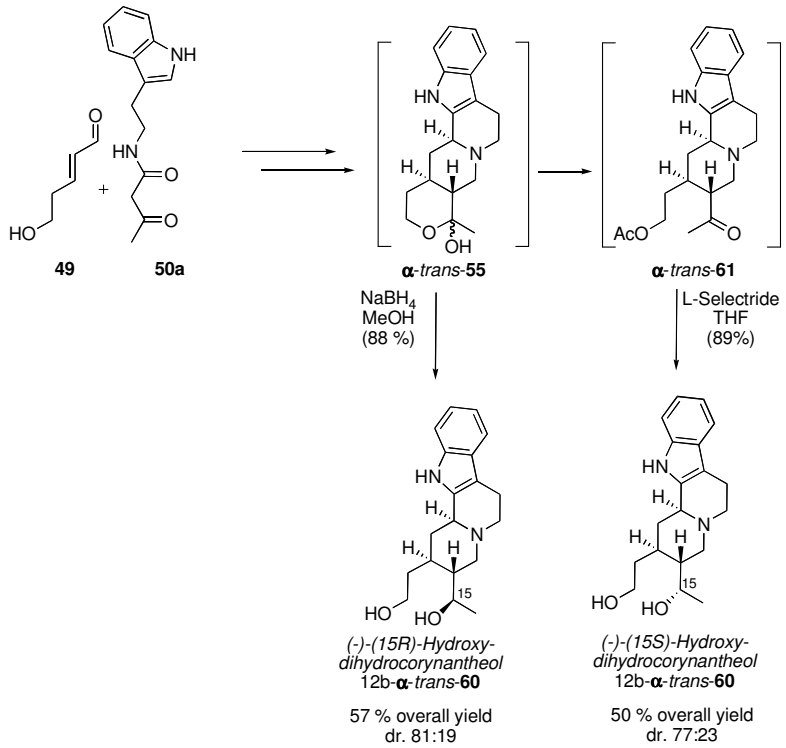
good yields (Scheme 17). It is worth to point out that through this synthetic pathway, it is possible to selectively access to three of the four possible epimers of several of the *corynanthe* and *ipecac* alkaloids in good overall yield using a common synthetic strategy.



Scheme 17. Chemodivergent reduction of hydrazone **56** for the synthesis of *corynanthe* and *ipecac* alkaloids, their epimers and analogs.



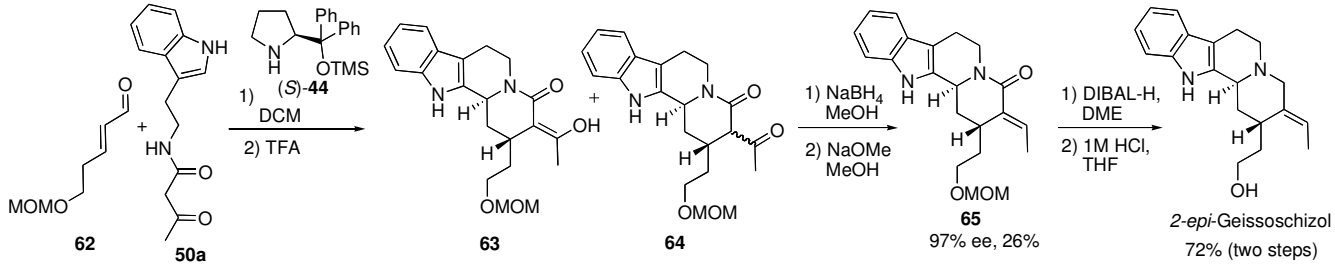
Scheme 18. Dess-Martin oxidation of alcohol **57** and **58**.



Scheme 19. Purification and protecting group free total synthesis of *(−)-(15S)-hydroxydihydrocorynantheol* and its non-naturally occurring epimer *(15R)-hydroxydihydrocorynantheol.*

The hydroxy-quinolizidines were smoothly oxidized using Dess-Martin periodinane to give the naturally occurring alkaloids (−)-*dihydrocorynantheal*, (−)-*corynantheal* and (−)-*protoemetine* and the analogs (+)-*11b-epi-dehydroprotoemetine* and thieno[3,2-*a*]quinolizidine 10b-α-*trans*-**59c** in high overall yields (Scheme 18).

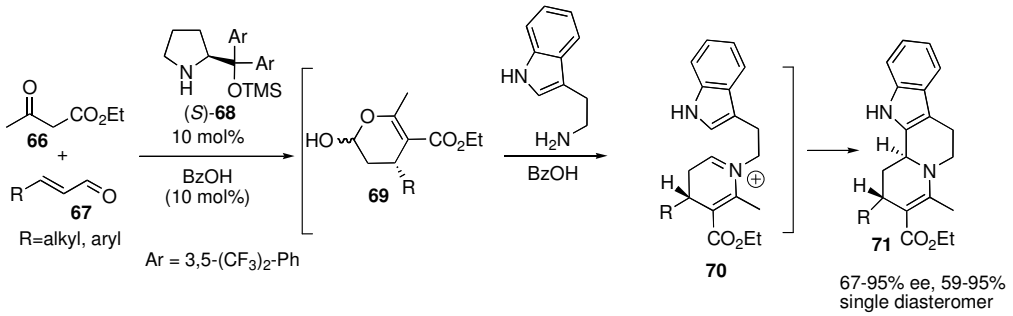
This methodology was also applied in the protecting group free total synthesis of alkaloid *(−)-(15S)-hydroxydihydrocorynantheol* (15*S*)-**60**, and its non-naturally occurring epimer *(15R)-hydroxy-dihydrocorynantheol* (15*R*)-**60**.[39] Lactol 12b-**α-***trans***-55a** was prepared without purifications of intermediates and the crude compound was directly reduced with $NaBH_4$ to give the non-natural *(15R)-hydroxydihydrocorynantheol* 12b**-** α**-***trans***-60** (d.r. 81:19) in 57% combined overall yield from amide **50a** (Scheme 13). However, opening of the lactol 12b-α-*trans*-**55** with acetic anhydride to the ketone 12b-α-*trans*-**61** and subsequent reduction using L-Selectride gave the natural product *(−)-(15S)-hydroxy-dihydrocorynantheol* 12b-α-*trans*-**60** was obtained with 77:23 diastereoselectivity and 50 % combined overall yield from β-ketoamide **50a**.



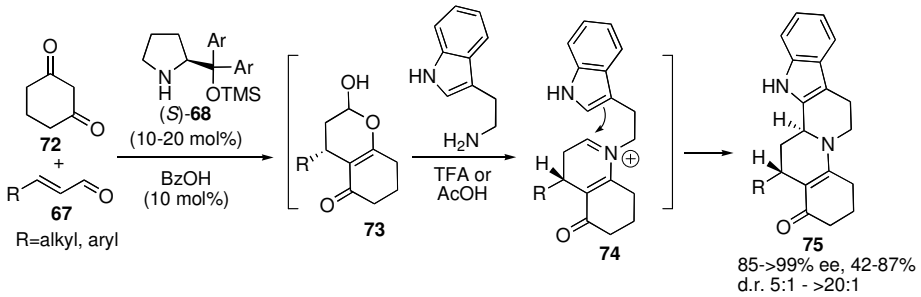
Scheme 20. Zhao's asymmetric catalytic total synthesis of *2-epi-geissoschizol*.

Zhao and co-workers used the β-keto-amide **50a** and MOM-protected hydroxy-enal **62** as a starting material in the synthesis of *2-epi-geissoschizol* (Scheme 20).[40] Prolinol (*S*)-**44** and TFA were used as the

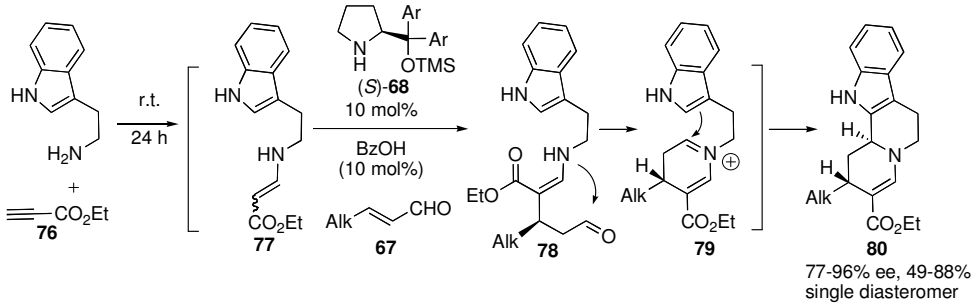
catalysts for the two-step one-pot reaction to give **63** and **64** as a 1:1 mixture of keto/enol tautomes. The mechanistic aspects of this reaction are analog to ones of the reaction developed by Franzén *et al.*[38] *(vide supra)*. The keto/enol tautomes were directly reduced and dehydrated under telescoping conditions to give **65** in low yield but with excellent enantioselectivity. The high *trans*-diastereoselectivity in the formation of the ring-junction stereocentre is very interesting and unexpected under these reaction conditions. Final reduction of the amide functionality and deprotection gave the target molecule *2-epi-geissoschizol*.



Scheme 21. Zhao's three-component asymmetric one-pot processes to indoloquinolizidines based on β-keto esters.



Scheme 22. Zhao's three-component asymmetric one-pot processes to indoloquinolizidines based on 1,3-diketones.

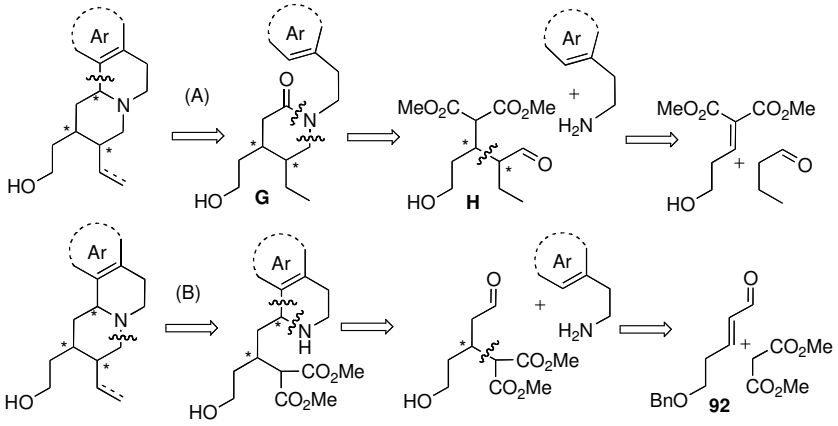


Scheme 23. Zhao's three-component asymmetric one-pot processes to indoloquinolizidines based on ethyl propiolate.

Zhao and co-workers also developed a series of three-component one-pot processes for the asymmetric catalytic preparation of indoloquinolizidines. In their first example, they employed β-ketoester **66**, α,β-unsaturated aldehydes **67** and tryptamine.[41] The one-pot sequence starts with the conjugate addition of the β-ketoester **66** to the α,β-unsaturated aldehyde **67** catalyzed by prolinol (*S*)-**68** yielding the optically active hemiacetal **69** (Scheme 21). The latter is trapped by tryptamine in the second step of this one-pot reaction giving iminium ion **70**. The subsequent intramolecular Pictet-Spengler cyclization resulted in the quinolizidine compounds **71** with excellent yields, enantiomeric purity and *trans*-diastereoselectivity. In 2011, Rueping[42] and Zhao[43] independently developed the analog three-component process using

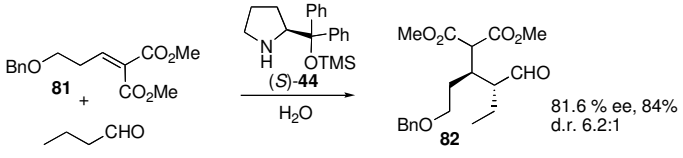
1,3-diketones **72** instead of β-ketoesters as the nucleophile (Scheme 22).[44] Similar hemiacetals **73** and iminium ion intermediates **74** were involved and the whole sequence proceeded smoothly and again enantiomeric enriched products **75** with high *trans*-selectivity of the formed stereocentres were obtained. Later, Zhao *et al.* developed an alternative approach toward generation of iminium ion intermediates **79** through a one-pot three-component cascade sequence of tryptamines, ethyl propiolate **76** and α,β-unsaturated aldehydes **67** (Scheme 23).[45] They found that the Michael addition of tryptamines to ethyl propiolate **76** gave β-enaminoesters **77**. The latter was an efficient nucleophile in the conjugate addition to α,β-unsaturated aldehydes **67** through the prolinol (*S*)-**68** catalyzed iminium ion activation to give adduct **78**. In the presence of benzoic acid, the iminium ion **79** was spontaneously formed after lost of water and subsequent Pictet-Spengler cyclization completed the formation to indoloquinolizidines **80**. This interesting one-pot cascade involves the formation of two new rings, two C–N and two C–C bonds with high *trans*-diastereoselectivity, moderate to high ee and moderate to high yields. In all cases, the authors ascribe the high *trans*-selectivity of C2 to and the ring junction stereocentre to selective formation kinetically favoured product (*cf.* **TS1** and **TS2**, Figure 4).

Recently, Ma[46] and Córdova[47] simultaneously reported on the total synthesis of *corynanthe* and *ipecac* alkaloids. In the retrosynthetic analysis by Ma *et al.*, they focused on lactam **G** as an advanced intermediate. Further disconnections lead back to their key intermediate, aldehyde **H**, which was suggested to be a common precursor for both the *corynanthe* and *ipecac* alkaloids through reaction with tryptamine and 3,4-dimethoxyphenethylamine, respectively.



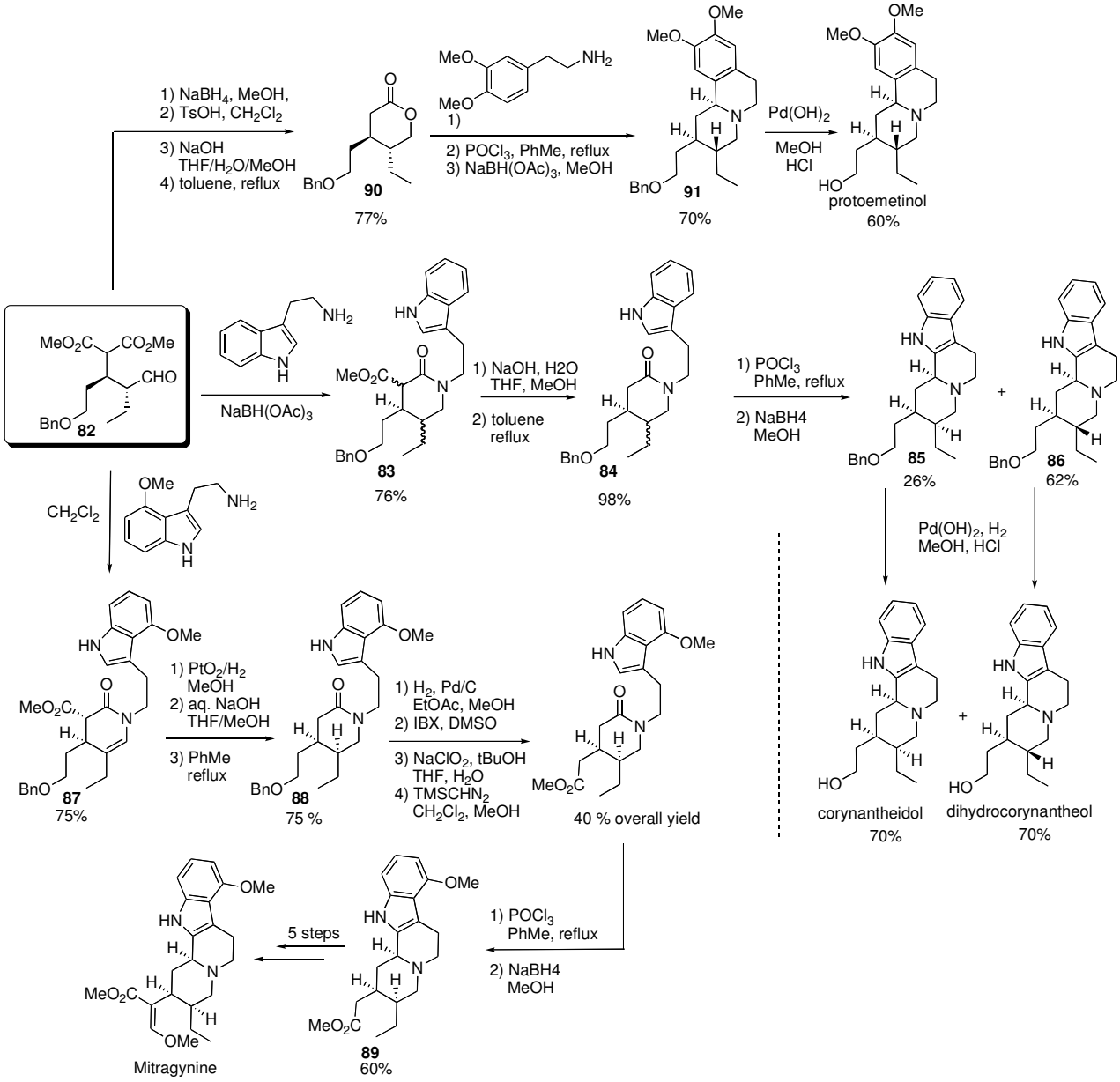
Scheme 24. Ma's (A) and Córdova's (B) retrosynthetic analysis of the *corynanthe* and *ipecac* alkaloids.

Following their strategy, Ma *et al.* applied the prolinol (*S*)-**44**-catalyzed enamine conjugate addition of *n*-butanal to alkylidene malonate **81** (Scheme 25). The resulting chiral aldehyde **82** posses an ethyl group and a hydroxyethyl moiety that correlate it to the target alkaloids. Interestingly, the reaction performed best in water and aldehyde **82** was isolated in 6.2:1 diastereomeric ration and 91% ee. Unfortunately, the enantioselectivity of the reaction dropped drastically to 82% ee when the reaction was scaled up to 1 mmol scale.



Scheme 25. Preparation of Ma's key intermediate.

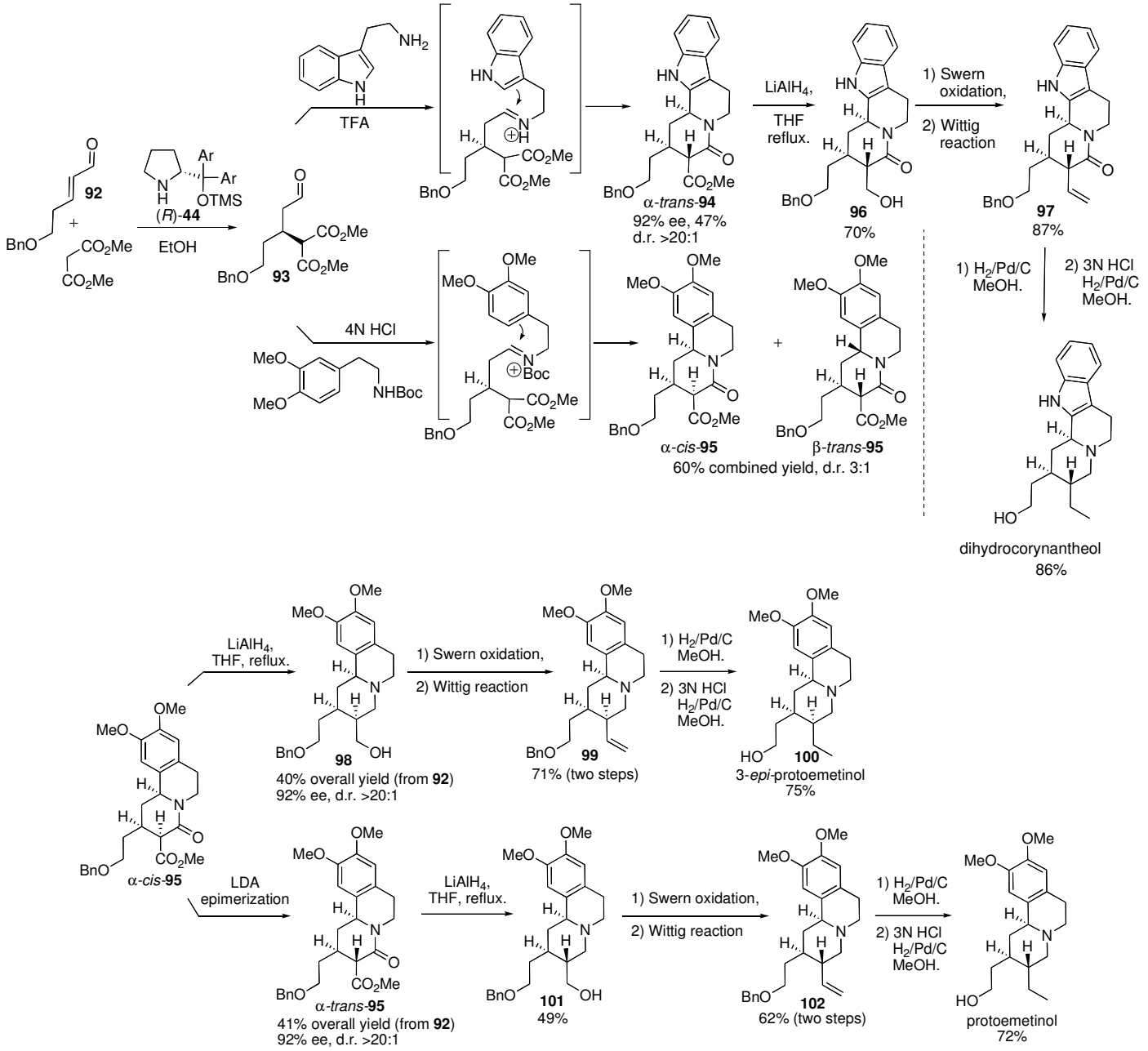
Subsequent reaction of aldehyde **82** with tryptamine under reductive amination conditions gave compound **83** followed by decarboxylation to lactam **84** as a 2–3:1 mixture of inseparable diastereoisomers (Scheme 26).



Scheme 26. Application of key intermediate **82** in the total synthesis of *corynanthe* and *ipecac* alkaloids.

In their approach, Ma *et al.* applied the Bischler-Napieralski reaction, followed by reduction with $NaBH_4$ to construct the piperidine ring which at this point gave separable diastereoisomers **85** and **86** in 26% and 62% isolated yield, respectively. It is interesting to point out that the ring-junction stereocentre is formed exclusively with the α-configuration. Finally, hydrogenation of the benzyl-protecting group of diastereoisomers **85** and **86** gave *corynantheidol* and *dihydrocorynantheol*, respectively. In a second application toward the formal synthesis of *mitragynine*, reaction of aldehyde **82** with 4-methoxytryptamine under non-reductive conditions gave enamine **87** in high yield as a single diastereoisomer (Scheme 26). Stereoselective hydrogenation of enamine **87** upon PtO_2 and subsequent decarboxylation gave the lactam **88**. Further side chain manipulation and Bischler-Napieralski reaction followed by reduction gave ester **89** with the α-*cis*-configuration corresponding to that of *mitragynine*.

In their final application of aldehyde **82** for the synthesis of protoemetinol, reductive amination with 3,4-dimethoxyphenethylamine gave poor or no diastereoselectivity. To avoid epimerization aldehyde **82** was converted to lacton **90** (Scheme 26). Subsequent reaction of the latter with 3,4-dimethoxyphenethylamine followed by Bischler-Napieralski reaction and reduction gave protected protoemetinol **91** with the correct α-*trans*-configuration. In this case, the α-*cis* diastereoisomer was isolated in only 9% yield.



Scheme 27. Córdova's total synthesis of the *corynanthe* and *ipecac* alkaloids.

Córdova's total synthesis is based on a one-pot strategy previously developed by Zhao *et al.*[48] where the three stereogenic centres of the target molecules are generated in a asymmetric conjugate addition/Pictet-Spengler/lactamization process and the retrosynthetic analysis leads back to malonate, 5-benzyloxypentenal **92** and tryptamine or 3,4-dimethoxyphenethylamine (Scheme 24).

The one-pot sequence was initiated by the asymmetric conjugate addition by reaction of malonate and 5-benzoxylpentenal **92** in the presences of catalyst (*R*)-**44** to give the key-intermediate **93** (Scheme 27). From this point, the reaction can be directed either towards the *corynanthe* or *ipecac* alkaloids by adding

tryptamine or 3,4-dimethoxyphenethylamine. Thus the addition of tryptamine and TFA to the reaction mixture containing intermediate **93** initiated a cascade sequence leading up to the α-*trans*-indoquinolizidine derivative α-*trans*-**94** together with its ring-junction epimer β-*tran*-**94** as the major by-product in the ratio of 87:13. The α-*trans*-indoquinolizidine derivative α-*trans*-**94** with the stereochemistry correlating to *dihydro-corynanthenol* was obtained as a single diastereoisomer in 40% overall yield and 92% ee after flash column. A straightforward reduction/oxidation/olefination/deprotection sequence of α-*trans*-indoquinolizidine **94** gave *dihydrocorynanthenol* (Scheme 27). In an attempt to apply this strategy for the synthesis of *ipecac* alkaloids, the authors investigated the three-component one-pot reaction of malonate, 5-benzyloxypentenal **92** and 3,4-dimethoxyphenethylamine in the presences of catalyst (*R*)-**44**. However, under these conditions, no Pictet-Spengler cyclization was observed which is most likely a result of the lower nucleophilicity of the dimethoxyphenyl-group compared to the indole-group. In order to increase the reactivity of the system they used the *N*-Boc-3,4-dimethoxyphenethylamine as the amine component, that, upon condensation with aldehyde **93**, will form the *N*-Boc-iminium ion which is a considerable stronger electrophile compared to the corresponding protonated iminium ion. Thus, reaction of *N*-Boc-3,4-dimethoxyphenethylamine in the one-pot sequence gave the benzoquinolizidine α-*cis*-**95** together with its β-*trans*-epimer in a 3:1 ratio (Scheme 27). The benzoquinolizidine α-*cis*-**95** was directly applied to reduction/oxidation/olefination/deprotection sequence used in the synthesis of *dihydrocorynanthenol* to give the non-natural epimer *3-epi-protoemetinol.* However, to install the relative stereochemistry corresponding to natural *protoemetinol* the diastereomeric mixture of benzoquinolizidine **95** was epimerized using LDA which converted the α-*cis*-benzoquinolizidine α-*cis*-**95** to the required α-*trans*-epimer α-*trans*-**95**. These latter was isolated as single diastereoisomer in 92% ee and 41% overall yield from *N*-Boc-3,4-dimethoxyphenethylamine. Further elaboration through the reduction/oxidation/olefination/deprotection sequence as previously gave *protoemetinol*.

3. Conclusions

The often low availability of natural products from their natural sources and their generally complex molecular scaffold, combined with the lack of structural analogues, create a need for efficient and selective laboratory synthesis. This is especially true if these compounds are to be used as biological probes for drug discovery programs. However, as complexity and size increase, as well as the number of chemical transformations required to assemble the desired molecule, the larger scale preparation of the target molecule is almost impossible. The key to efficiency is to implement asymmetric one-pot multiple reactions and asymmetric cascade/tandem reactions in synthetic strategies. Here the most recent developments of such synthetic strategies are summarized that allow for efficient preparation of a vast number of *corynanthe* and *ipecac* alkaloids, their epimers and analogs. As a result of their efficiency, these strategies open up for quantitative preparations of this class of natural products but also, and more importantly from a pharmaceutical perspective, they provide easy access to a multitude of epimeric and structural analogs that will allow for a much more comprehensive biological study of these natural products, their epimers and analogs.

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THE PRINCIPLE OF VINYLOGY AS APPLIED TO HETEROCYCLIC DONOR SYSTEMS

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Abstract. *Vinylogy and the reactions inspired by this principle occupy a rewarding position in the arsenal of chemical transformations. This review celebrates this principle, as applied to three enabling carbon–carbon bond formations, the aldol, Mannich and Michael reactions. Highlighted are those reactions involving heterocyclic vinylogous nucleophilic or pro-nucleophilic candidates, through which myriad of multifunctional molecular frameworks and targets could be synthesized. In this review, we mainly discuss investigations focusing on furan- and pyrrole-based donors, which appeared in the literature during the 2010–2012 triennium.*

Contents

1. Introduction

About 80 years ago, Reynold C. Fuson[1] published a limpid paper entitled "The Principle of Vinylogy". It was 1935 and organic chemistry had just finished celebrating its first hundredth birthday, with many pillars of organic synthesis being firmly established. The first sentence of the article read: "*It has long been recognized that, in a molecule containing a system of conjugated double linkages, the influence of a functional group may sometimes be propagated along the chain and make itself apparent at a remote point in the molecule*". In other words, it simply states that a given functional group within a molecule may exert its function beyond the boundaries of the attached atoms and it may be relayed to a distant point in the molecule provided that interposed conjugated unsaturated linkages are present. Fuson's principle took the following form: "*When in a compound of type A–E_1=E_2 or A–E_1≡E_2, a structural unit of type –(CH=CH)$_n$–*

is interposed between A and E_1, the function of E_2 remains qualitatively unchanged, but that of E_1 may be usurped by the carbon atom attached to A".[1]

Typical examples of vinylogous series are displayed in Figure 1. Thus, glutaconic ester **2**, oxalyl crotonic ester **3** and homophthalic ester **4** are the vinylogous extensions of malonic ester **1**, while acrylonitrile **6**, sorbic nitrile **7** and *p*-methyl-substituted aryl cyanides **8**–**10** are the vinylogous counterparts of acetonitrile **5**. As a consequence, the molecules within these series share common properties, such as the acidic character of the methylene or methyl groups, as well as the pro-nucleophilic reactivity of the enolizable positions.

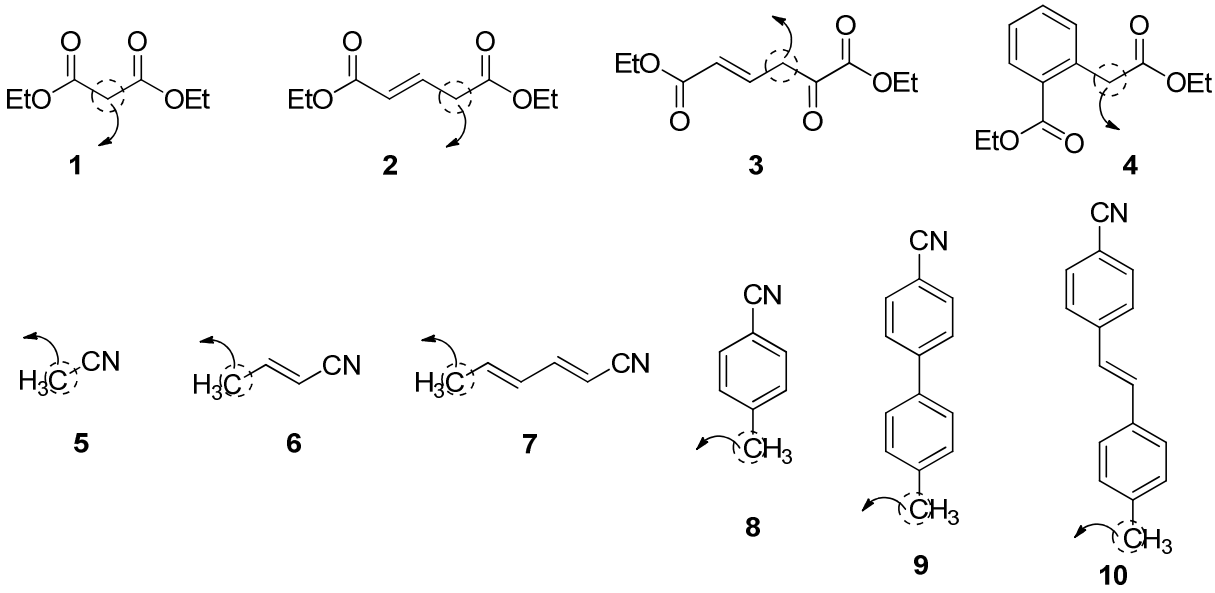


Figure 1. Malonic ester- and acetonitrile-based vinylogous series. Arrows show the reactive points in the molecules. Reactivity is qualitatively independent of the number of interposed conjugated vinylene linkages.

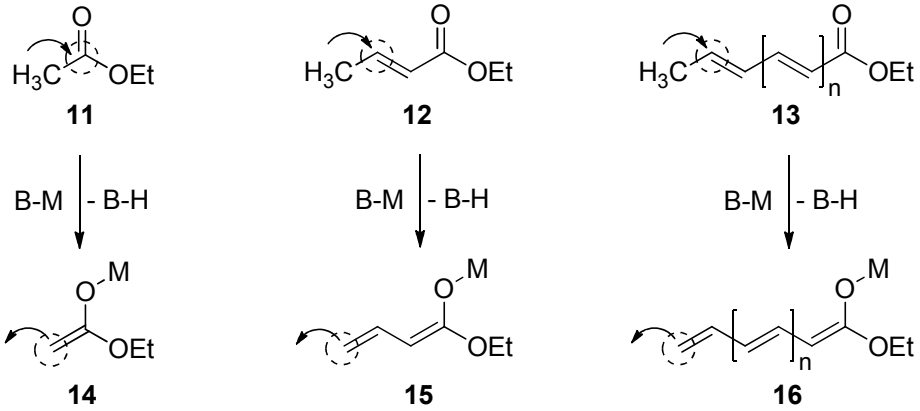


Figure 2. Acetate ester-based vinylogous series. Arrows show the reactive points in the molecules. Reactivity is qualitatively independent of the number of interposed conjugated vinylene linkages.

Focusing on the aldol domain, a classical vinylogous series is given by ethyl acetate **11**, ethyl crotonate **12** and higher homologues **13** (Figure 2). Considering the carbonyl electrophilicity as a function, the "normal" 1,2-nucleophilic addition in **11** may be usurped by the 1,4-, 1,6-, 1,8-, etc. additions in **12** and **13**. Thus, the popular Michael addition reaction can be viewed as the vinylogous version of the simple 1,2-nucleophilic addition to a carbonyl. Swapping from acceptor to donor character, say for example by

base-promoted enolization, an emblematic vinylogous donor series is unveiled, including the normal enolate ester **14**, the vinylogous enolate **15** and higher enolates **16**. Here, the normal electrophilic attack at the α-position may be usurped by the competing γ-, ε-, η-, etc. sites, thus extensively widening the synthetic opportunities of the aldol chemistry.

In the same manner, imine-to-enamine swapping generates two additional acceptor/donor vinylogous series, with imines **17–19** and enamines **20–22** involved (Figure 3). In this special case, enamines **20–22** are the nitrogen counterparts of the enolate scaffolds, possibly sharing similar reactivity.

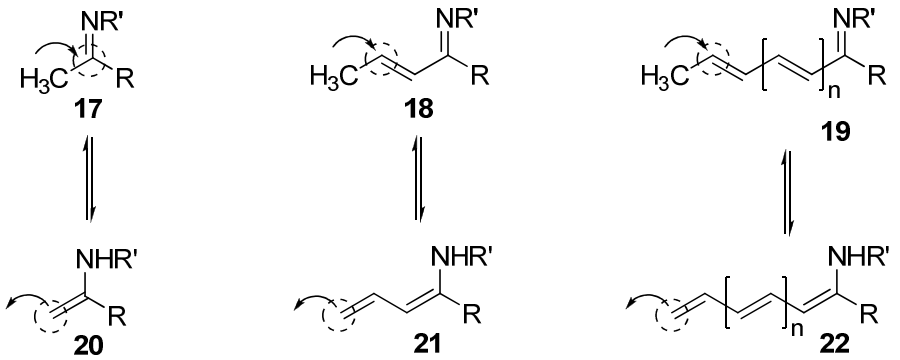


Figure 3. Imine- and enamine-based vinylogous series. Arrows show the reactive points in the molecules. Reactivity is qualitatively independent of the number of interposed conjugated vinylene linkages.

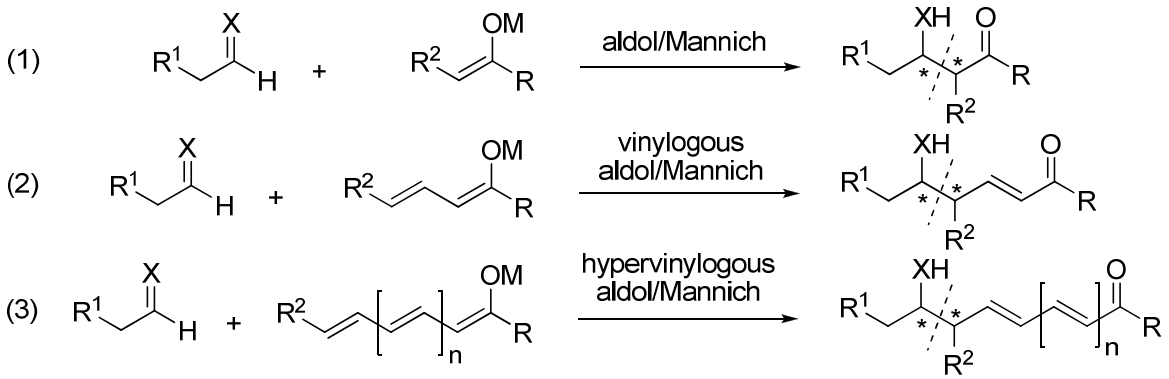


Figure 4. The evolution of the aldol/Mannich chemistry: how vinylogy impacts the product complexity (X=O, NR).

Noteworthy, products arising from vinylogous transformations – be they aldol, Mannich or Michael adducts – inherently embody much higher complexity as compared to their normal addition counterparts, as shown in Figures 4 and 5. Strictly speaking, a reaction may be translated to its vinylogous counterparts by using either an extended donor (the most common practice, *e.g.* Figure 4, eqs 2 and 3), an extended acceptor (the Michael-type technology, *e.g.* Figure 5, eqs 1 and 3) or both (almost neglected for highly extended executions, *e.g.* Figure 5, eqs 2 and 4).

Thus, in passing from normal to vinylogous extensions, the distance between the emerging functionalities within the products increases, as the number of the interposed conjugated double bonds increases. However, the higher the molecular complexity, the greater the critical issues concerning the reaction become: that is, production and control of the (poly)enolate geometry; channeling correct reactivity; governing chemo-, regio- and stereoselectivity; directing the geometry and positioning of the emerging double bonds. Full mastery of these issues gauges how vinylogy has evolved within these fundamental domains of organic chemistry.

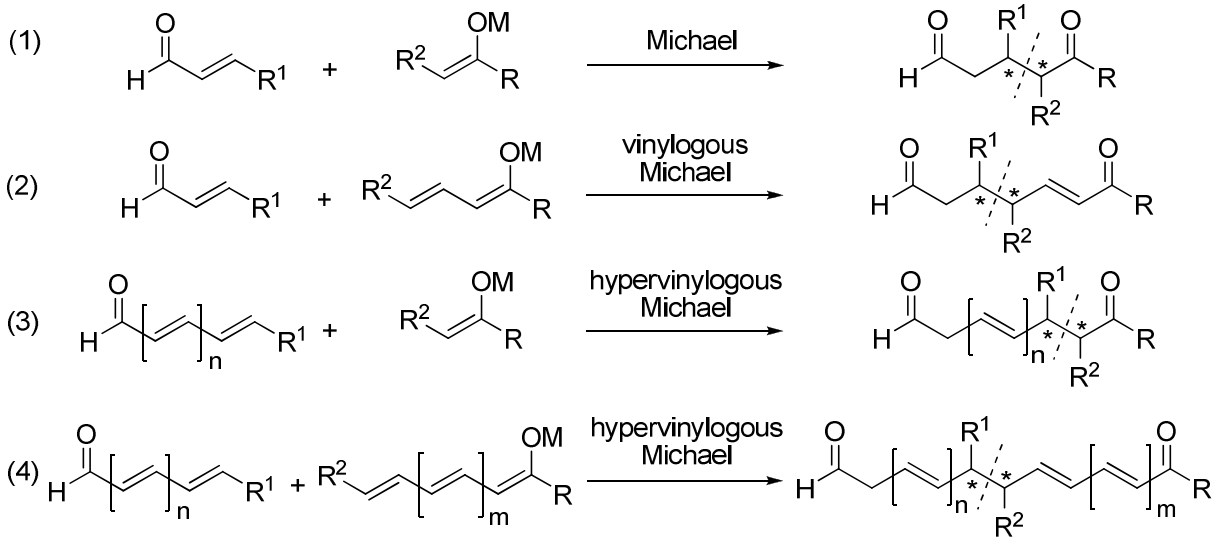


Figure 5. The evolution of the Michael chemistry: how vinylogy impacts the product complexity.

2. About this review

Both indirect and direct methodologies using vinylogous carbon nucleophiles and featuring an heterocyclic scaffold are covered in this article. Attention is paid to reactions involving vinylogous and multi-vinylogous donor entities, while examples where simple donors and extended acceptors are involved do not fall within the scope of this review.[2] Prototypical donors in this review are listed in Figure 6, including Mukaiyama-type furan- and pyrrole-based silyl dienolates and polyenolates, their pro-nucleophilic counterparts, as well as few candidates embodying the indole, γ-pyrone, phthalide, phenol and azlactone skeletons.

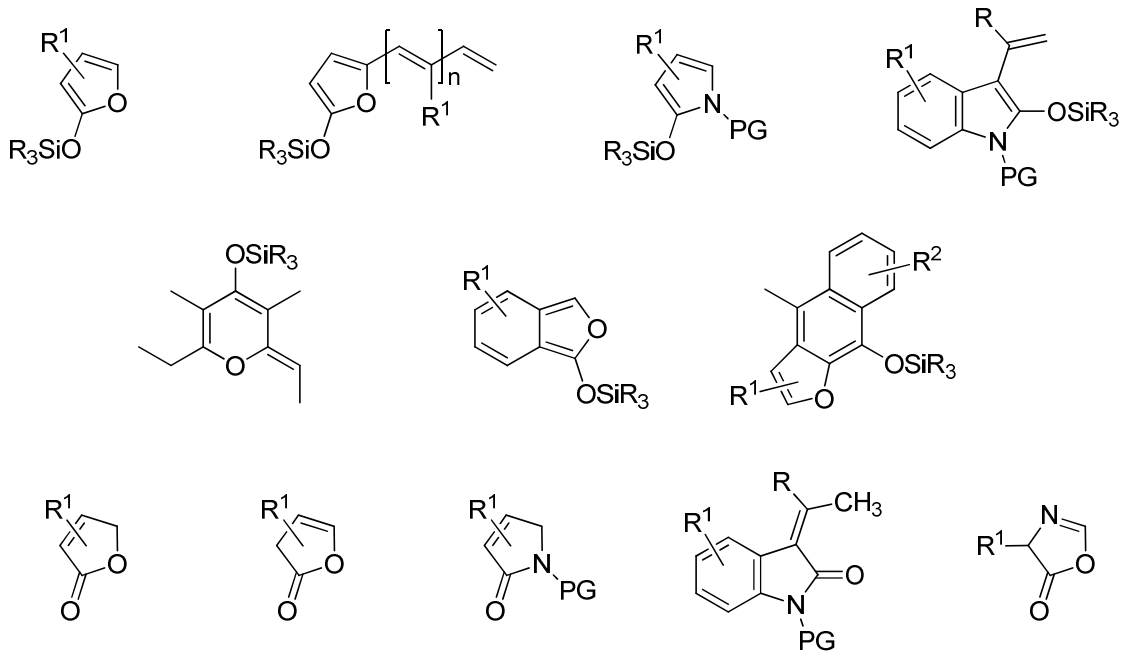


Figure 6. The structures of nucleophilic and pro-nucleophilic vinylogous donor heterocycles in this review.

While the reactivity of these compounds spans a wide synthetic domain, with a number of carbon-carbon and carbon-heteroatom bond-forming reactions involved, it is the aim of this article to direct the focus to pivotal transformations related to aldol, Mannich and Michael chemistry. Our choice here is to highlight examples covering the very recent literature (2010–2012), with a brief digression to condense

previous important achievements of the new millennium. Special emphasis is due to asymmetric syntheses allowing access to chiral nonracemic substances, exploiting both diastereoselective and enantioselective catalytic strategies. This review is intended to be selective rather than exhaustive; for comprehensive coverage of this emerging topic we direct the reader to general and specialized review articles in the current literature.[3]

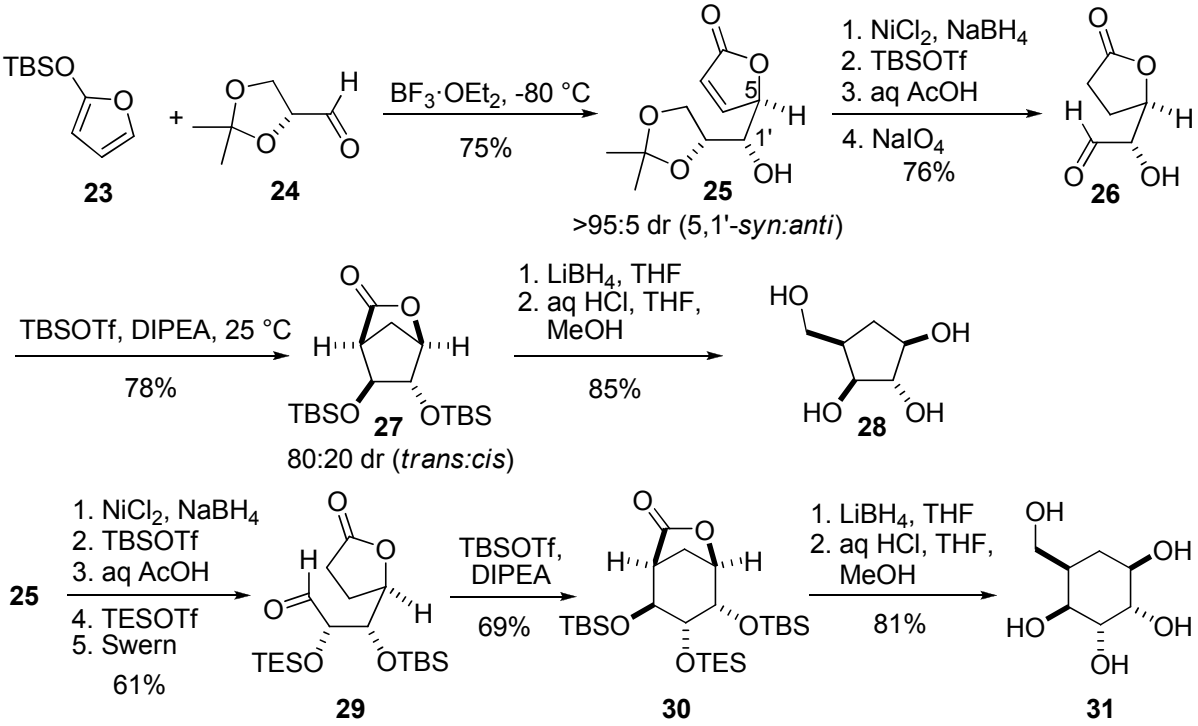
3. Indirect Mukaiyama-type methodologies

Indirect executions are those reactions where the donor substrates are stoichiometrically activated prior to the reactant approach. The most common practice involves preparation of relatively stable silicon enolates – Mukaiyama-type donors – which can be either isolated or generated *in situ*. In the vinylogous realm, useful matrices are γ-enolizable α,β-unsaturated carbonyl frameworks which can be embodied into variously shaped molecules, spanning from linear carbon skeletons to alicyclic or heterocyclic scaffolds. Remarkably, silicon lends a big hand to vinylogy, since extended silyl enolates have the intrinsic propensity to privilege reactions at their remote sites, as demonstrated by a plethora of experimental evidences, as well as confirmed by calculations.[3f] Analyses here are organized according to the nature of the heterocyclic donors, with aldol, Mannich and Michael executions grouped and discussed sequentially.

3.1. Furan-based silicon enolates

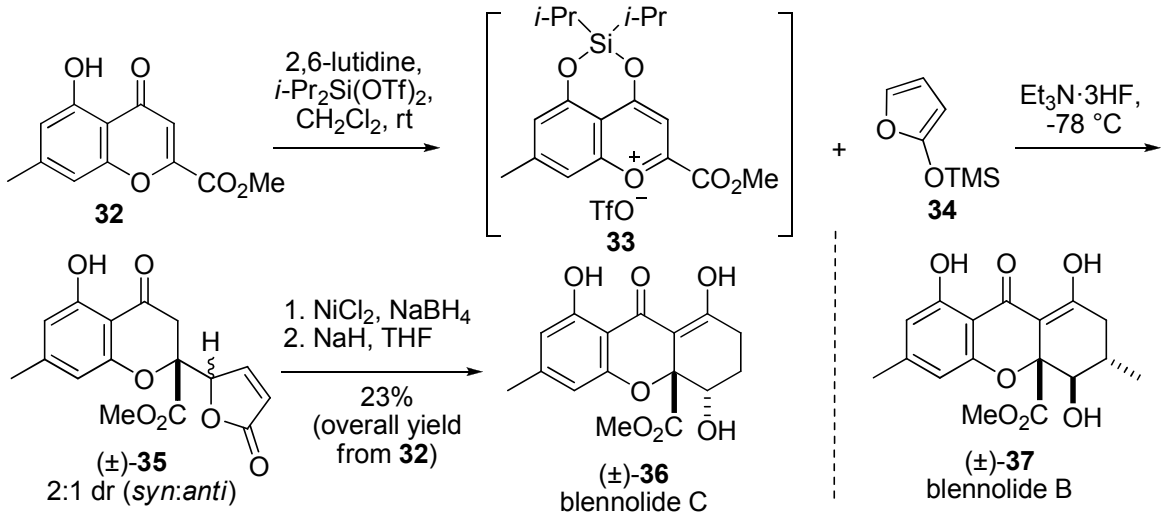
Furan compounds, including tetrahydrofuran and γ-butenolide polyketide scaffolds, are privileged structures widely encountered in Nature and their synthesis has therefore received considerable attention. Among the various ways to access these compounds, the elaboration and functionalization of furan-based precursors occupy a relevant position, owing to the intrinsic directness and simplicity of execution. In this context, γ-functionalization of nucleophilic 2-silyloxyfurans by means of proper electrophilic acceptors, such as carbonyl compounds, imine or iminium derivatives and α,β-unsaturated carbonyls has been definitely established as an attractive synthetic technique, through which realms of simple and complex molecular entities have been assembled.

In 2002–2004, Casiraghi and co-workers[4,5] designed and exploited a general, diastereoselective methodology to access cyclitol and carbasugar compounds in a chiral, nonracemic form by starting with heterocyclic dienoxy silane compounds and sugar-related enantiopure carbonyls. Key to the success of the technique was a sequence of two diastereoselective manoeuvres, a vinylogous aldol reaction followed by a highly productive silylative intramolecular aldolization. As an example, Scheme 1 illustrates how 2-*tert*-butyldimethylsilyloxy furan **23** served in the synthesis of both five-membered and six-membered cyclitols of type **28** and **31**. Initially, the vinylogous aldol reaction between **23** and protected D-glyceraldehyde **24** under $BF_3{\cdot}OEt_2$ agency gave the expected butenolide adduct **25** in high yield, with complete γ-site-selectivity and excellent diastereoselectivity in favour of the *syn*-configured isomer. Subsequent manipulation, including one-carbon shortening of the carbon skeleton, provided protected aldehyde **26** ready for the crucial carbocyclization. After extensive optimization, this manoeuvre was successfully accomplished by exposure of **26** to a balanced mixture of TBSOTf and DIPEA (3.0 equiv each), to furnish the bicycle **27** in high yield and 80:20 *dr*. With the carbocycle installed, simple reductive excision of the lactone ring and global deprotection finally provided the targeted carbasugar **28** in good yield. Paralleling this chemistry, butenolide **25** was advanced to carbapyranose **31** *via* the intermediacy of aldehyde **29** and bicycle **30**.



Scheme 1. Synthesis of 4a-carba-β-D-xylofuranose **28** and 5a-carba-β-D-gulopyranose **31**.[4,5]

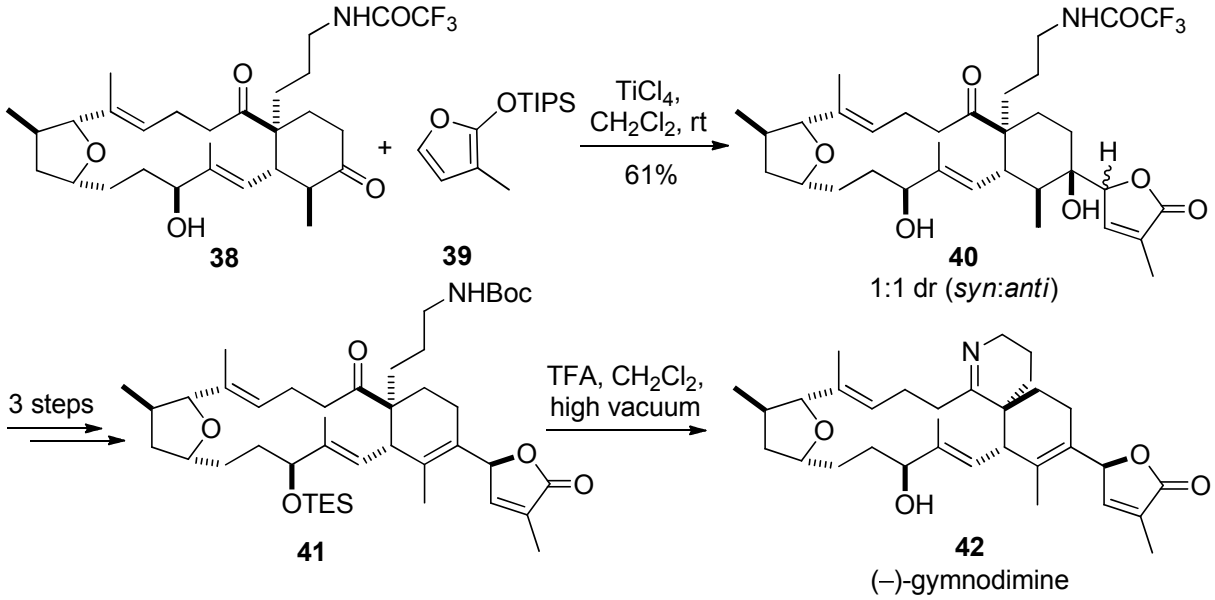
The utility of furan-based dienoxy silane nucleophiles was further demonstrated by Porco Jr. *et al.*[6] in a concise diastereoselective synthesis of racemic blennolides C and B, representative members of the tetrahydroxantone class of mycotoxins. As shown in Scheme 2, addition of furan **34** to benzopyryllium salt **33**, generated *in situ* from hydroxychromone **32**, gave butenolide adduct **35** as a 2:1 mixture of epimers (thermodynamic control). After double bond saturation, Dieckmann cyclization using NaH in THF led to blennolide C (±)-**36** in 23% overall yield for the entire sequence. In about a similar manner, blennolide B (±)-**37** and few epimeric congeners were also prepared.



Scheme 2. Diastereoselective entry to blennolide C (±)-**36**.[6]

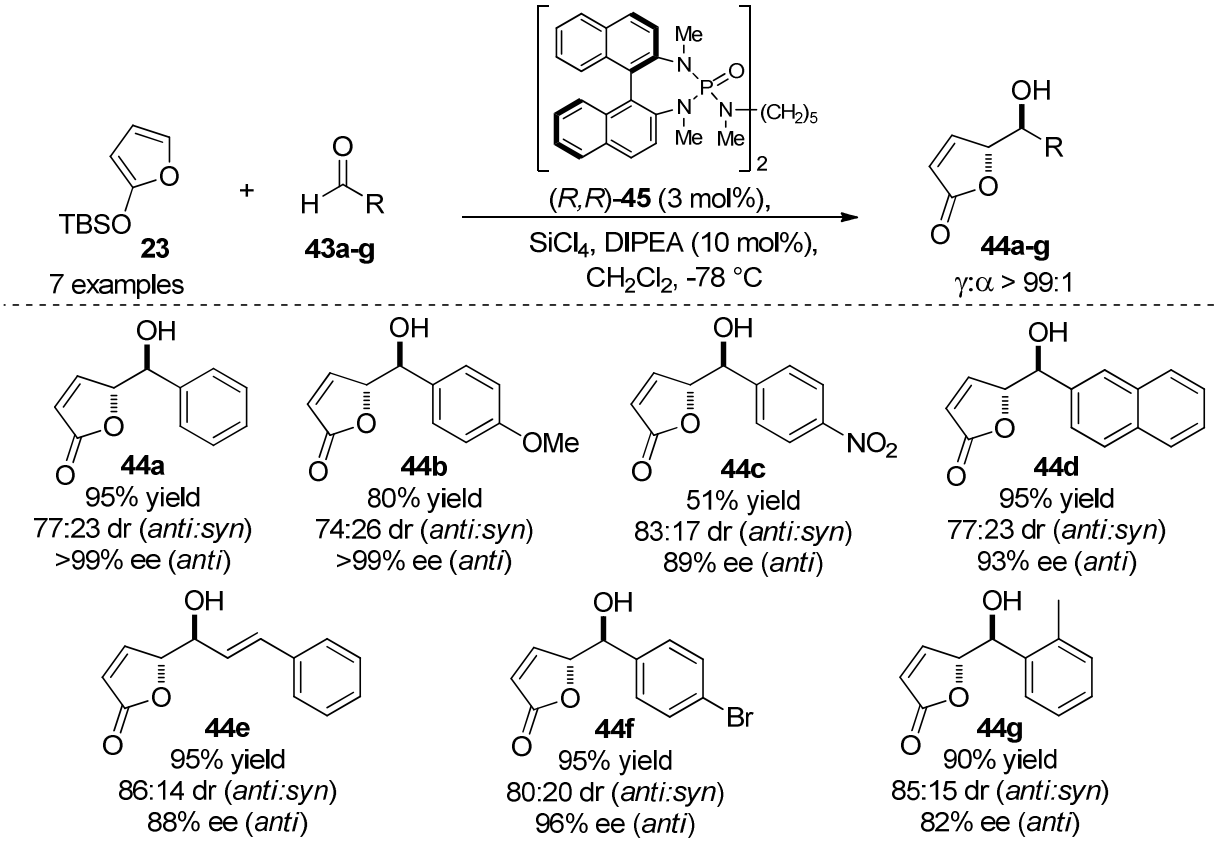
The imine-containing marine toxin (−)-gymnodimine **42** was the target of a brilliant total synthesis by Romo and co-workers (Scheme 3).[7] The butenolide moiety of this complex metabolite was introduced at a late stage of the synthesis employing a vinylogous Mukaiyama aldol addition of a silyloxy furan to a complex cyclohexanone intermediate. Thus, brief exposure of ketone **38** and methyl-substituted furan **39** to

$TiCl_4$ in CH_2Cl_2 gave an almost 1:1 mixture of epimeric butenolides **40** in 61% yield. Subsequent enrichment in the desired epimer, dehydration and protecting groups adjustment produced **41**, the immediate precursor of the target. Treatment of protected amine **41** with TFA cleaved the *N*-Boc group with concomitant desilylation. Upon standing under high vacuum, the free amine underwent smooth cyclization to provide the corresponding imine **42**. In an analogous fashion the C4 epimer of the target was prepared.



Scheme 3. Synthesis of (–)-gymnodimine **42**.[7]

The vinylogous aldol reaction of furan-based silyl dienolates proved to work well even in an enantioselective environment.[8]

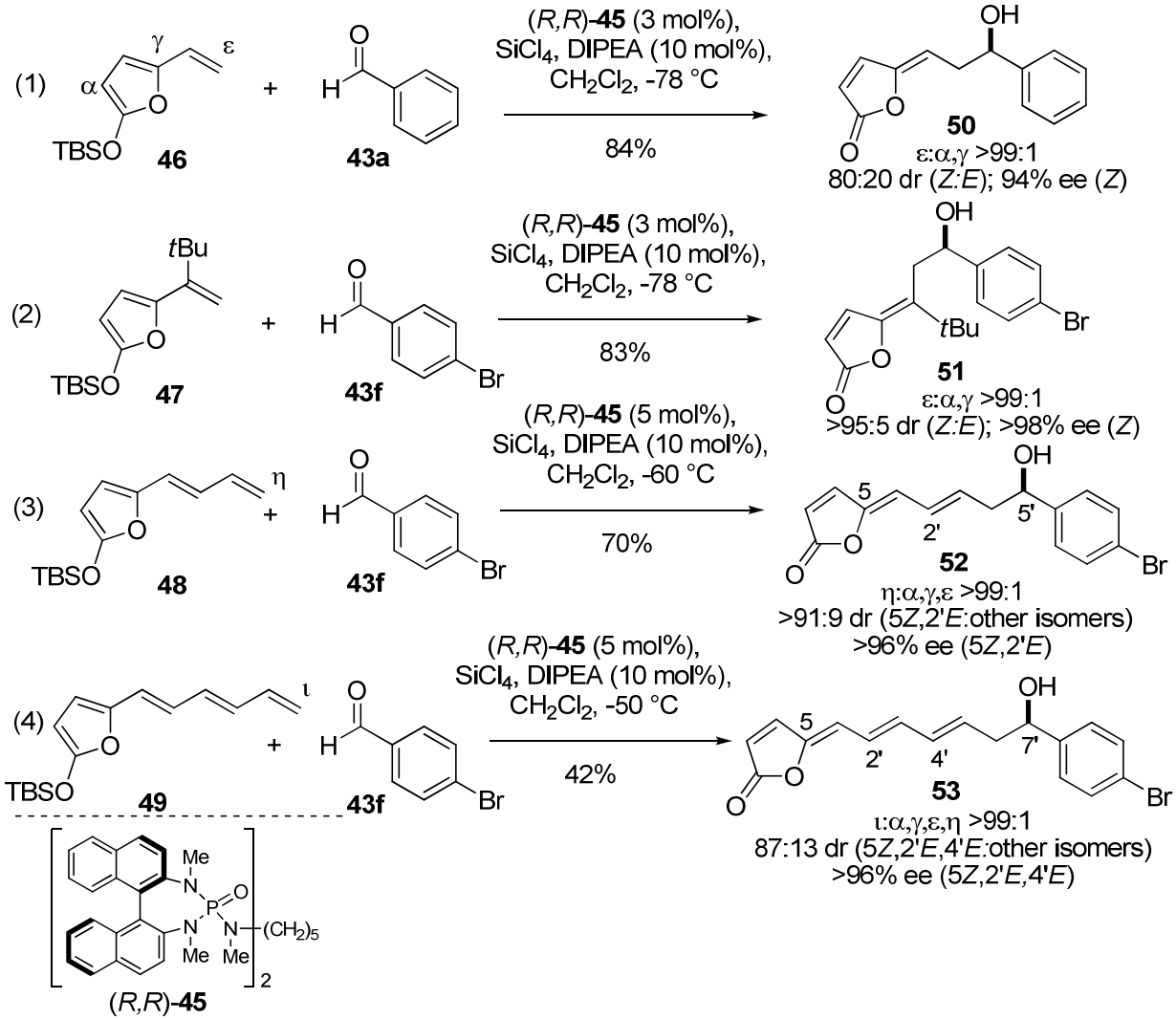


Scheme 4. Catalytic, asymmetric vinylogous Mukaiyama-aldol reactions of furan silyl dienolates.[8a]

After scrutinizing a series of known chiral metal- and organocatalysts, Zanardi *et al.*[8a] found that the bis-phosphoramide/silicon tetrachloride dual system – introduced and widely exploited by Denmark[9] in the aldol and vinylogous aldol chemistry – catalyzed the asymmetric addition of furan **23** to aromatic aldehydes **43** (Scheme 4).

Irrespective of the nature of the substituents in the aromatic aldehydes, be they neutral, π or σ electron-donating or electron-withdrawing groups, all reactions were productive using as little as 3 mol% catalyst and gave rise to the desired vinylogous adducts **44a–g** in excellent yields, perfect regioselectivity and good diastereoselectivity in favour of the *anti*-isomers, with outstanding levels of enantioselectivity (for comparison with the behaviour of the pyrrole counterparts, see Section 3.2.).

A valuable advance toward the multivinylogous variant of these heterocycles was introduced by the same research group very recently,[10] by synthesizing variously elongated polyene furans of type **46**–**49** *via* mild ω-deprotonation and silyl trapping of the corresponding butenolide polyene precursors. The reactivity of these extended matrices was explored in the asymmetric aldol reaction domain by using the previously mentioned Denmark's catalyst system **45**·$SiCl_4$. Emblematic examples are given in Scheme 5 (eqs 1–4).

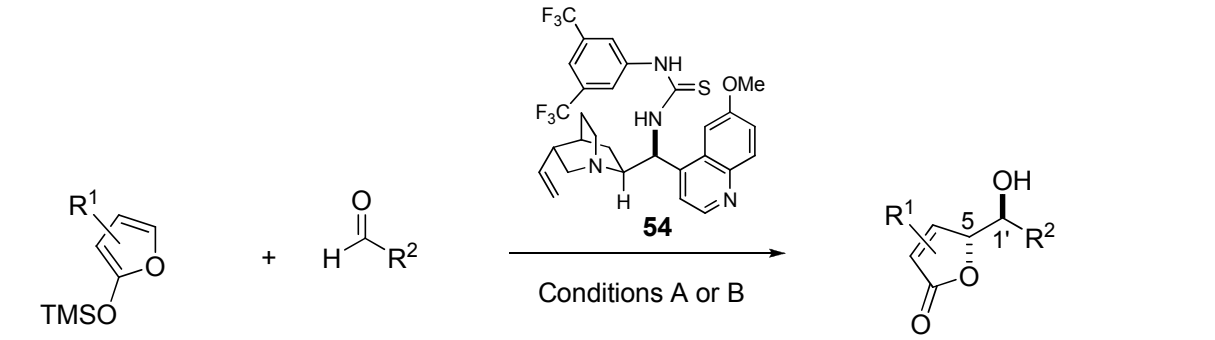


Scheme 5. Catalytic, asymmetric hypervinylogous Mukaiyama-aldol reactions of extended furan silyl dienolates.[10]

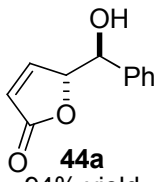
A matter of concern with the elongated nucleophiles **46**–**49** might be the concomitant activation of more than one nucleophilic site. Density Functional Theory (DFT) and Fukui function calculations were

performed to support the rationale for a favoured activation at the most remote site of the chain. Indeed, atomic Fukui indices at the reacting carbon atoms foresee a preferential electrophilic attack of the aldehyde carbonyl at the terminal carbon sites of the nucleophiles. Actually, results went beyond the expectations and reactions performed well with all candidates, providing the desired elongated butenolides of type **50**–**53** (Scheme 5) in moderate-good yields, perfect ω-site selectivity, and excellent enantioinduction. Noteworthy, in many instances, control of the geometry of the newly installed double bonds was rewarding.

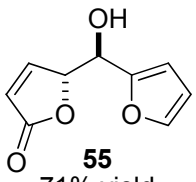
In 2010, Deng and co-workers[11] and Wang and co-workers[12] independently reported the first examples of asymmetric vinylogous aldol reactions of silyloxy furans utilizing bifunctional *Cinchona* alkaloid-thiourea organocatalysts. Salient results are grouped and confronted in Scheme 6.



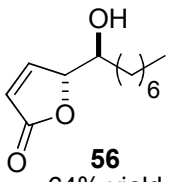
Conditions A[ref. 11]: **54**·CF_3CO_2H (10 mol%), Et_2O/CH_2Cl_2 (1:1), -20/23 °C; 1N HCl/THF; 21 examples



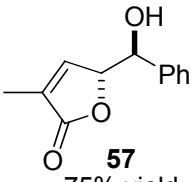
44a
94% yield
95:5 dr (*anti*:*syn*)
95% ee (*anti*)



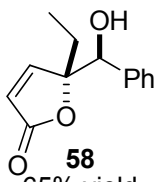
55
71% yield
84:16 dr (*anti*:*syn*)
93% ee (*anti*)



56
64% yield
82:18 dr (*anti*:*syn*)
80% ee (*anti*)

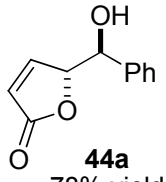


57
75% yield
93:7 dr (*anti*:*syn*)
94% ee (*anti*)

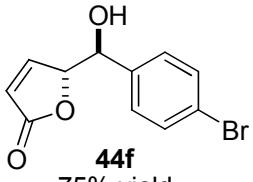


58
65% yield
95:5 dr (*anti*:*syn*)
81% ee (*anti*)

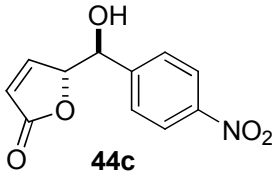
Conditions B[ref. 12]: **54** (20 mol%), $CHCl_3$, -20 to 0 °C; 13 examples



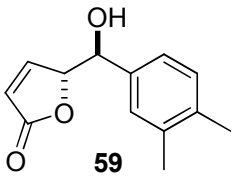
44a
78% yield
89:11 dr (*anti*:*syn*)
86% ee (*anti*)



44f
75% yield
88:12 dr (*anti*:*syn*)
84% ee (*anti*)



44c
78% yield
88:12 dr (*anti*:*syn*)
91% ee (*anti*)



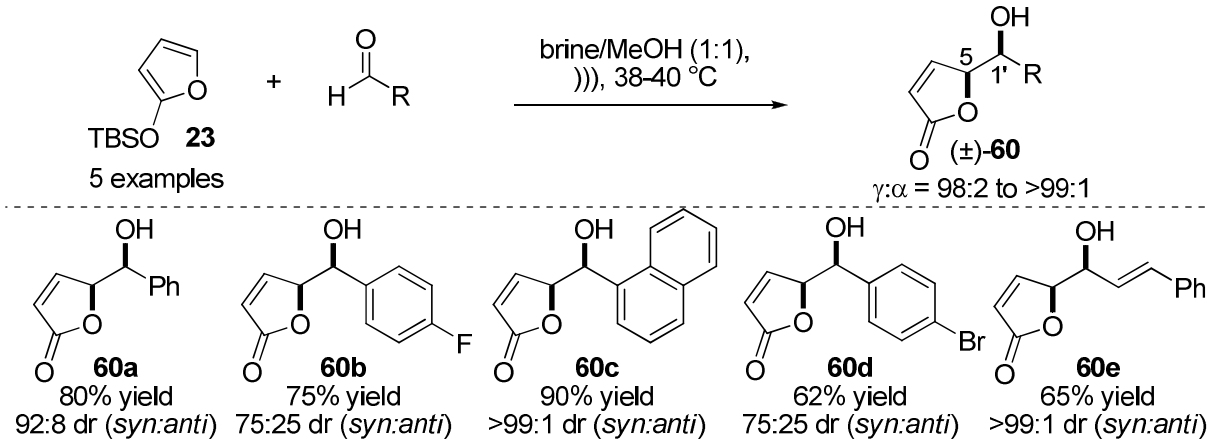
59
82% yield
86:14 dr (*anti*:*syn*)
86% ee (*anti*)

Scheme 6. Organocatalyzed asymmetric vinylogous aldol reactions of silyloxy furans with aldehydes.[11,12]

Deng[11] found that a carboxylate ammonium salt prepared from thiourea-quinine **54** and trifluoroacetic acid in a 1:1 CH_2Cl_2/Et_2O solvent mixture was extremely effective to trigger the reactions of variously substituted silyloxy furan donors with aromatic and aliphatic aldehydes. Reactions performed well and furnished the corresponding *anti*-disposed butenolides in high yields, good diastereoselectivity and enantioselectivity for the (5*R*,1′*S*)-configured isomers. A catalytic cycle was proposed where the carboxylate of the organocatalytic complex is postulated to serve a dual role: activating the silyloxy furan and facilitating the silyl transfer from the nucleophile to the aldolate product. Of note, stereostructures were diligently

established by X-ray crystallographic analyses and chiro-optical measurements. In a parallel work, Wang[12] studied the same reaction utilizing free quinine-thiourea base **54** as the catalyst. With 20 mol% catalyst loading in $CHCl_3$ at −20 to 0 °C, unsubstituted furan donor coupled to various aromatic aldehydes to return *anti*-adducts with good results. Although the relative and absolute configuration of the aldols were not adequately certified, the major products were claimed to possess an *anti*-(5*R*,1′*S*)-configuration, in line with the previously reported results of Deng and co-workers.

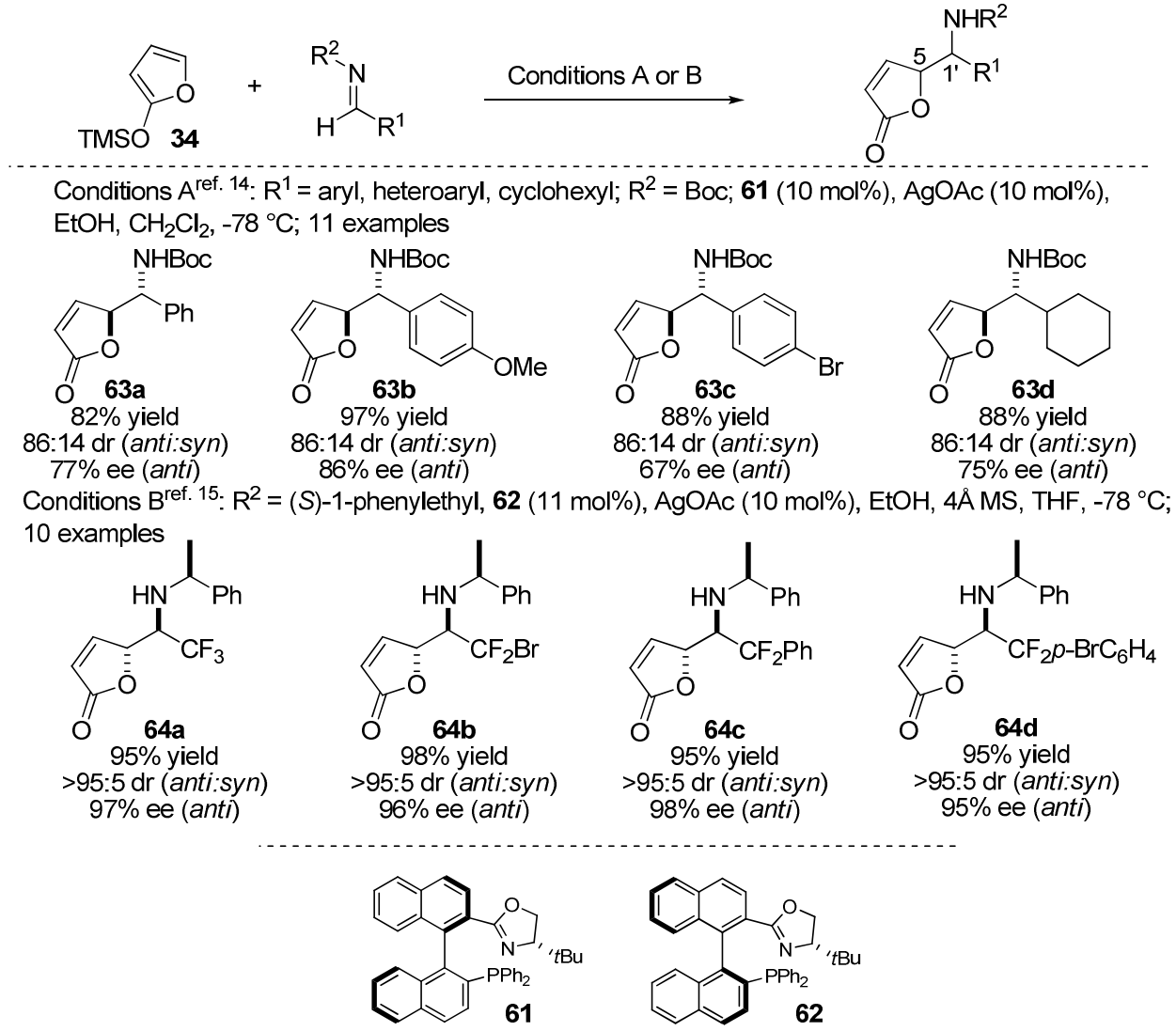
The classical Mukaiyama aldol reaction is carried out under the agency of Lewis acid activators. Indeed, a couple of years ago, Curti *et al.*[13] performed the vinylogous aldol reaction of furan (and pyrrole, see Section 3.2.) silyloxy dienes in an aqueous environment without any other catalyst or additive. Simply using salty water in methanol, silyloxy furan **23** underwent smooth addition to various aromatic and α,β-unsaturated aldehydes at about 40 °C under ultrasonic irradiation (Scheme 7). Interestingly, reactions proved to be *syn*-selective, providing butenolides of type **60** in good isolated yields, with complete γ-site-selectivity and moderate to excellent diastereomeric excesses. It was speculated that the reaction occurs at the boundary between water and dispersed droplets of lipophilic reactants, with some molecules of water acting as H-bond donor species. With furan-based nucleophiles, a stacking synclinal transition state model would seem favoured with both the aldehyde carbonyl and furan oxygen exposed to the aqueous interface.



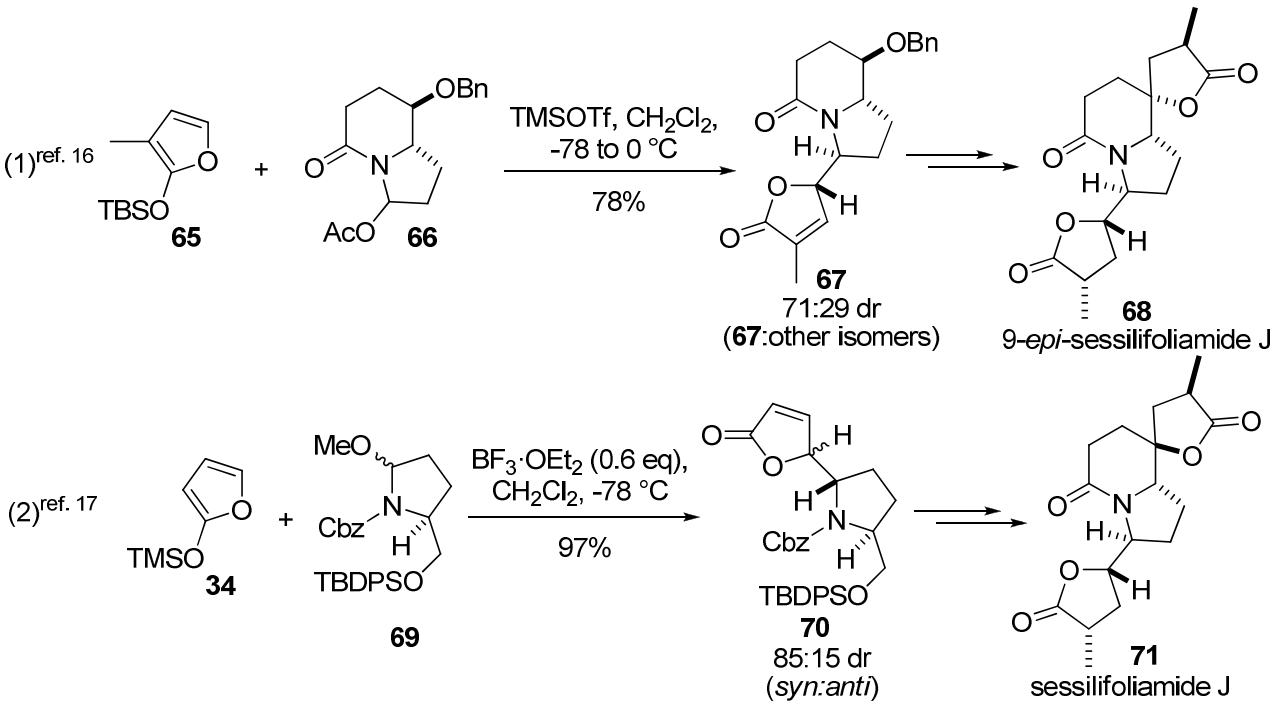
Scheme 7. Uncatalyzed, diastereoselective vinylogous Mukaiyama aldol reactions in aqueous media.[13]

Axially chiral phosphine-oxazoline ligands of type **61** and **62** (Scheme 8) were found to be fairly effective chiral ligands in silver(I)-catalyzed asymmetric vinylogous Mannich reactions of trimethyl silyloxy furan **34** to *N*-Boc aldimines,[14] or fluorinated and chiral imines.[15] Specifically, Shi *et al.*[14,15] discovered that the reaction behaviours proved to be extremely efficient, furnishing the expected chiral adducts with good *anti*-selectivity and moderate to excellent margins of enantioselectivity. While exploitation of (a*R*,*S*)-configured catalyst **61** produced (5*S*)-*anti* products **63**, reaction with (a*S*,*S*)-catalyst **62** led to (5*R*)-*anti* products of type **64**, highlighting the crucial role of the axial chirality in the chirality transmittal to the products. The phenyl-ethyl chiral auxiliary within the imines only exerts a moderate matched effect that proved beneficial to the overall diastereo- and enantiocontrol.

Furan-based silyloxy dienes **65** and **34** were the scaffolds of choice during two remarkable total syntheses of 9-*epi*-sessilifoliamide J **68**[16] and sessilifoliamide J **71**,[17] two members of the polycyclic alkaloid family isolated from plants of the genus *Stemona* (Scheme 9). In the first contribution, Huang and co-workers[16] utilized a diastereoselective vinylogous Mannich addition of methyl-substituted furan **65** as the key reaction, with which intermediate **67** was assembled.



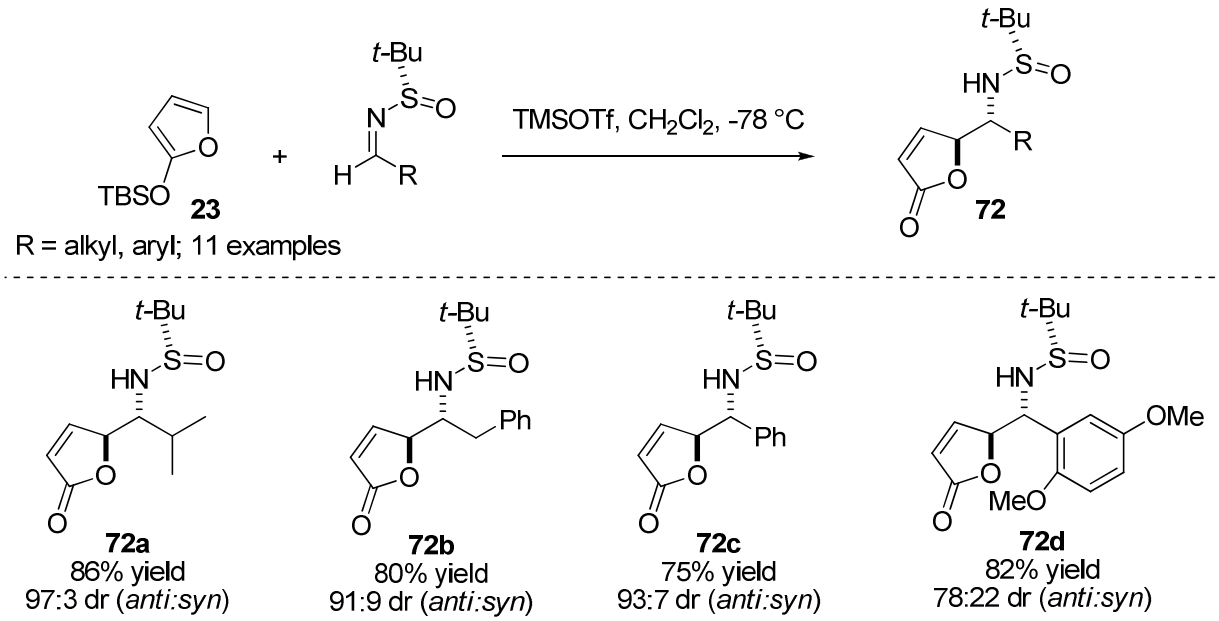
Scheme 8. Diastereo- and enantioselective vinylogous Mannich reactions of 2-trimethylsilyloxy furan **34**.[14,15]



Scheme 9. Key vinylogous Mannich reactions during the total synthesis of *Stemona* alkaloids **68** and **71**.[16,17]

Advancement to the target **68** required four additional steps to conclude the synthesis in 10 steps, with a 4.3% overall yield. Here, the furan matrix **65** was used to forge the non-spirocyclic butanolide fragment of the molecule.

On the other hand, in a subsequent contribution, the same authors[17] utilized furan **34** to assemble the fused piperidin-2-one core of the alkaloid *via* a highly diastereoselective vinylogous Mannich reaction with the iminium ion derived from *N*,*O*-acetal **69**, followed by ring enlargement. Overall, the entire sequence to sessilifoliamide J encompassed 12 steps with a 7.7% global yield.

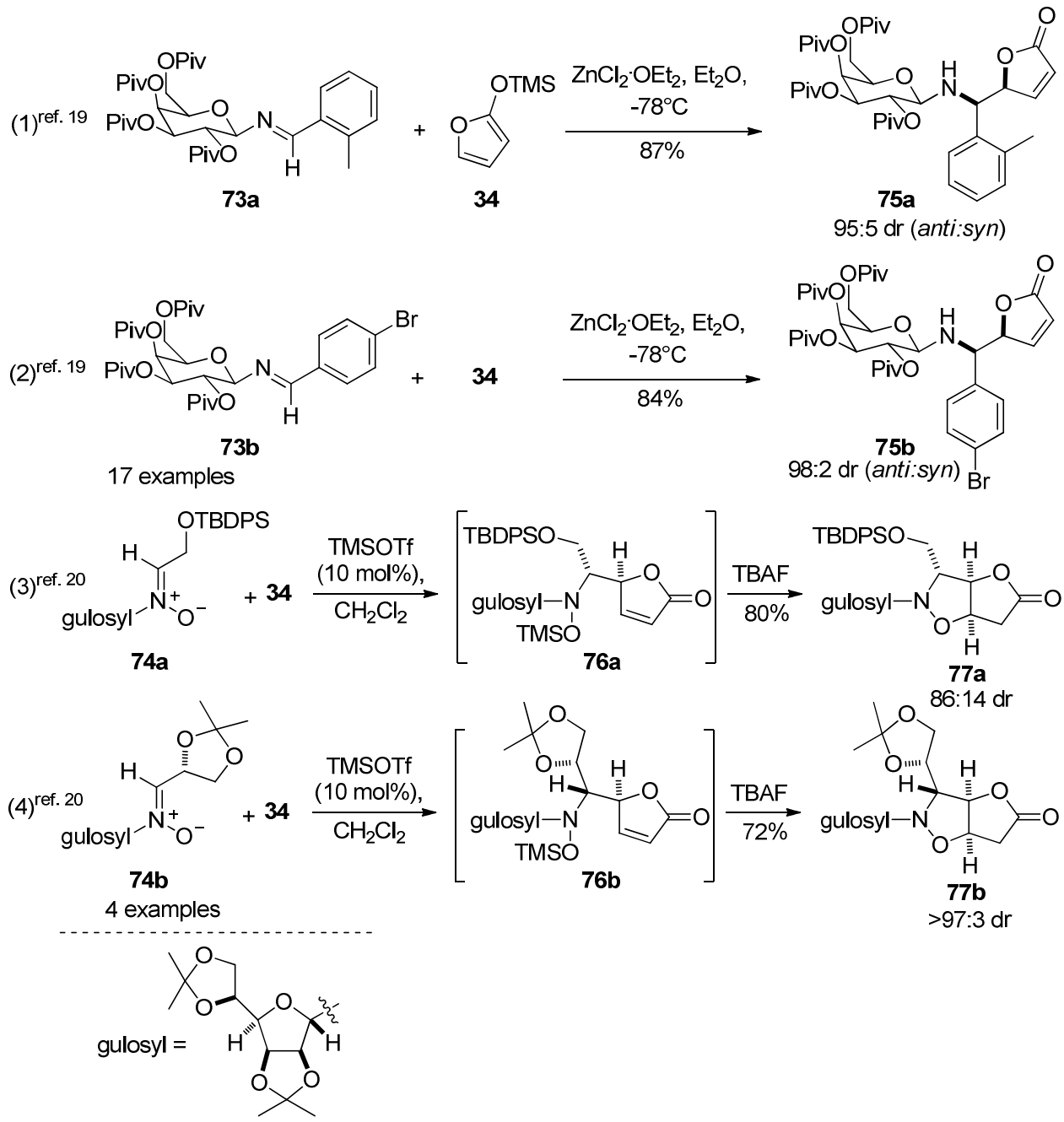


Scheme 10. Asymmetric vinylogous Mannich reactions of furan **23** with chiral nonracemic *N-tert*-butanesulfinimines.[18]

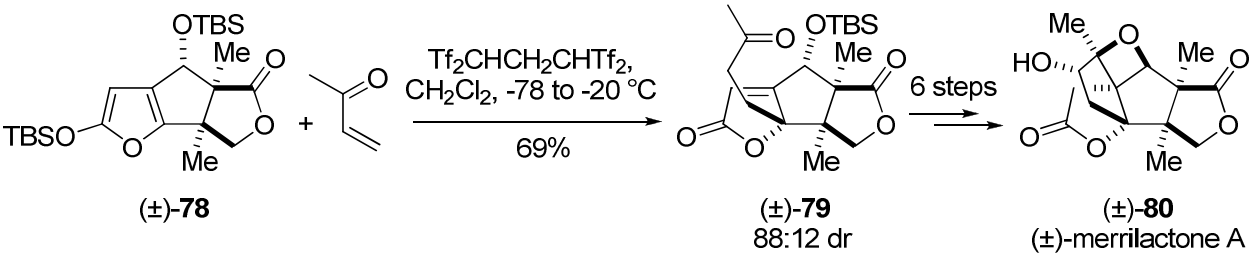
A chiral auxiliary-type asymmetric approach to functionalized aminated butenolide scaffolds and chiral nonracemic piperidine derivatives was developed by Huang's research group[18] utilizing various *N-tert*-butanesulfinimines as the chiral amine templates. Reactions with furan dienoxy silane **23** eventually returned a repertoire of aminated butenolides of type **72** where *anti*-disposed representatives uniformly predominated (typically >90:10 *dr*) (Scheme 10). The utility of the butenolide products in this study was nicely demonstrated by their transformation into a variety of enantioenriched nitrogen heterocycles, including five-membered lactone and six-membered lactam compounds.

The chiral auxiliary technique to access δ-amino-α,β-unsaturated lactones and derivatives thereof was independently explored by the Chen[19] and Tamura[20] groups utilizing vinylogous Mannich reactions between silyloxy furan **34** and *N*-galactosyl imine (**73**) or *N*-gulosyl nitrone (**74**) acceptors (Scheme 11).

In the former examples (eqs 1 and 2), zinc chloride etherate in Et_2O was employed as the activator, while in the latter (eqs 3 and 4) the reactions were driven by catalytic amounts of Me_3SiOTf in CH_2Cl_2. Upon removal of the sugar moiety, compounds **75** were transformed to the corresponding free amines, whereas *in situ* treatment of intermediary compounds **76** with catalytic TBAF allowed for intramolecular oxa-Michael addition to furnish bicyclic products **77**. Of note, the major isomers **77a** and **77b** were elaborated to an advanced intermediate toward polyoxin J, while **77b** also served to access a dysiherbaine-related furopyrane intermediate.



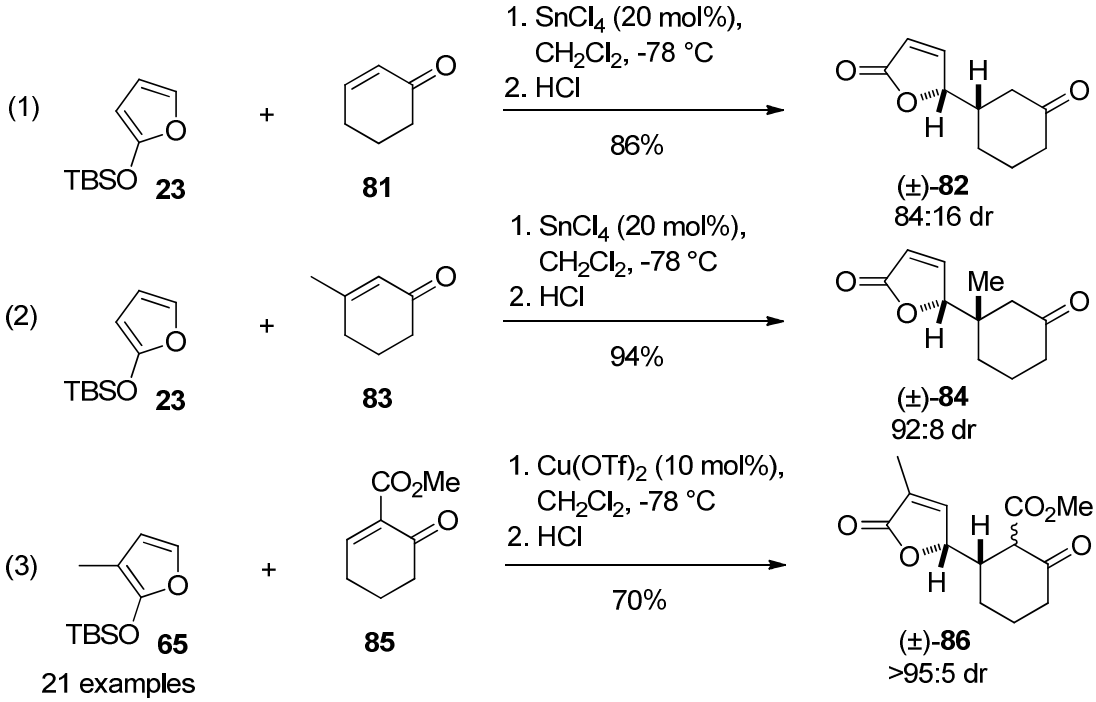
Scheme 11. Stereoselective vinylogous Mannich reactions of trimethylsilyloxy furan **34** with *N*-galactosyl or *N*-gulosyl acceptors.[19,20]



Scheme 12. The key vinylogous Mukaiyama-Michael reaction in the total synthesis of (±)-merrilactone A.[21]

One key reaction in the clever total synthesis of (±)-merrilactone A (**80**),[21] a complex cage-shaped pentacyclic sesquiterpene from *Illicium Merrillianum*, was a vinylogous Michael addition of tricyclic silyloxyfuran derivative **78** to methyl vinyl ketone (Scheme 12). Upon exposure to Taguchi's 1,1,3,3-tetrakis [(trifluoromethyl)sulfonyl]propane, γ,γ-disubstituted tricyclic lactone intermediate **79** was obtained as a

88:12 diastereomeric mixture, along with a minute amount of a further isomer. Of note, switching the catalyst to BF_3, $TiCl_4$, or $SnCl_4$ resulted in lower yields. Advance to the target encompassed six further operations consigning merrilactone A in 15 reaction steps for the shortest sequence.



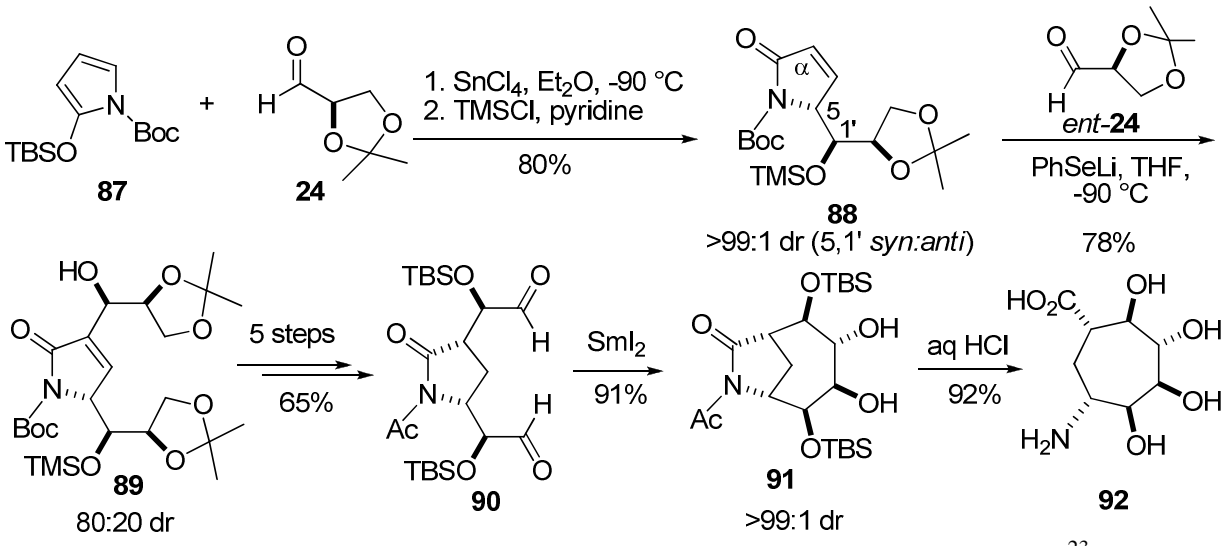
Scheme 13. Diastereoselective entries to racemic butenolides **82**, **84** and **86**.[22]

Lewis acid catalyzed vinylogous Mukaiyama-Michael reactions between silyloxy furans of type **23** or **65** and α,β-unsaturated cyclic enones or oxoesters of type **81**, **83** or **85** were investigated by Guillou *et al.* (Scheme 13).[22] Both substrates proved to be pertinent Michael acceptors giving butenolides of type **82**, **84** and **86** in good yields and moderate to good diastereomeric ratios. The stereostructure of the products was certified by X-ray crystallographic analyses that definitely assessed the *anti*-relationship of the newly formed stereocentres.

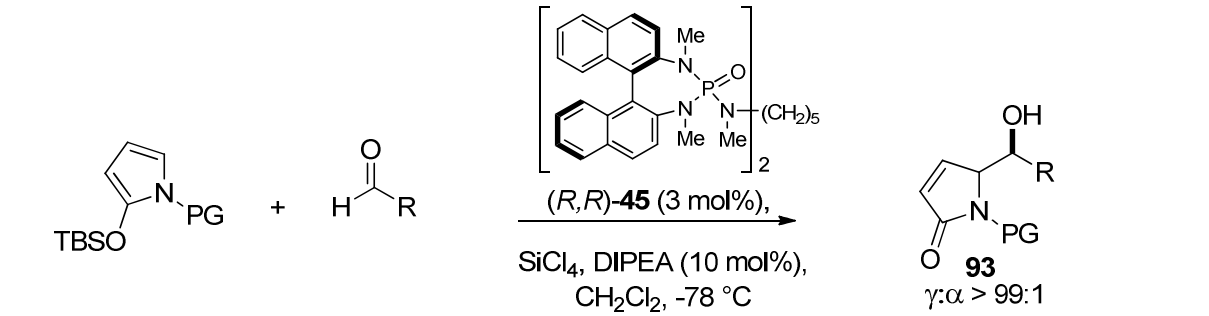
3.2. Pyrrole-based silicon enolates

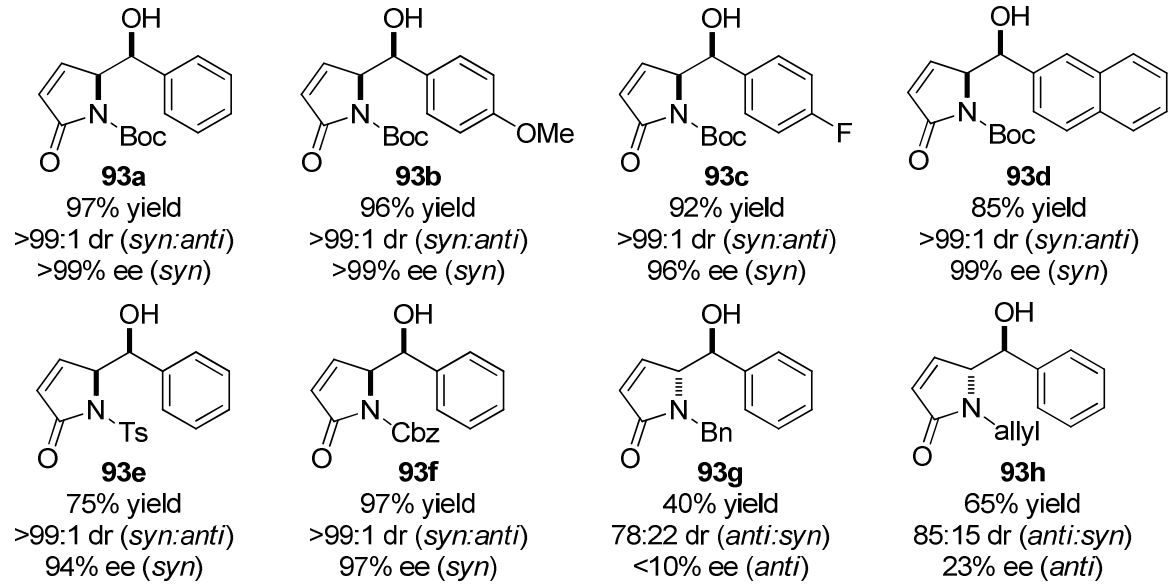
Chiral γ-butyrolactams represent structural motifs widely encountered in Nature as well as in many important bioactive compounds. These nitrogen-containing frameworks are also important synthetic intermediates en route to nitrogen heterocyclic and carbocyclic structures. As difficult as they are to construct and as rare as they appear to be in Nature, densely hydroxylated medium-sized carbocyclic amino acids are intriguing molecular entities, since they merge the structural characteristics of amino acids and carbohydrates within a robust carbocycle.

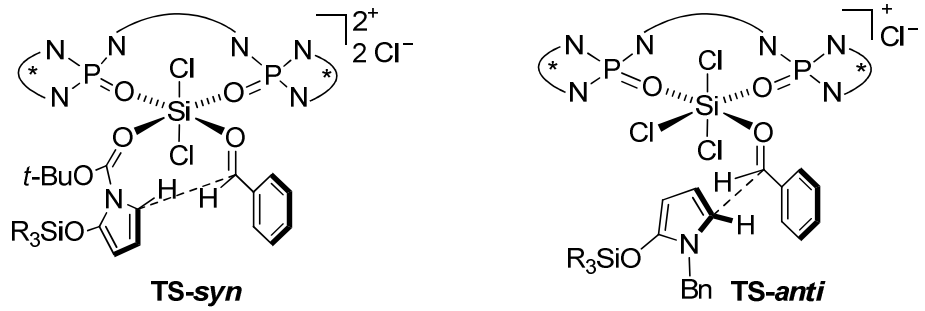
As an example, to arrive at the seven-membered carbasugar amino acid **92**, Casiraghi and co-workers[23] envisaged to utilize the pyrrole silyloxy diene **87** as the synthetic equivalent of a γ-aminobutyric acid α,γ-dianion. As shown in Scheme 14, the synthesis of **92** started with the vinylogous aldol reaction between **87** and D-glyceraldehyde acetonide **24** to produce, after protection, unsaturated lactam **88** with excellent *syn*-diastereoselectivity for the newly created stereocentres. α-Functionalization of **88** was then carried out *via* a Morita-Baylis-Hillman protocol using L-glyceraldehyde acetonide *ent*-**24** as the electrophile.



Scheme 14. Enantioselective entry to cycloheptane amino acids polyols.[23]







Scheme 15. Catalytic, asymmetric vinylogous Mukaiyama aldol reactions of pyrrole-based dienoxy silanes.[8a,b]

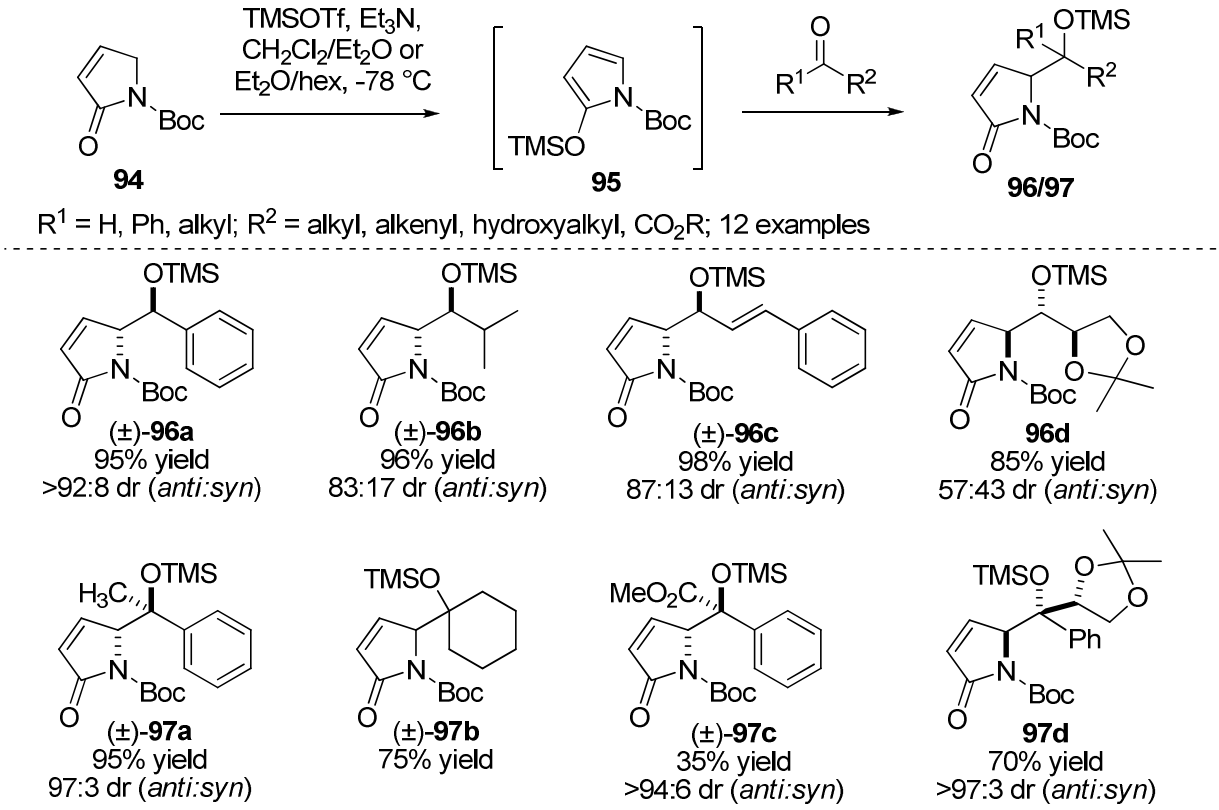
This furnished α,γ-disubstituted pyrrolinone lactam **89** in a good 80:20 *dr*. Protecting group manipulation and oxidative one-carbon shortening of both the lateral polyol chains gave dialdehyde **90** ready for the crucial carbocyclization. This manoeuvre was conducted using an intramolecular pinacol coupling to connect the two aldehyde terminals, so that bicycle **91** was created in high yield and complete stereoselectivity. The final steps only required lactam opening and deprotection to arrive at amino acid **92**. The versatility of the process was quite good allowing for the preparation of diverse stereoisomeric variants of **92**, by simply manipulating the chirality of the glyceraldehyde electrophiles during their installation into the pyrrole nucleus.

As a continuation of a program aiming at the development of heterocyclic dienoxy silane donors in catalytic asymmetric syntheses, the same research group[8a,b] reported a methodological study focused on the vinylogous aldol reaction of 2-silyloxypyrroles with aromatic aldehydes. After a preliminary screening of various well established metal-based catalyst systems, it was found that the bisphosphoramide/$SiCl_4$ catalyst couple **45**·$SiCl_4$ efficiently guided the aldol reaction in a strictly vinylogous sense, producing the expected lactams **93a–h** with high efficiency and stereocontrol (Scheme 15).

Importantly, it was shown that the nature of the heteroatom in the silyloxy diene scaffolds heavily impacted the stereochemical reaction behaviour; that is, the *syn*-configured adducts were preferentially obtained with pyrroles carrying electron-withdrawing *N*-substituents (Boc, Ts, Cbz), while the use of pyrroles having electron-donating *N*-substituents (Bn, PMB, allyl) (as well as furans, see Section 3.1.) provided reversal of stereocontrol, giving rise to *anti*-disposed adducts, preferentially. A plausible rationale accounting for the observed reaction stereodivergence, dictated by the nature of the heteroatom substituent, involves participation of two diverse transition state models, **TS-*syn*** and **TS-*anti*** (Scheme 15). With "chelatable" *N*-substituents capable to bind to hypervalent silicon atom of the chiral catalyst, engagement of the *re*-face of the aldehyde carbonyl with the *re*-face of the pyrrole γ-site results in preferential formation of *syn*-disposed adducts. On the contrary, lacking supplementary coordination at silicon, steric effects prevail to favour functionalization at the pyrrole *si*-face with preferential generation of *anti*-structures.

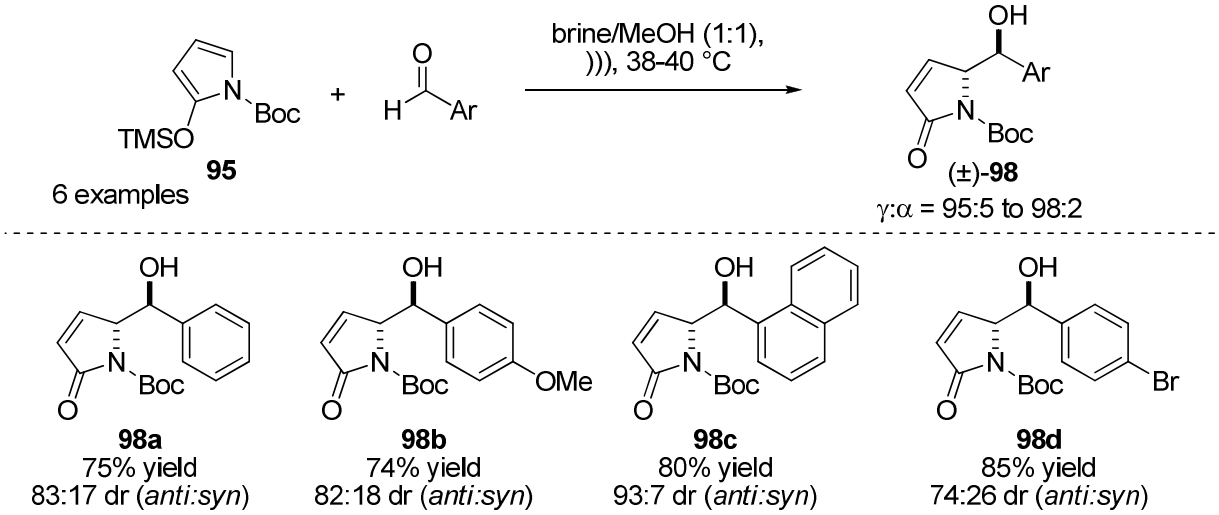
A conceptually novel strategy to promote Mukaiyama-type aldol tranformations avoiding preliminary formation of individual silicon enolate species was introduced by Zanardi *et al.*,[24] utilizing pyrrolinone vinylogous pro-nucleophiles. The protocol was based on a reaction cascade triggered by the combination of a silicon Lewis acid coupled to a tertiary amine Brønsted base. According to a one-pot operation, the dual silicon/amine system triggers formation of a silyl enol ether *in situ* (intermediate **95**), while activating the acceptor component and advancing the process by capturing and stabilizing the formed aldolate by silylation (Scheme 16).

Actually, the approach involved the simultaneous addition of all reactants in one vessel – the donor, the acceptor, the solvent and the Lewis acid/ Brønsted base mixture – and markedly differs from the classical Mukaiyama methodology, where isolated enolates or dienolates are involved. As a proof of concept, treatment of *N*-Boc pyrrolinone **94** and benzaldehyde in the presence of Et_3N/TMSOTf mixture in diethyl ether/hexane returned silylated aldol **96a** in high isolated yield, with >92:8 diastereomeric ratio favouring the *anti*-isomer. The reaction scope was quite large and the process not only tolerated aromatic, aliphatic and α,β-unsaturated aldehydes (compounds **96**), but also proved viable with ketones and keto-esters, including chiral non-racemic α-hydroxy substrates (compounds **97**). In general, yields were good, site-selectivity complete and *anti*/*syn* ratio very good for many candidates.



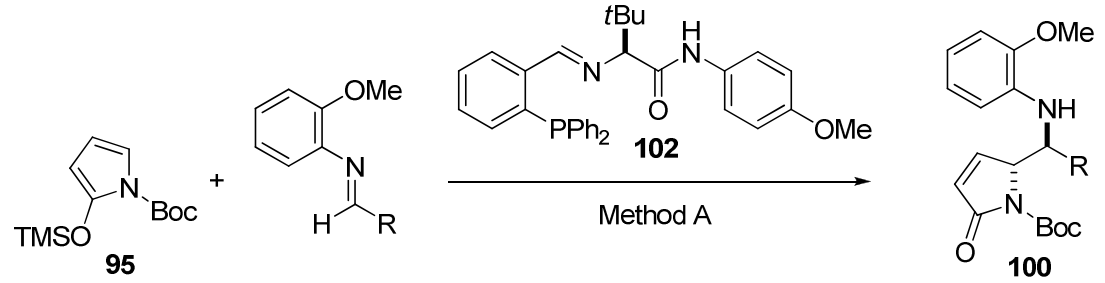
Scheme 16. One-pot silylative vinylogous Mukaiyama aldol reaction of pyrrolinone **94**.[24]

As previously described with furan-based silyl dienolates (see Section 3.1.), the uncatalyzed vinylogous aldol reaction in aqueous media proved equally viable with the pyrrole counterpart **95** (Scheme 17).[13] Also in this case, the reaction scope was large for aromatic aldehydes and several lactam adducts of type **98** were formed in good yields, virtual complete γ-site selectivity and moderate to good diastereoselectivity. However, a remarkable switch in diastereoselectivity was observed when passing from furan (*syn*-selective) to pyrrole silyl dienolates (*anti*-selective), highlighting how the nature of the heteroatom in the donor critically impacts diastereocontrol. Here, the bulky, lipophilic *N-tert*-butoxycarbonyl group (as well as the *N*-benzyl group) is shifted away from the water interface entering the inner pocket of the reactant droplets, thus reverting diastereocontrol.

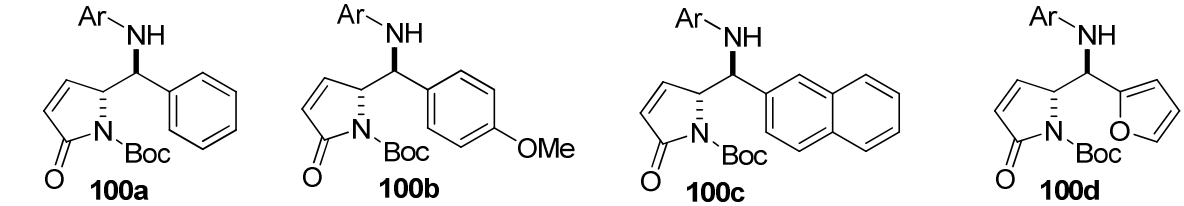


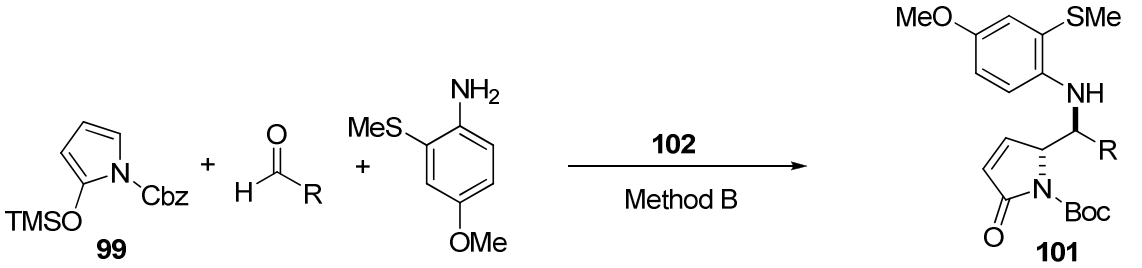
Scheme 17. Substrate scope of *anti*-selective vinylogous aldol reaction of pyrrole **95** in aqueous systems.[13]

The vinylogous, asymmetric Mukaiyama-type Mannich reactions of imines with pyrrole silicon dienolates provide an effective way to construct rare α,β-unsaturated γ,δ-diaminocarbonyl frameworks directly, which are crucial motifs in many natural and man-made compound classes. In recent investigations, Casiraghi *et al.*[25,26] developed *anti*-selective, catalytic asymmetric protocols to access these aminated entities by exploiting suitably protected pyrrole nucleophiles and preformed or *in situ* generated aldimine acceptors. Excellent results in terms of regioselectivity, diastereoselectivity and enantioselectivity were attained utilizing, as the catalyst of choice, amino acid-derived ligand **102** in complex with silver(I) acetate, a system ideated and used by the Hoveyda and Snapper groups a few years ago.[27] As shown in Scheme 18, two different optimal protocols were elaborated according to the nature of aldimine acceptors.

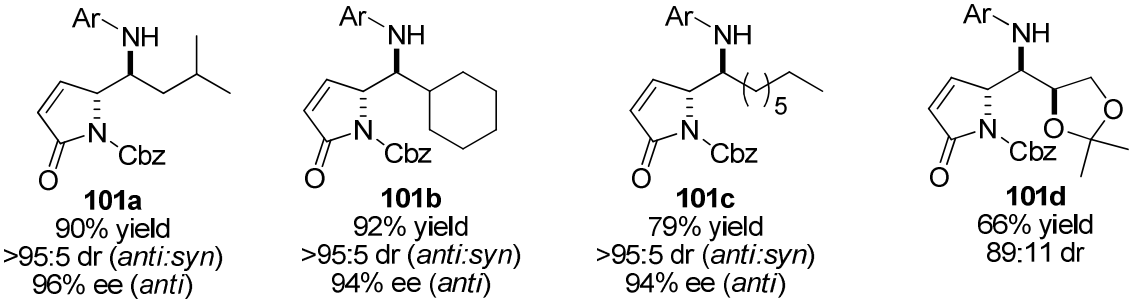


Method A[ref. 25]: R = aryl, heteroaryl, alkyl; **102** (10 mol%), AgOAc (10 mol%), *i*-PrOH/H_2O, THF, 0 °C; 8 examples





Method B[ref. 26]: R = alkyl, hydroxyalkyl; **102** (5 mol%), AgOAc (5 mol%), $MgSO_4$, *i*-PrOH/H_2O, THF, -30 °C; 9 examples

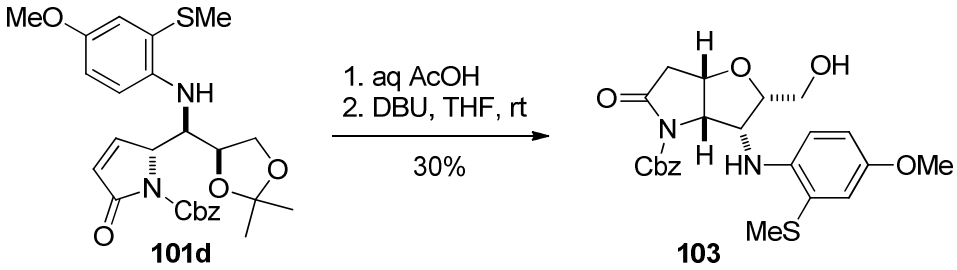


Scheme 18. Diastereo- and enantioselective catalytic vinylogous Mukaiyama-Mannich reactions of pyrrole silyl dienolates.[25,26]

Protocol A (aromatic aldehyde substrates) involved the use of *N*-Boc pyrrole **95** and preformed *N*-aryl imines with 10 mol% each ligand **102** and AgOAc, while protocol B (alkyl and hydroxyalkyl aldehyde substrates) entailed a sort of three-component sequential addition modality, where the imines were formed *in situ* prior to the addition of the catalyst and the donor reactants (*N*-Cbz candidate **99** in this instance). Invariably, both protocols performed well, returning the expected *anti*-configured Mannich adducts **100** and **101** in high yields, excellent *dr* and moderate to good *ee*.

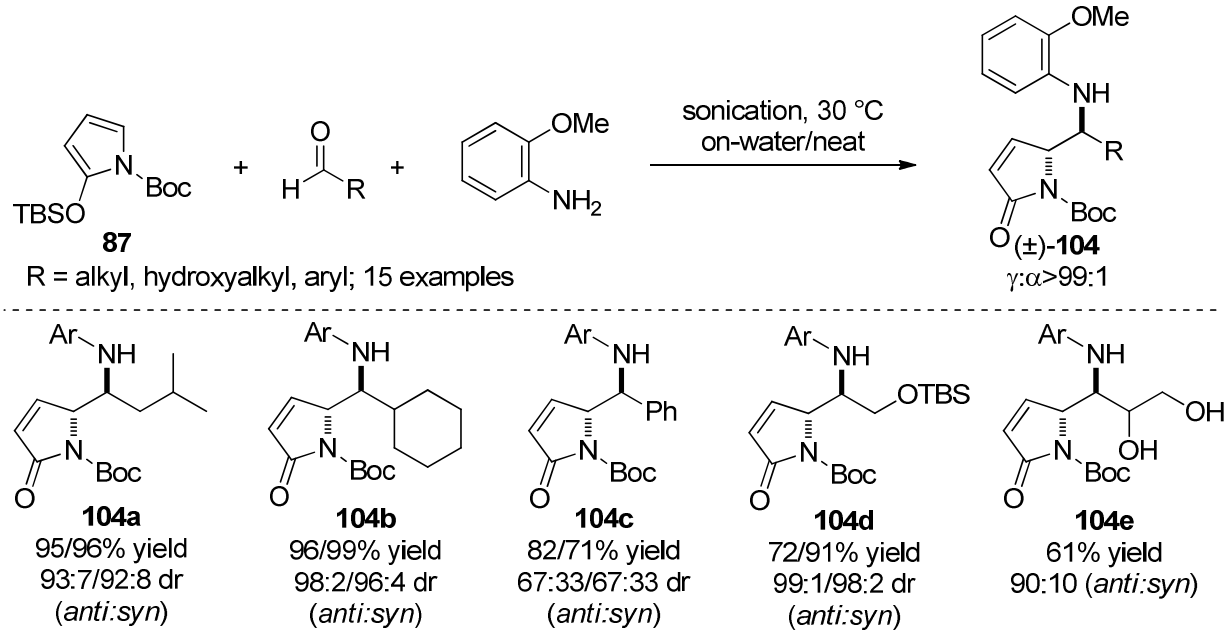
The synthetic versatility of the unsaturated lactam products was demonstrated by transformation of hydroxylated lactam **101d** into unprecedented furopyrrolone **103** by simple manipulation, including acetonide deprotection and subsequent DBU-assisted oxa-Michael annulation (Scheme 19).[26]

The development of enabling chemical methodologies that include such emblematic keywords as water, solvent-free, environment awareness, practicality and atom economy is one of the greatest challenges of contemporary organic synthesis.



Scheme 19. Synthesis of hexahydrofuro[3,2-*b*]pyrrolone **103**.[26]

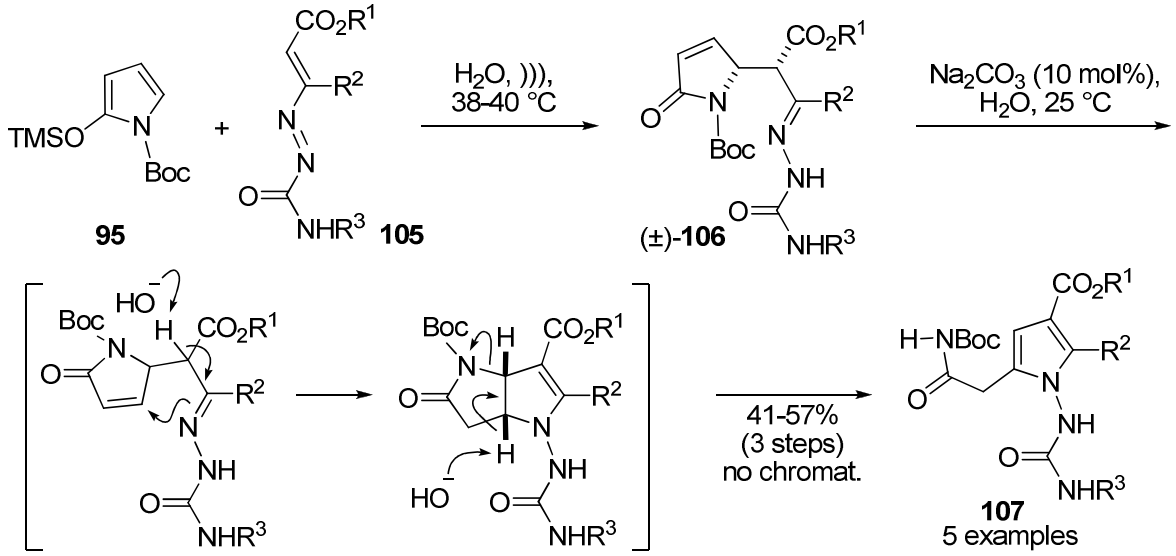
On this line, Zanardi *et al.*[28] launched a catalyst-free three-component vinylogous Mukaiyama-Mannich reaction of pyrrole dienolates of type **87**, which worked well in both aqueous and solvent-free environments (Scheme 20). Both lipophilic and hydrophilic aromatic and aliphatic aldehydes proved to be competent substrates allowing access to a varied repertoire of unsaturated aminolactams of type **104** with complete regioselectivity and good diastereoselectivity in favour of *anti*-configured compounds.



Scheme 20. Aqueous and solvent-free uncatalyzed three-component vinylogous Mukaiyama-Mannich reactions of pyrrole silyl dienolate **87**.[28]

Even though a full rationale for this vinylogous Mannich reaction is hard to formulate, it was believed that water is an indispensable ingredient which acts as both proton donor, to activate the *in situ* generated imine, and silicon scavenger, to sequester the silicon ion from the donor into an inactive R_3SiOH species, the sole by-product in these environmentally benign transformations.

Pure water, 40 °C and sonication in an open-air vessel were the optimized conditions for the reaction between pyrrole **95** and 1,2-diaza-1,3-diene Michael acceptors of type **105** (Scheme 21).[29] These conditions proved superior to the classical Mukaiyama-type Lewis acid conditions in apolar solvents and provided access to a variety of *syn*-configured ureido-lactam intermediates of type **106** in high yield and selectivity. According to a one-pot procedure, these intermediates underwent a clean base-catalyzed reaction cascade furnishing functionality-rich pyrroles **107**, which were recovered as pure substances by simple filtration. The authors surmised that the added base triggers a cascade of events featuring an intramolecular aza-Michael reaction to give a diazabicyclo intermediate, which is promptly subjected to lactam ring opening and aromatization to return the pyrrole products.



Scheme 21. On-water vinylogous Mukaiyama-Michael addition of silyloxy pyrrole **95** to 1,2-diaza-1,3-dienes.[29]

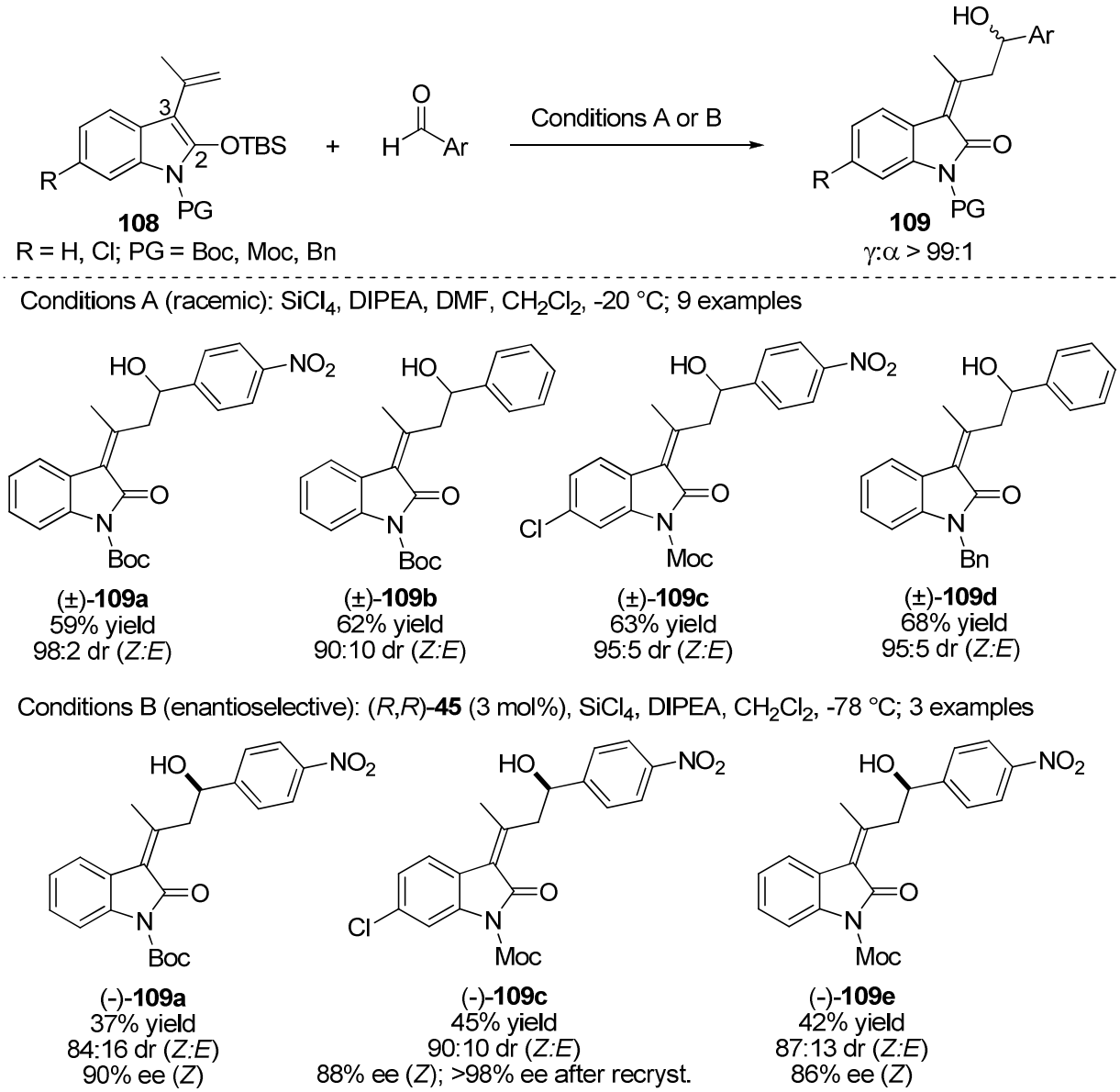
3.3. Other silicon enolates

In spite of the wide, ubiquitous occurrence of heterocyclic compounds in Nature and their application as functional reactants, their utility as vinylogous nucleophiles or pro-nucleophiles has been rather underquoted, the majority of synthons being limited to furan- and pyrrole matrices.

Indoles are arguably the most abundant heterocycles in Nature, but only recently representative members of this progeny have been developed as vinylogous nucleophilic or pro-nucleophilic reactants. As an example, 3-alkylidene-2-oxindoles are well known for their electrophilic reactivity at C-β position, but the ambident nucleophilic properties of γ-enolizable congeners remained unexplored. In 2012, Casiraghi *et al.*[30] reported the first example of the synthesis of 3-alkenyl-2-silyloxy indoles and their use in asymmetric vinylogous aldol reactions with aromatic aldehydes (Scheme 22). Using silicon tetrachloride and diisopropyl ethylamine in CH_2Cl_2 in the presence of DMF, variously substituted 2-silyloxy indoles **108** reacted with aromatic aldehydes providing the corresponding vinylogous aldol adducts **109** in moderate yields with complete γ-site selectivity and excellent diastereoselectivity favouring the *Z*-configured alkenes (Scheme 22,

Conditions A). During an exploratory trial, an enantioselective version of the process was also discovered using Denmark's bisphosphoramide catalyst **45** in combination with $SiCl_4$ (Scheme 22, Conditions B). Chiral non-racemic products **109a**, **109c** and **109e** eventually formed in acceptable yields, with appreciable *Z*-diastereoselectivity and enantioselectivity up to 90%.

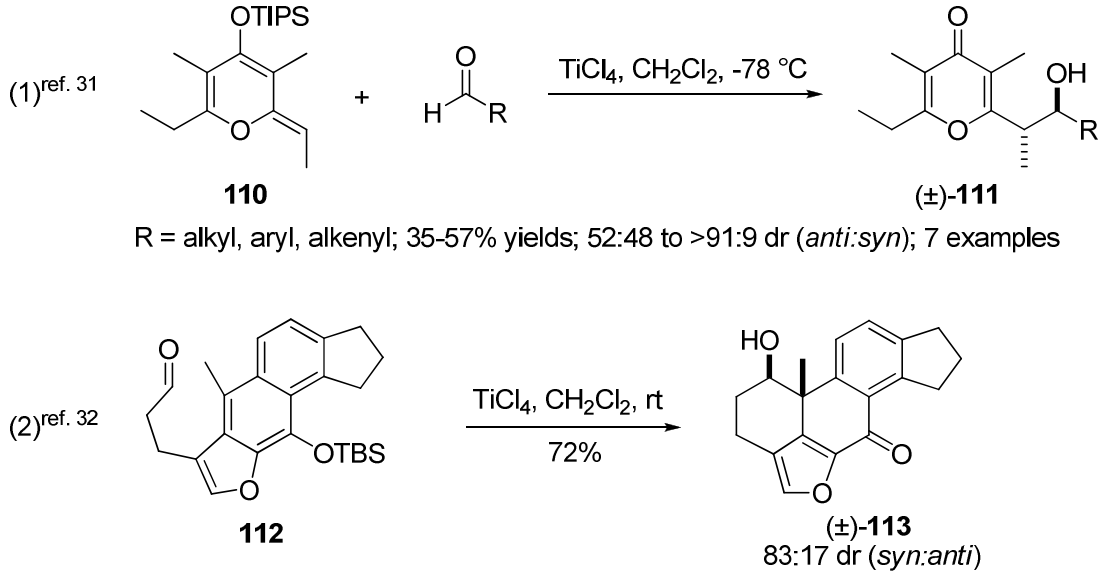
A rare example of diastereoselective vinylogous Mukaiyama aldol reaction of a triisopropylsilyl enol ether of γ-pyrone derivatives with both aliphatic and aromatic aldehydes was reported by Kigoshi and co-workers.[31] In the presence of $TiCl_4$ as the Lewis acid activator, the reactions returned the expected functionalized γ-pyrone derivatives **111** in moderate yields and diastereoselectivity favouring, in many instances, *anti*-configured isomers (Scheme 23, eq 1).



Scheme 22. Racemic and enantioselective executions of vinylogous aldol reactions of 3-alkenyl-2-silyloxy indoles.[30]

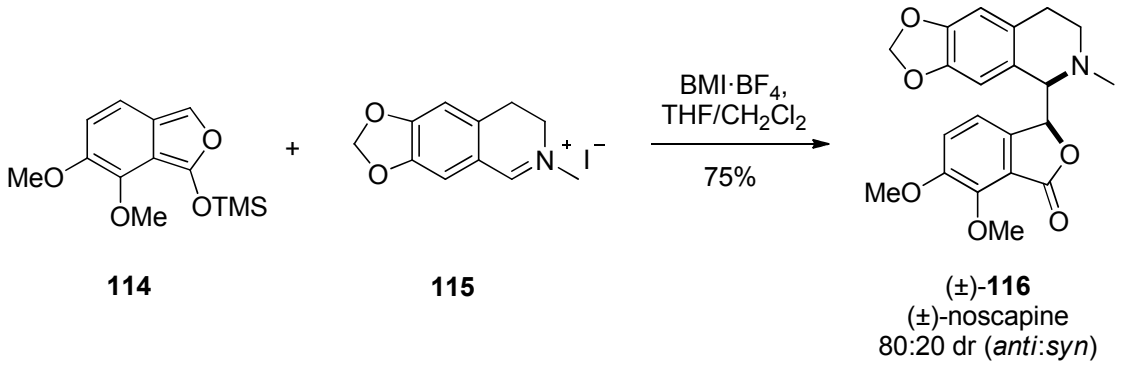
During synthetic studies directed towards the construction of the viridin pentacyclic furanosteroid core structures, Onyango and Jacobi[32] utilized a remarkable vinylogous cycloaldolization of the heterocyclic silyl dienol ether intermediate **112** (Scheme 23, eq 2). After considerable experimentation, it was eventually determined that stirring a rigorously degassed CH_2Cl_2 solution of aldehyde **112** with 4 mol equiv $TiCl_4$ at

room temperature provided pentacyclic viridin-related target **113** in a 72% overall yield as a 83:17 *syn*:*anti* diastereomeric mixture. This reaction constitutes a rare example where the vinylogy effect propagates along a diene functionality embedded into a polycyclic aromatic motif.



Scheme 23. Vinylogous Mukaiyama aldol-type reactions of γ-pyrone- and naphthofuranone-derived silyl dienol ethers **110** and **112**.[31,32]

A clever example of vinylogous Mukaiyama-Mannich addition reaction involving isobenzofuranone-based silyloxy diene of type **114** was reported by Silva Santos *et al.*[33] during a study directed to the synthesis of a series of racemic phthalide tetrahydroisoquinoline alkaloids. As an example, the concise synthesis of noscapine **116** is outlined in Scheme 24.



Scheme 24. Short synthesis of noscapine **116**.[33]

Thus, unstable silyloxy diene **114** coupled to *in situ*-generated *N*-methylisoquinolinium ion **115** under the assistance of butyl-methylimidazolium tetrafluoroborate. Of note, the addition proved to be diastereoselective, producing the *anti*-configured product (±)-**116** in 75% yield and 80:20 *dr*. In an analogous manner, 9-*epi*-noscapine, bicuculline and capnoidine were synthesized by starting with suitably substituted silyloxy isobenzofuranone scaffolds.

4. Direct catalytic methodologies

Surveyed in this chapter are those aldol-related reactions that utilize potential nucleophilic reactants directly (pro-nucleophilic systems), avoiding preliminary formation of the active species. The actual

nucleophile is generated *in situ* in a substoichiometric way and lives together with its pro-nucleophilic parent compound. Direct methodologies are highly attractive in terms of atom economy and time-saving, however they are the most demanding options, as far as the control of the chemo-, regio- and stereoselectivity are concerned. Recent advances in metal- and organocatalysis greatly contributed to the evolution of direct vinylogous aldol, Mannich, and Michael reactions, rendering their direct executions easy to perform, control and discipline. Activation of the pro-nucleophile (HOMO-raising activation) may be attained according to two general principles, *i.e.* non-covalent activation by means of a Brønsted base catalyst (a tertiary amine, for example), generating the nucleophilic active species (an ion pair) or covalent activation where, for example, a dienamine nucleophile is generated by reaction of the starting pro-nucleophile with an amine catalyst. Maximum efficiency in direct executions will be gained by those catalysts capable to activate both the reaction components simultaneously as, for example, by using bifunctional catalyst systems (HOMO-raising/LUMO-lowering activation). As for the previously disclosed indirect modalities, the chapter is subdivided into three sections, featuring furan-based pro-nucleophiles, pyrrole-based counterparts and other heterocyclic entities. Of note, this compilation solely analyzes very recent contributions in this field, which appeared in the literature during the last triennium.

4.1. Furan-based pro-nucleophiles

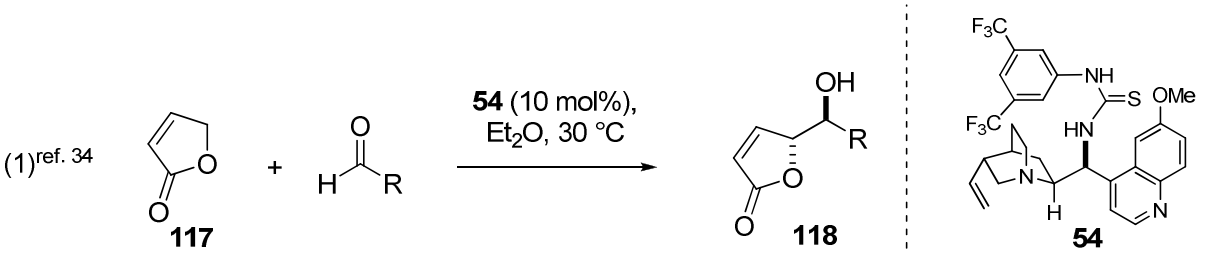
The direct vinylogous asymmetric aldol reaction of unactivated or activated γ-butyrolactones of type **117**, **121** and **124** with simple carbonyl compounds has been the subject of four independent studies by Feng,[34] Pansare,[35,36] Lu[37] and Terada[38] (Scheme 25). In the first article, Feng *et al.*[34] reported the preparation of a collection of enantiomerically enriched hydroxylated butenolide derivatives **118** *via* direct coupling of furanone **117** to aromatic, heteroaromatic and aliphatic aldehydes (Scheme 25, eq 1). Reactions were catalyzed by 10 mol% bifunctional *Cinchona* catalyst **54** and furnished the desired aldols in high yields, good *anti*-diastereoselectivity, and good levels of enantioselectivity for the major *anti*-isomers. On the basis of the relative and absolute configuration of the butenolide products, it was claimed that a preferential transition state model is operative, where the aldehyde is activated by the thiourea moiety through double hydrogen bonding, while the basic quinuclidine nitrogen of the catalyst activates the pro-nucleophile and coordinates the emerging dienolate.

About the same chemistry was utilized by Pansare *et al.*[35] to couple **117** to diverse aromatic aldehydes (Scheme 25, eq 2). In this case, the best catalyst was stilbene diamine-squaramide **120** (20 mol% loading) providing the products **119** in moderate yields, good diastereocontrol (*anti*-isomers preferred) and excellent enantiomeric excesses. Simultaneous activation of the aldehyde carbonyl by the squaramide function and activation of the nucleophile *via* ion pairing to the ammonium group from the catalyst was invoked to account for the observed reaction behaviour. Of note, one of the synthesized γ-butenolides served as the key starting material in the expedient enantioselective synthesis of three neurokinin receptor antagonists featuring 2,3-disubstituted piperidine nuclei.[36]

Activated, halogen-bearing furanones of type **121** were the pro-nucleophiles of choice in direct vinylogous aldol reactions with several α-ketoester acceptors (Scheme 25, eq 3).[37] Under asymmetric catalysis with L-tryptophan-derived bifunctional catalyst **123**, a wide repertoire of highly substituted butenolides **122** harbouring a quaternary hydroxyl stereocentre was assembled in good overall yields and excellent margins of diastereoselectivity (*syn*-isomers preferred) and enantioselectivity. The non-halogenated

furanone could also be used, although a much longer reaction time was required to reach an acceptable substrate conversion. Starting with a suitable butenolide candidate, biologically important enantiopure glycerol derivatives containing a tertiary carbinol moiety were prepared, by simple functional group elaboration.

A further example of direct, enantioselective vinylogous aldol reaction between halogen- or sulfur-bearing γ-lactones **124** and aromatic or heteroaromatic aldehydes was reported by Terada's group in 2010,[38] emphasizing the use of guanidine organocatalyst **126** (Scheme 25, eq 4). Butenolides of type **125** were obtained in moderate to good yields and with appreciable levels of *syn*-diastereoselectivity and excellent enantioselectivity. Interestingly, 3-phenylthiofuranone also proved to be a competent substrate, producing the corresponding butenolide adduct with high efficiency and stereocontrol. Of note, unsubstituted furanone was not an appropriate donor in these reactions.

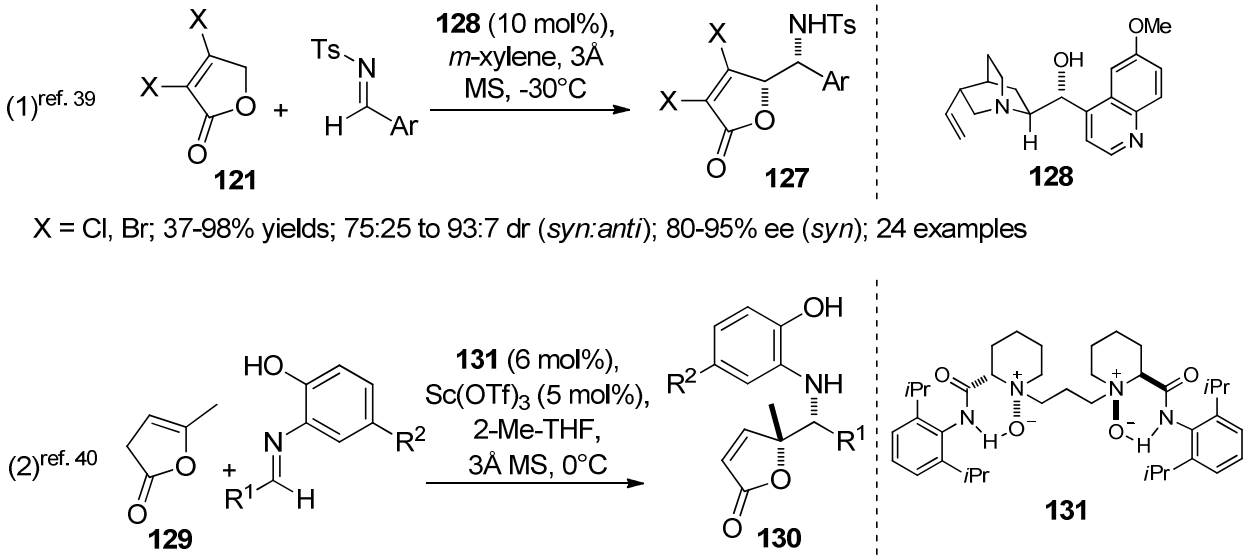


Scheme 25. Asymmetric direct vinylogous aldol reactions of γ-butenolides.[34,35,37,38]

3,4-Disubstituted butenolides of type **121** were also used by Wang and co-workers[39] as pro-nucleophilic substrates in asymmetric vinylogous Mannich reactions with aldimines catalyzed by natural

quinine **128** (Scheme 26, eq 1). Using 10 mol% catalyst in *m*-xylene in the presence of 3Å molecular sieves at −30 °C, a rich repertoire of vinylogous Mannich adducts was formed in moderate/good yields, up to 93:7 *dr* (*syn*-isomers preferred) and up to 95% *ee*. The scope of the reaction proved to be wide, although limited to aromatic *N*-tosyl aldimines. Reduction and dehalogenation of a butenolide product led to an interesting vicinal amino alcohol, thus exemplifying the synthetic utility of these butenolide products.

The natural, deconjugated α-*Angelica* lactone **129**, a cheap industrial material, has attracted particular attention as a butenolide variant due to its potential in the construction of γ,γ-disubstituted butenolides. In 2011, this lactone has been cleverly utilized by Feng *et al.*[40] in direct asymmetric vinylogous Mannich additions to *N*-aryl aromatic and heteroaromatic aldimines (Scheme 26, eq 2). The catalyst of choice was a scandium(III)-*N*,*N*-dioxide complex from ligand **131**, which nicely served as a chiral Lewis acid activator of the lactone substrates *via in situ* scandium dienolate formation. Upon 6 mol% ligand loading in the presence of 5 mol% $Sc(OTf)_3$, a variety of δ-amino-γ,γ-disubstituted butenolide adducts **130** formed with rewarding stereocontrol. Remarkably, under the optimized conditions, conjugated furanones of type **117** did not work, suggesting here a quite different reaction mechanism where Lewis acid-triggered α-enolization is responsible for the occurrence of the reaction.

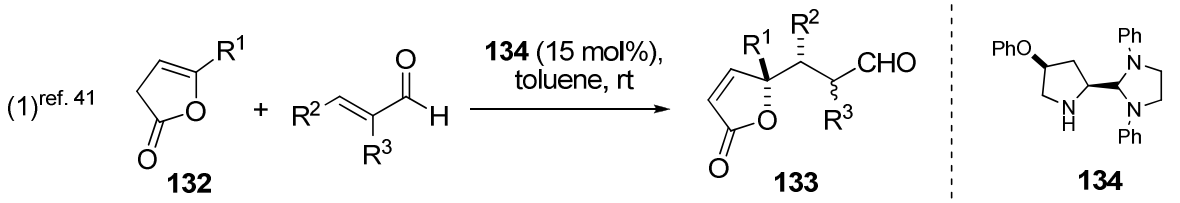


Scheme 26. Direct organocatalyzed vinylogous Mannich reactions of conjugated and deconjugated furanones.[39,40]

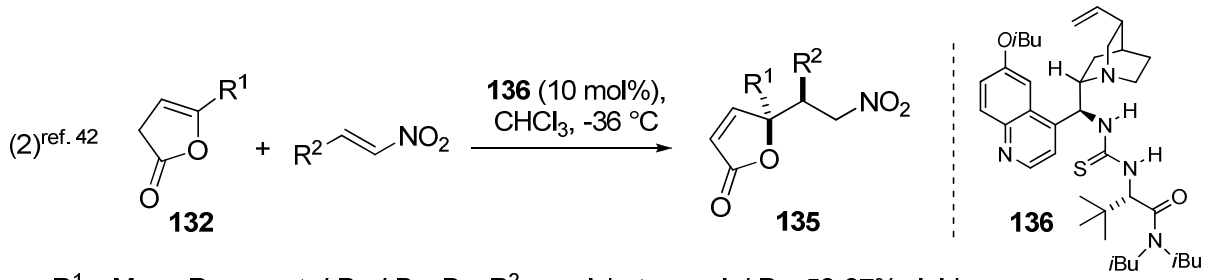
Deconjugated butenolides related to *Angelica* lactone of type **132** were also investigated by Alexakis,[41] Mukherjee[42] and Jiang[43] as pro-nucleophile candidates in direct, enantioselective organocatalytic vinylogous Michael additions to enals, nitroolefins and enone imides, respectively (Scheme 27).

In the first report (Scheme 27, eq 1),[41] the addition was directed by the aminal-pyrrolidine catalyst **134**, resulting in clean formation of a variety of enantioenriched γ-butenolide aldehydes of type **133** in good yields, where the 5,1′-*syn*-stereoisomers prevailed. Except for C1′-unsubstituted adducts (**133**, R^2=H) where the stereocontrol was poor, products were obtained with very good enantioselectivity up to 97% *ee*. Mechanistically, the reaction possibly occurred *via* iminium ion activation, resulting from covalent interaction between the α,β-unsaturated aldehyde acceptor and the secondary amine catalyst. It was

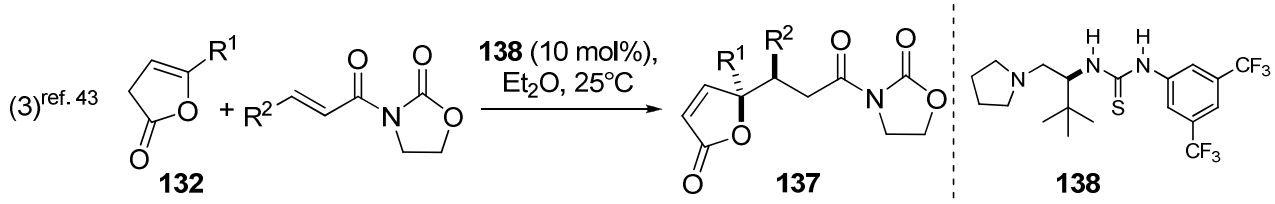
hypothesized that the simple diastereoselection is dictated by the R^2 substituent of the acceptor, with the catalyst only controlling the face attack of the iminium intermediate; and this is consistent with the fact that chiral and achiral catalysts led to the same *syn*-stereoisomers in nearly equal amounts.



R^1 = Me, Et; R^2 = H, alkyl, alkenyl; R^3 = H, Me; 60-95% yields; 50:50 to 88:12 dr (*syn:anti*); 88-97% ee (*syn*); 11 examples



R^1 = Me, *n*-Pr, *n*-pent, *i*-Pr, *i*-Bu, Bn; R^2 = aryl, heteroaryl, *i*-Bu; 59-97% yields; >95:5 dr (*syn:anti*); 80-98% ee (*syn*); 30 examples



R^1 = aryl, alkyl; R^2 = H, ArC=O, Me, CF_3; 71-93% yields; 94:6 to >99:1 dr (*syn:anti*); 91-99% ee (*syn*); 35 examples

Scheme 27. Catalytic, enantioselective direct Michael additions of deconjugated γ-butenolides.[41–43]

The second study (Scheme 27, eq 2)[42] focused on the addition to a series of β-nitroalkenes bearing aryl, heteroaryl and alkyl substituents. Reactions performed very well with the newly introduced *Cinchona* alkaloid thiourea catalyst **136** (10 mol% loading), which bears three isobutyl substituents and a further *tert*-leucine-based element of chirality. Irrespective of the nature of the acceptor and donor substituents, good to excellent yields, almost complete diastereocontrol for the *syn*-isomers and rewarding enantioselectivity were attained, highlighting the unique ability of the *Cinchona* catalyst to govern the reaction in an exemplary manner. While the structural assignment of the products was supported by X-ray diffraction studies, no models for the observed stereoinduction were suggested by the authors. Continuing this theme, the same authors[44] further expanded this methodology to C_{2v} symmetric maleimide acceptors, rendering a number of butenolide adducts available in high optical purity and with appreciable margins of diastereoselectivity.

In the third investigation (Scheme 27, eq 3),[43] Jiang *et al.* analyzed the enantio- and diastereoselective addition of γ-substituted butenolides of type **132** to a number of butene-imide acceptors. Catalysts of choice were chiral pyrrolidine sulphonamides and thioureas, with catalyst **138** proving to be optimal. In the event, a wide repertoire of butenolides **137** were obtained in good isolated yields, remarkable diastereoselectivity and excellent enantioselectivity. To elucidate the role of the oxazolidinone group of the acceptor and the origin

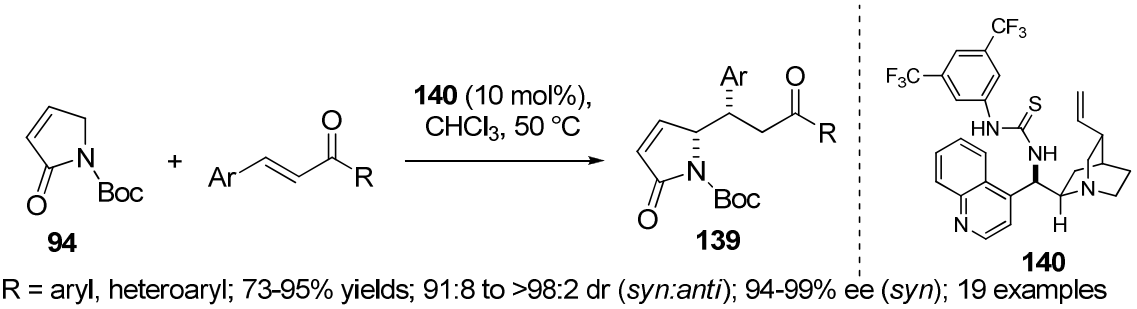
of the stereoselectivity, DFT calculations were performed. On the basis of these calculations and according to experimental observations, the authors claimed that the carbonyl group of the oxazolidinone moiety is responsible for interaction with the catalyst *via* weak non-bonding contacts.

Capitalizing on previous investigations on the use of α-thio-substituted γ-butenolides as pro-nucleophilic reactants in vinylogous aldol reactions, Terada and Ando[45] extended this chemistry to direct Michael additions to nitroalkenes using an axially chiral guanidine-based organocatalyst. Working with several aryl- and alkyl-substituted nitroalkenes, variously shaped *syn*-configured thiobutenolides were collected in moderate to good yields and excellent diastereo- and enantioselectivities.

4.2. Pyrrole-based pro-nucleophiles

N-Boc pyrrolinone **94**, the prototypical member of the family of pyrrole-based pro-nucleophiles, has been extensively employed as the immediate precursor of the corresponding silyl dienolates, which admirably served in a large number of vinylogous indirect aldol, Mannich and Michael transformations (see Section 3.2.). On the other hand, the use of this simple nitrogen heterocycle in direct versions of such pivotal addition reactions has been marginally explored and only recently have few direct asymmetric vinylogous Michael reactions been reported using this synthon.[46]

In 2011, Wang and colleagues[47] investigated an organocatalytic, direct addition between **94** and diverse chalcones under the guidance of the popular bifunctional *Cinchona* thiourea catalyst **140**. Applying the conditions described in Scheme 28, this protocol afforded the respective Michael adducts **139** in high yields and with very high margins of diastereo- and enantioselectivity. The generality of the reaction was quite large, tolerating either electron-donating or electron-withdrawing enone substituents. Heterocyclic systems were also applicable, while aliphatic counterparts failed to give appreciable results.

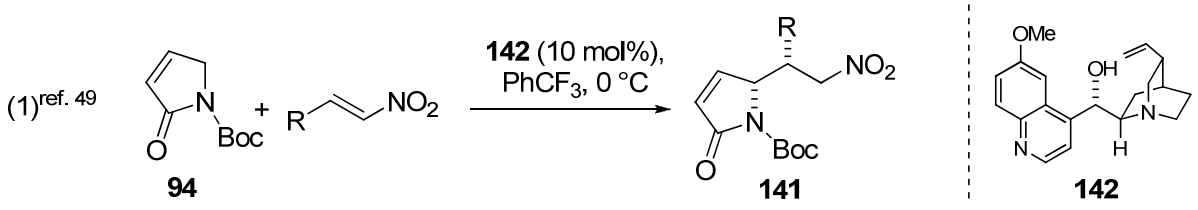


R = aryl, heteroaryl; 73-95% yields; 91:8 to >98:2 dr (*syn:anti*); 94-99% ee (*syn*); 19 examples

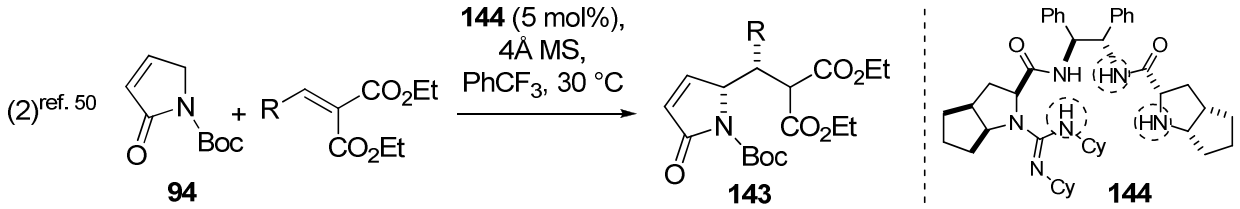
Scheme 28. Organocatalytic direct asymmetric vinylogous Michael reactions of *N*-Boc pyrrolinone **94** with enones.[47]

Possible routes for the formation of the carbon-carbon bonds were postulated by the authors, presenting two distinct models for the interaction of the bifunctional catalyst with the reacting donor and acceptor partners. According to previous studies, a favourite model could be operative, where the carbonyl group of the chalcone is activated by the ammonium nitrogen derived from the catalyst *via* hydrogen bonding, while the thiourea moiety coordinates to the *N*-Boc lactam dienolate. In a subsequent paper,[48] Wang performed in-depth studies of the same reaction through a combination of experimental (NMR) and theoretical (DFT) approaches, through which a new dual activation pathway was demonstrated. The key feature of this new activation mechanism is that the NH of the thiourea moiety and the NH of the protonated amine in the catalyst simultaneously activate the nucleophile, while the second NH of the thiourea activates the electrophile.

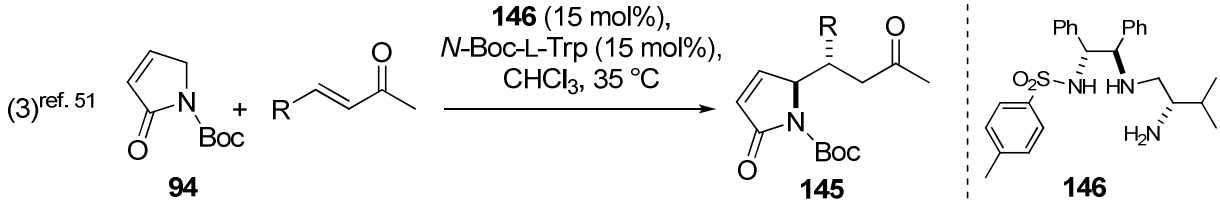
The utility of pyrrolinone **94** was also explored by several authors as the pro-nucleophilic substrate in organocatalyzed or metal-catalyzed asymmetric and direct vinylogous Michael addition to various acceptors as, for example, nitroolefins, alkylidene malonates, enones and chalcones. The results are condensed in Scheme 29. Mukherjee[49] investigated the reaction of **94** with a series of aryl, heteroaryl and alkyl β-nitro-olefins under catalysis of quinidine (or dihydroquinine) derivatives **142** (Scheme 29, eq 1). Products were consistently obtained in good yields, excellent diastereoselectivity for *syn*-isomers and moderate to high enantiomeric excesses. As for the mechanism, the authors postulated that the activation of the nitroolefin is obtained *via* hydrogen-bonding to the catalyst hydroxyl group, whereas the Brønsted basic tertiary amine of the catalyst provides for activation of the pro-nucleophile.



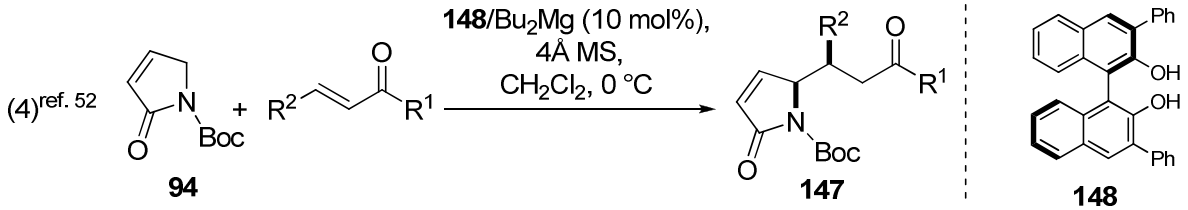
R = aryl, heteroaryl, alkyl; 72-88% yields; >95:5 dr (*syn:anti*); 54-89% ee (*syn*); 22 examples



R = aryl, heteroaryl, alkyl; 64-93% yields; 81:19 to 95:5 dr (*syn:anti*); 78-94% ee (*syn*); 21 examples
Circled are the claimed binding areas in the catalyst involved in reactant activation and selectivity control



R = aryl, heteroaryl, alkyl; 75-90% yields; 80:20 to >97:3 dr (*anti:syn*); 95-99% ee (*anti*); 30 examples



R[1], R[2] = aryl, heteroaryl, alkyl; 60-94% yields; 88:12 to >95:5 dr (*syn:anti*); 54-98% ee (*syn*); 20 examples

Scheme 29. Organocatalytic asymmetric direct vinylogous Michael addition of *N*-Boc pyrrolinone **94** to nitroolefins, alkylidene malonates, enones and chalcones.[49–52]

Feng[50] analyzed the behaviour of the reaction involving alkylidene malonate acceptors using unsymmetrical guanidine-secondary amine multifunctional catalyst **144** (Scheme 29, eq 2). After brief optimization, optimal conditions were found using 5 mol% catalyst **144** in combination with 4Å molecular

sieves in trifluoromethyl benzene. Reactions proved efficient and selective as for *dr* and *ee* are concerned. A mechanistic rationale was proposed, based on control experiments and previous investigations. Thus, the basic guanidine in the catalyst accelerates γ-deprotonation of lactam **94** to form the active dienolate; the *N*-Boc protecting group contributes in supplementary H-bonding to the guanidine moiety; meanwhile, the alkylidene malonate is activated through a network of hydrogen bonds with both the secondary amine and amide moieties of the catalyst.

Trans-stilbene-derived chiral catalysts of type **146** (Scheme 29, eq 3) in conjunction with *N*-Boc-L-tryptophan was the catalyst system with which Ye *et al.*[51] investigated the vinylogous Michael addition of **94** to rather lethargic enone acceptors. The generality of the reaction with respect to the acceptor entities proved large, encompassing β-aryl, heteroaryl, alkyl and cycloalkyl enone substituents. In any case, uniformly excellent yields, *dr*, and *ee*'s were witnessed for *anti-S*,*S*-configured pyrrolinone products **145**. In the proposed transition state, LUMO-lowering iminium covalent activation of the acceptor by the primary amine of the catalyst, as well as HOMO-raising non-covalent activation of the dienolate donor *via* H-bonding network are simultaneously operative, along with a substantial participation of the tryptophan carboxylate *via* ion pair interaction.

A quite different approach was devised by Wang and co-workers[52] to direct the asymmetric vinylogous Michael addition of **94** to a series of chalcones and related derivatives (Scheme 29, eq 4). The optimum catalyst system was the magnesium/(a*R*)-BINOL **148** complex, which was prepared *in situ* by reacting the ligand **148** with dibutyl magnesium. The addition to a variety of enones afforded products **147** in good yields, high diastereoselectivities up to 95:5 and excellent enantioselectivities up to 98% *ee*. The selectivity of the reaction was only slightly affected by the R^1 substituent, but highly affected by the R^2 group. A bidentate chelation between the *in situ*-generated *N*-Boc pyrrole dienolate and the chiral BINOL/magnesium complex activates the nucleophile, while providing the chemical environment for stereocontrol.

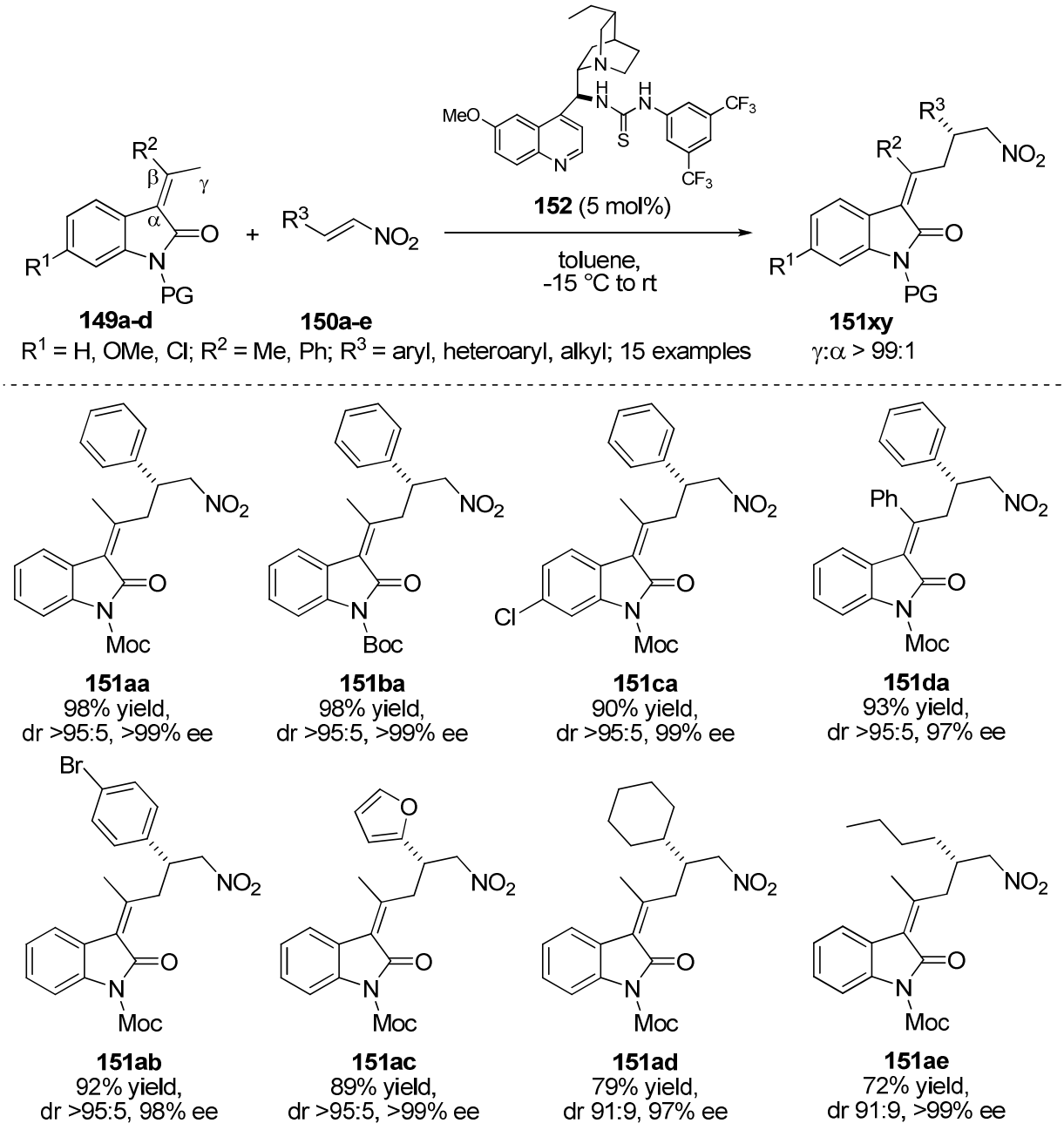
4.3. Other heterocyclic pro-nucleophiles

While direct asymmetric strategies using furan- and pyrrole-based pro-nucleophilic synthons have successfully delivered many reactions and useful products, investigations utilizing other heterocyclic candidates remain elusive.

To fill this void, we recently introduced γ-enolizable 3-alkylidene-2-oxindoles as potential vinylogous pro-nucleophilic scaffolds. While these heterocycles are well known for their electrophilic reactivity at Cβ position, the nucleophilic properties of the related dienolate-type intermediates at the Cγ position in vinylogous functionalization reactions are rarely disclosed. As a proof of concept, Casiraghi *et al.*[53] recently investigated the potential of a bifunctional *Cinchona* alkaloid thiourea catalyst in the direct and enantioselective vinylogous Michael addition of 3-alkylidene oxindoles **149** to a variety of nitroolefins **150**. As shown in Scheme 30, the reactions were admirably orchestrated by the *Cinchona* catalyst **152** to deliver almost enantiopure γ-substituted 3-alkylidene oxindoles **151** with outstanding levels of regio-, diastereo- and enantioselectivity. Provided that *N*-carbamoyl protecting groups within the oxindole substrates were used (Boc, Moc), the reaction scope and generality were substantial, regardless of the presence of neutral, electron-withdrawing or electron-releasing substituents on the two reaction components.

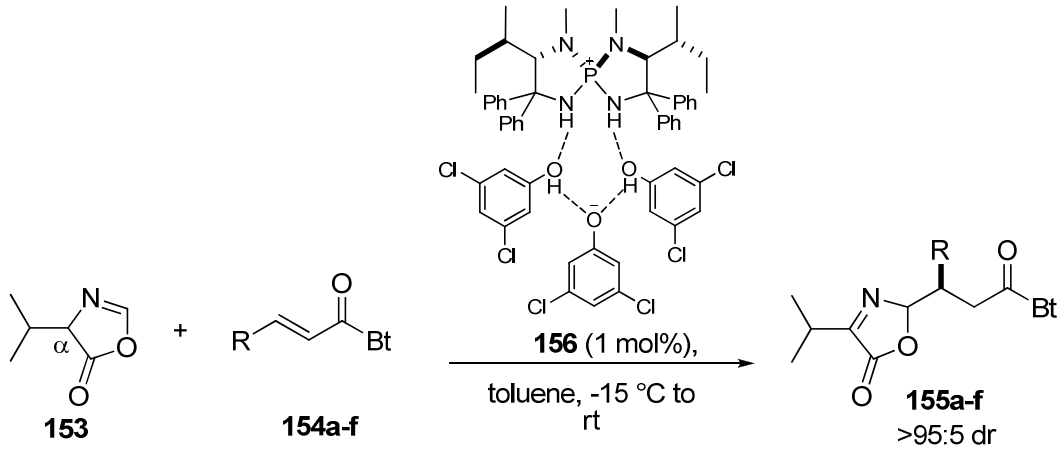
Based on the results and several precedents with these bifunctional catalysts, possible models of the dual activation of both the nucleophilic and the electrophilic reaction components by means of the *Cinchona*

catalyst were proposed: the thiourea unit could activate the nitroalkene by double hydrogen bonding, while the quinuclidine base deprotonates the oxindole to afford the active dienolate species.

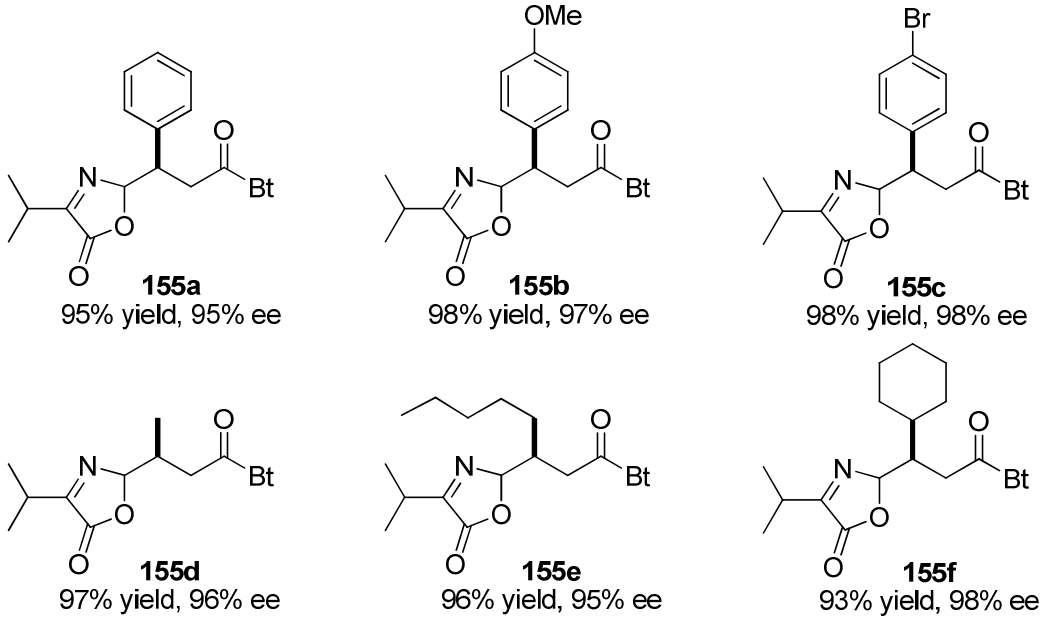


Scheme 30. Direct and enantioselective vinylogous Michael addition of 3-alkylidene oxindoles to nitroolefins.[53]

An extra hydrogen bond between the carbonyl of the indole *N*-protecting group and the protonated quinuclidine base of the catalyst further contributes to stabilization of the transition state, thus ensuring stereocontrol and chirality transmittal from the catalyst to the products. An alternative transition state model involving electrophile activation by the protonated amine group of the catalyst and nucleophilic activation by the thiourea moiety could be also operative. Recent experimental and theoretical works by Pápai,[54] Zhong[55] and Wang[48] appeared, dealing with the rationalization of possible transition state models involving these bifunctional *Cinchona* thiourea organocatalysts; this could contribute to shed light on this important issue.



R = aryl, heteroaryl, alkyl; Bt = benzotriazole; the relative stereochemistry of the products was not determined; 10 examples



Scheme 31. Organocatalytic, asymmetric vinylogous Michael reaction of azlactone **153**.[56]

In an outstanding contribution, Ooi and colleagues[56] ideated a novel family of chiral supramolecular assemblies to be used as asymmetric organocatalysts in enantioselective carbon-carbon bond-forming processes. In a remarkable example (Scheme 31), 2-unsubstituted oxazol-5(4*H*)-one, namely azlactone **153**, served as a pro-nucleophile with the expectation that the dienolate generated through α-deprotonation would behave as the active vinylogous donor. Indeed, with a wide number of α,β-unsaturated acylbenzotriazoles **154** and using as little as 1 mol% catalyst **156**, Michael reactions returned almost diastereomerically pure vinylogous adducts **155** in high yields and enantioselectivities (93–98% *ee*). The actual catalyst **156** was readily synthesized from L-valine and its solid state structure determined by single crystal X-ray diffraction analysis. In reacting with **153**, an active dienolate forms, which is soon trapped by the catalyst *via* ligand exchange, creating the proper chiral environment that discriminates the sense of the stereoinduction.

5. Closing remarks

Vinylogy and reactions inspired by this principle are rapidly expanding research themes, that have greatly added to the arsenal of efficient carbon–carbon bond-forming transformations over the past decades. In this context, the focus of this article is on vinylogous aldol, Mannich and Michael reactions involving

nucleophilic and pro-nucleophilic heterocyclic systems which, on reacting with proper acceptor molecules, pave the way to a realm of multifunctional compounds of various shapes and complexity. Following the evolution of this chemistry over the past few years, one soon realizes that the majority of the achievements covers furan- and pyrrole-based matrices, with only few scattered digressions to other vinylogous nuclei. By comparing the scientific production in the last triennium with contributions in the 2000–2009 decade,[3a] a striking increase of enantioselective and direct synthetic methodologies is observed, at the expense of diastereoselective or racemic indirect procedures; and this is in line with the general trend of contemporary research in synthetic organic chemistry.

Future opening towards the exploration of novel heterocyclic vinylogous systems and even more efficient catalytic activation modalities could further widen the horizon of vinylogy and enrich the chemical space of natural and man-made products.

Acknowledgments

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THE DIELS-ALDER REACTIVITY OF THE FUROXAN RING OF SUBSTITUTED BENZOFUROXANS. SYNTHESIS OF SUBSTITUTED IMINES AND EVIDENCE OF THE INTERMEDIACY OF ORTHO-DINITROSOARENES IN THE 1-OXIDE/3-OXIDE INTERCONVERSION

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Abstract. *Many papers have shown that the carbocyclic ring of nitrobenzofuroxans is involved in Diels-Alder reactions being capable of acting as a dienophile, a heterodiene or a carbodiene depending on the experimental conditions, the nature and the position of the substituents of the carbocyclic ring and the structure of the diene. In this paper, we report on the Diels-Alder reactivity of substituted benzofuroxans involving the furoxan ring. Convincing evidence is presented that the ortho-dinitroso intermediate involved in the exchange of the 1-oxide/3-oxide tautomers of benzofuroxans is the precursor of Diels-Alder diadduct supporting the transient formation of the dinitroso intermediate in the 1-oxide/3-oxide interconversion. Also reported are the evidences that the N3=C9–C8=N1 fragment of the annelated ring of some substituted benzofuroxans act as a heterodiene in the reaction with cyclohexa-1,3-diene and isoprene, highlighting that this new behaviour could be related to that of azadienes. As a minor result is also reported the reaction of the two tautomers, involved in the 1-oxide/3-oxide interconversion, with 2,3-dimethylbutadiene.*

Contents

1. Introduction

2,1,3-Benzoxadiazoles **1** and related 1-oxides **2** (Figure 1), commonly referred to as benzofurazans and benzofuroxans, respectively, are heteroaromatic 10π-electron ring systems whose carbocyclic ring is intrinsically very susceptible to nucleophilic attack. Most importantly, the introduction of a NO_2 group at C4 enhances the electrophilic reactivity of this ring by several orders of magnitude, making it comparable to that of a trinitro substituted benzene ring. This property has raised considerable interest in the 1970–1980's, mostly in connection with the recognition that the ease of covalent nucleophilic addition to the carbocyclic ring is responsible for the inhibitory effect exerted by some mononitrobenzofurazans and benzofuroxans on the biosynthesis of nucleic acid and protein in leucocytes and the observed activity against leukaemia. Also much attention was directed to the S_NAr reactivity of compounds like 4-chloro- and 4-fluoro-7-nitro-benzofurazans (**3** and **4**, Figure 1) which have become commonly used as fluorogenic reagents for detection and quantification of amino and thiol residues of proteins, drugs and biologically active molecules.[1–9]

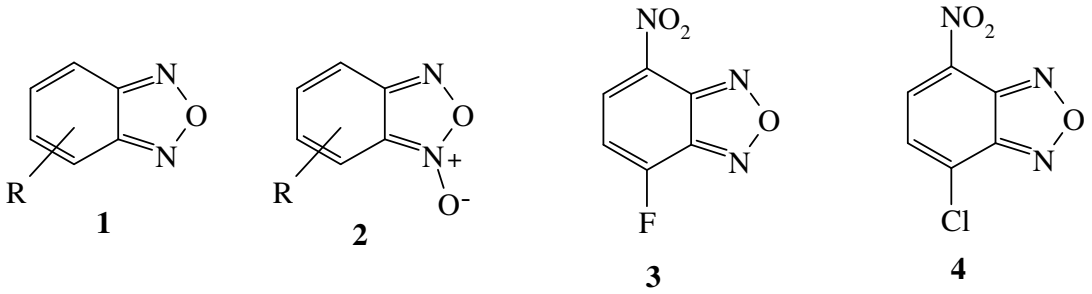


Figure 1

In the last decade, we have been engaged in an effort to investigate the reactivity of strongly electrophilic aromatic and heteroaromatic substitutions and related σ-complex processes. In this context, we discovered that some appropriate substitutions of the carbocyclic ring of benzofurazan and benzofuroxan structures enhance so much the electron-deficiency of this ring that the resulting compounds can be reasonably ranked as superelectrophilic heteroaromatics.

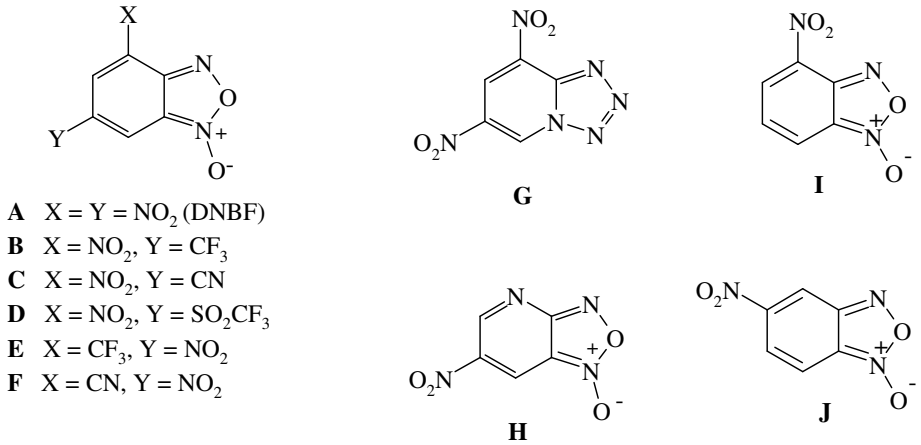
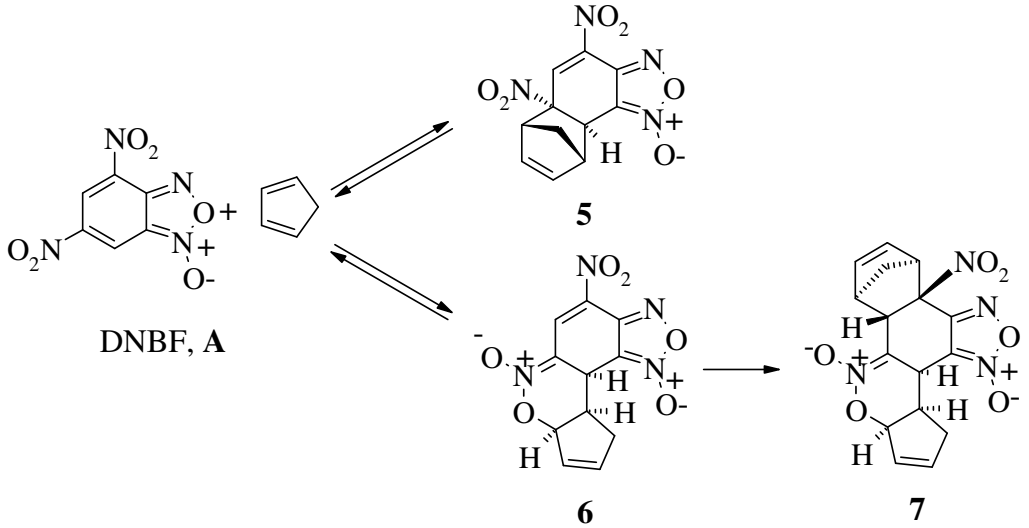


Figure 2

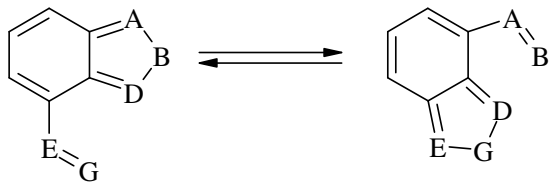
Referring mainly to the readily accessible prototype substrates, namely 4,6-dinitrobenzofuroxan (DNBF, **A**, Figure 2), we demonstrated that highly electrophilic benzofuroxans, benzofurazans and related heteroaromatic substrates (**B–J**, Figure 2) have the potential to react in a variety of pericyclic patterns being able to contribute as dienophiles, heterodienes or carbodienes depending on the experimental conditions and the reaction patterns at hand. Recently, it has been convincingly recognized that the exceptional electrophilic character of nitrobenzofuroxans is closely related to the low aromaticity of the carbocyclic ring.[10–16]

Crucial evidence for this relationship has been the discovery that the nitro-activated double bonds of this ring behave similarly to nitroalkene fragments in a variety of Diels-Alder processes. A first illustrative sequence refers to the reaction of DNBF with cyclopentadiene. As shown in Scheme 1, it leads to the competitive initial formation of the monoadducts **5** and **6** (in their racemic forms). This is followed by the stereoselective formation of the highly functionalized diadduct **7** which is eventually obtained and isolated in high yield. In as much as the C6=C7 double bond of DNBF is involved in the two initial Normal Electron-Demand Diels-Alder (NEDDA) and Inverse Electron-demand Diels-Alder (IEDDA) processes, the formation of the NEDDA and IEDDA adducts **5** and **6** is a clear-cut example of the potentially ambident nitroalkene Diels-Alder reactivity of DNBF. On the other hand, the preferred formation of the unsymmetrical IEDDA-NEDDA adduct **7** implies a greater dienophilic reactivity of the remaining nitroolefinic moiety in the IEDDA adduct **6** than in the NEDDA adduct **5**.[11a]



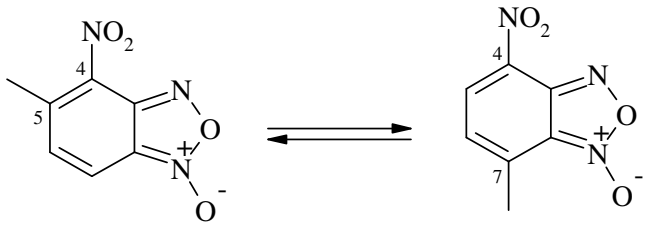
Scheme 1. Reaction of DNBF (**A**) with cyclopentadiene.

Substituted benzofuroxans are also known to undergo structural rearrangements such as the interconversion 1-oxide/3-oxide (*N*-oxide tautomerism) and the Boulton-Katritzky rearrangement (BKR, Scheme 2), which have been extensively reported in literature.[17]



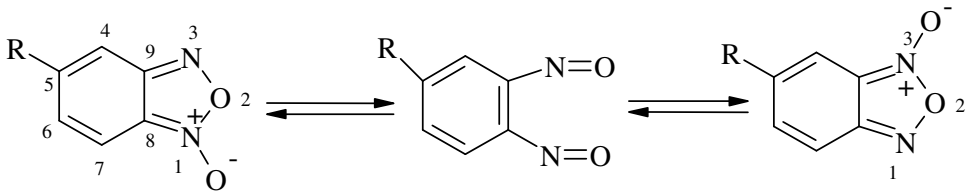
Scheme 2. Generalization of the BK rearrangement.

The BKR of 4-nitrobenzofuroxan can be considered as a prototype reaction for a class of molecular rearrangement. It was found that the mechanism reaction proceeds in one step *via* a tricyclic concerted transition state. For example, 5-methyl-4-nitrobenzofuroxan isomerizes to 7-methyl-4-nitrobenzofuroxan upon gentle heating. It was assumed that this isomerization is controlled by steric hindrance in the 5-isomer (Scheme 3).[17–20]



Scheme 3. BK rearrangement of 5-methyl-4-nitrobenzofuroxan.

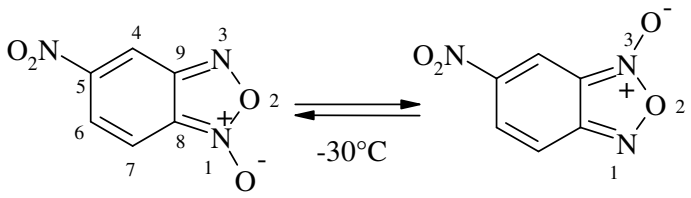
In addition to BKR, another rearrangement involving substituted benzofuroxan has been studied and well-known as the *N*-oxide tautomerism. Benzofuroxan itself (**8**, R=H) has been shown by low-temperature NMR studies to be a rapidly equilibrating system: the transformation between the 1- and 3-oxide structure proceeds *via o*-dinitrosobenzene (**9**, R=H) as an intermediate. Ring chain tautomerism of this type (Scheme 4) also occurs in substituted benzofuroxans. In the case of benzofuroxans substituted in the 5 position (for the numbering of benzofuroxan, see Scheme 4), the amount of each tautomer is dependent on the nature of the substituent R.



8 **9** **10**

Scheme 4. Interconversion 1-oxide/3-oxide of benzofuroxans.

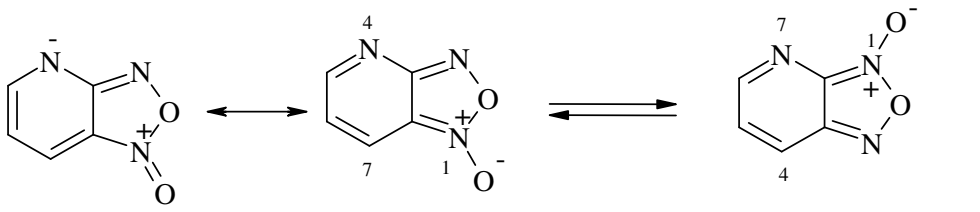
When R is an electron-donor group, structure **8** is more abundant, while an electron-withdrawing group favours structure **10**. When an electron-withdrawing group is located in the 4 position (the case of the 4-nitro-benzofuroxan, **I**), the benzofuroxan exists in one form with the *N*-oxide in the 1 position at all temperatures.[21,22] When the nitro group is at the 5 position (the case of the 5-nitrobenzofuroxan, **J**), both isomers exist at room temperature. The low temperature proton spectra recorded at −30 °C allow a rapid determination of the proportions of these two isomers, which appear to be 70/30 in favour of the 3-oxide isomer (**J-N$_3$**, Scheme 5).



J-N$_1$ - 70% **J-N$_3$** - 30%

Scheme 5. Interconversion 5-nitrobenzofuroxan **J**.

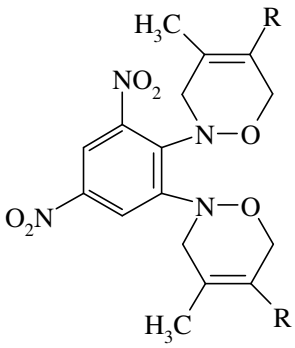
The steric and electronic effects of aza-groups on the benzofuroxan equilibrium have also been studied and are summarized in Scheme 6. The aza-group exhibits considerable preference for the 4-position of the benzofuroxan skeleton, as a result of electronic repulsions between the lone pairs of the oxygen and the aza-group. Energetically favourable charge delocalization can also contribute to the position of this equilibrium (Scheme 6). The 4-azabenzofuroxan is favoured by 0.95 kcalmol^{-1} compared to the 7-azabenzofuroxan.[17]



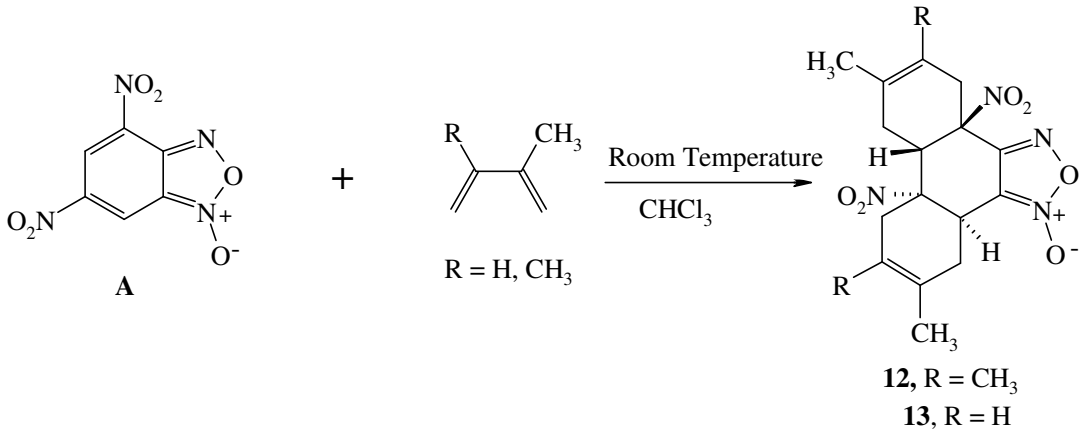
4-azabenzofuroxan **7-azabenzofuroxan**

Scheme 6. Aza-group effect in 4-azabenzofuroxan.

Numerous studies on the tautomerism of benzofuroxans show that the chemical behaviour of above mentioned heterocycles is consistent with the mechanism of Scheme 4. However, definitive evidence for the intermediacy of *ortho*-dinitrosoarenes (Scheme 4) was presented in 1991. It is only through photolysis of unsubstituted benzofuroxans and *o*-nitrophenylazide in Ar matrices at 14K that the existence of such unstable species could be demonstrated by IR and UV spectroscopy. Other attempts to trap this intermediate to provide convincing evidence supporting that this mechanism of interconversion proceeds through formation of an *ortho*-dinitroso intermediate have failed.[23]



11, R = H, CH_3



A R = H, CH_3 **12,** R = CH_3 **13**, R = H

Scheme 7. Trapping strategy of Kresze and Bathelt.

However, an interesting and pioneering study has to be mentioned. Kresze and Bathelt are the first to envision that the *o*-dinitroarenes could be trapped using Diels-Alder reaction. In that peculiar case, they postulate that the two N=O double bonds could react as dienophile with dienes, such a 2,3-dimethyl-butadiene or isoprene, leading to compounds of general structure **11**. Unfortunately, they only obtained adducts of type **12** and **13** involving the addition of two molecules of diene on the C4=C5 and C6=C7 double bonds of the benzofuroxan carbocycle (Scheme 7). Although the formation of these two compounds was accounted for in terms of Normal Electronic Diels-Alder processes, this promising discovery did not lead to further investigation and neither the stereochemistry nor the mechanistic sequence leading to **12** and **13** was elucidated.[24]

In this paper, we report on the first examples of the Diels-Alder trapping of an *o*-dinitroso intermediate. In a first part, we will describe the isolation and characterization of numerous compounds deriving from the interaction between the N=O double bonds of the *ortho*-dinitrosoarene and the double bonds of the diene. We will show that the formation of these derivatives is closely dependent on the structure of the diene and of the nature of the substituent borne by the carbocyclic ring of the benzofuroxan. In a second part, we will highlight that the two tautomers of 1-oxide/3-oxide interconversion can be involved in Diels-Alder processes leading to the isolation of two Diels-Alder adducts deriving from the position of the *N*-oxide functionality. In the last part, we will describe how some peculiar benzofuroxan derivatives react through the N3=C9–C8=N1 fragment of the annelated furoxan ring, acting as a heterodienic system to give highly functionalized imines.

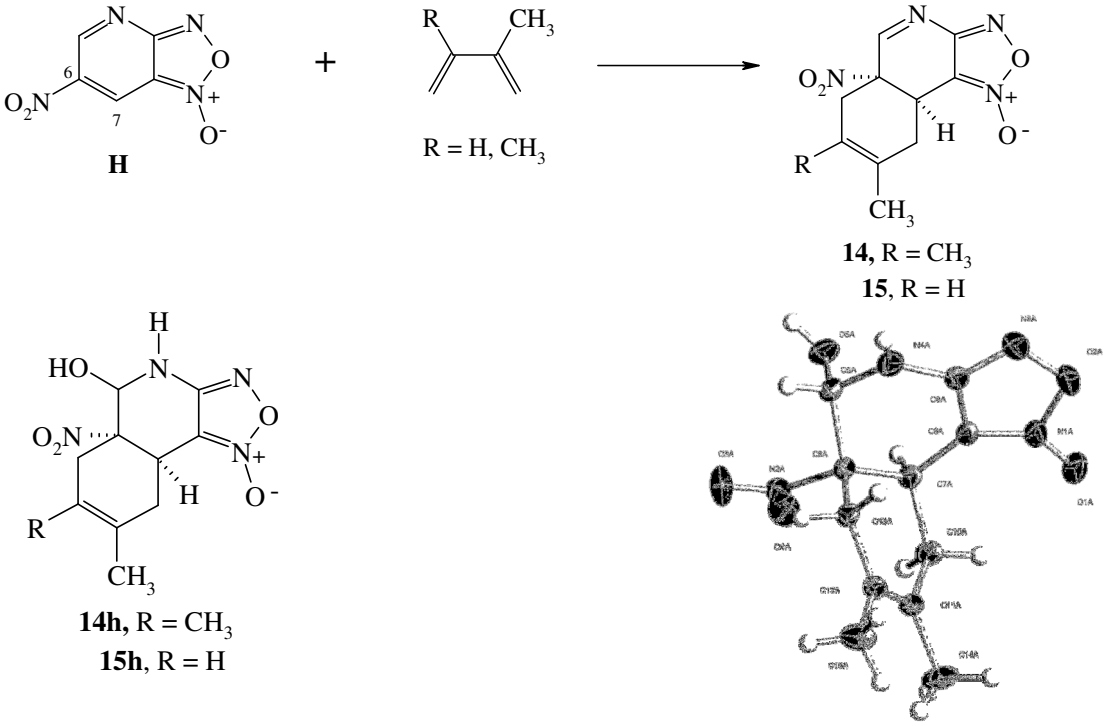
2. Trapping of *ortho*-dinitrosoarene: first convincing evidences for the intermediacy of this intermediate in the 1-oxide/3-oxide interconversion[25,26]

The reactions reported in the review are generally carried out at room temperature in chloroform or dichloromethane and in $CDCl_3$ for NMR *in situ* study of the Diels-Alder reactions. If other experimental conditions are used, the reaction conditions will be clearly specified in the corresponding scheme.

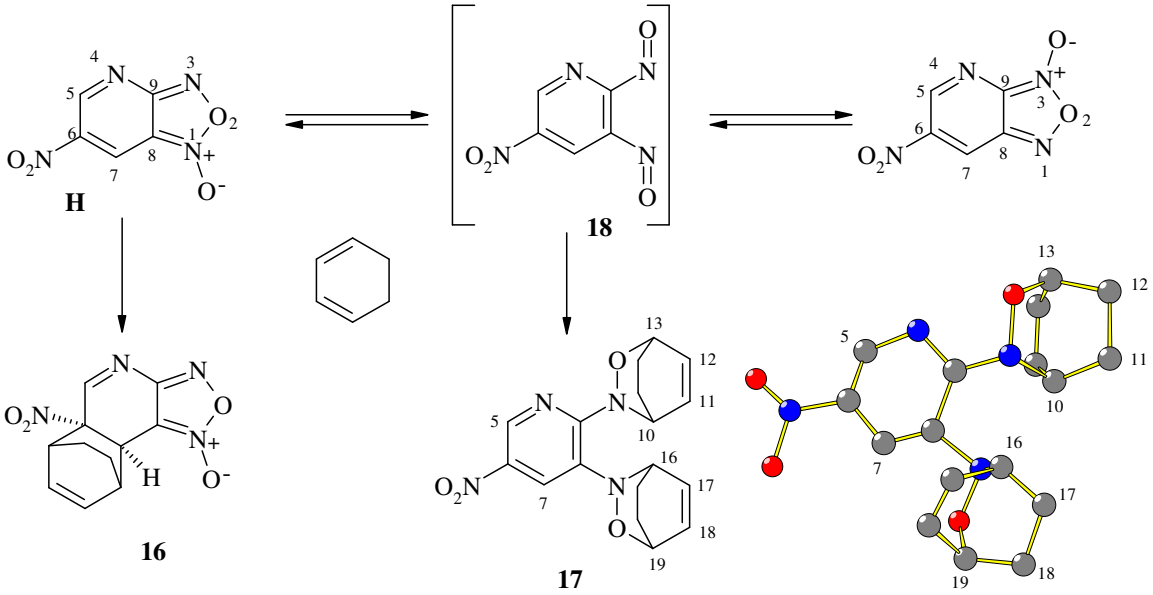
2.1. The case example of 4-aza-6-nitrobenzofuroxan H

Classically, benzofuroxan **H** reacts readily with 2,3-dimethylbutadiene or isoprene to give the two adducts **14** and **15**. The formation of these adducts can be accounted for in terms of Normal Electronic Demand Diels-Alder adduct, in which the C6=C7 double bond of the carbocyclic ring is acting as the dienophile. To be noted is that these two mono-adducts are sensitive to hydration and react with adventitious water to give the corresponding hydrate **14h** and **15h**. The structure of **14h** has been confirmed by a radiocrystallographic study, assessing the stereochemistry of these adducts (Scheme 8).

The reaction of **H** with cyclohexa-1,3-diene leads to an unexpected and interesting result. The reaction carried out in chloroform at room temperature affords a 2:1 mixture of two products **16** and **17**, which were readily separated by column chromatography and isolated as pale yellow solids. In view of the ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$, the minor product can be formulated as the cycloadduct **16**, which is resulting from a regioselective NEDDA process involving the C6=C7 double bond of **H**. More importantly, the structure of the major product has been confirmed through a radiocrystallographic study, leaving no doubt that this compound is a diadduct **17**, whose formation can only be accounted for in terms of two NEDDA processes, in which the two N=O double bonds of the *ortho*-dinitroso intermediate **18** play the role of the dienophiles (Scheme 9).[25]



Scheme 8. Reaction of **H** with isoprene and 2,3-dimethylbutadiene. Structure of the hydrates.

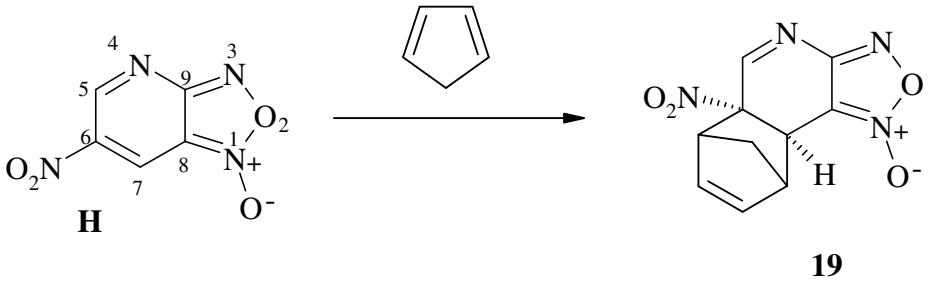


Scheme 9. Reaction of **H** with cyclohexa-1,3-diene: trapping of the intermediate **18**.

In accordance with the structure of **17** was the observation in the ^{1}H NMR spectra of two doublets at 7.88 and 8.62 ppm (^{3}J=2.6 Hz), characteristic of the two aromatic protons H7 and H5, respectively. These data are the main diagnostic features indicating the recovery of a pyridine ring. To be noted is that the disappearance in the ^{13}C NMR spectra of the resonance typical for the C8 carbon of a benzofuroxan structure (δ_{C8}=108.79 ppm in **H**) and its replacement by a resonance at 137.59 ppm for **17**, a typical value for the chemical shift of a carbon in an aromatic system, is also in favour of the pyridinic structure of **17**. More importantly, also typical for this structure, are the presence on the ^{1}H NMR spectra of the signals pertaining to the cycles resulting from the addition of cyclohexa-1,3-diene: four olefinic protons (H11, H12, H17, H18)

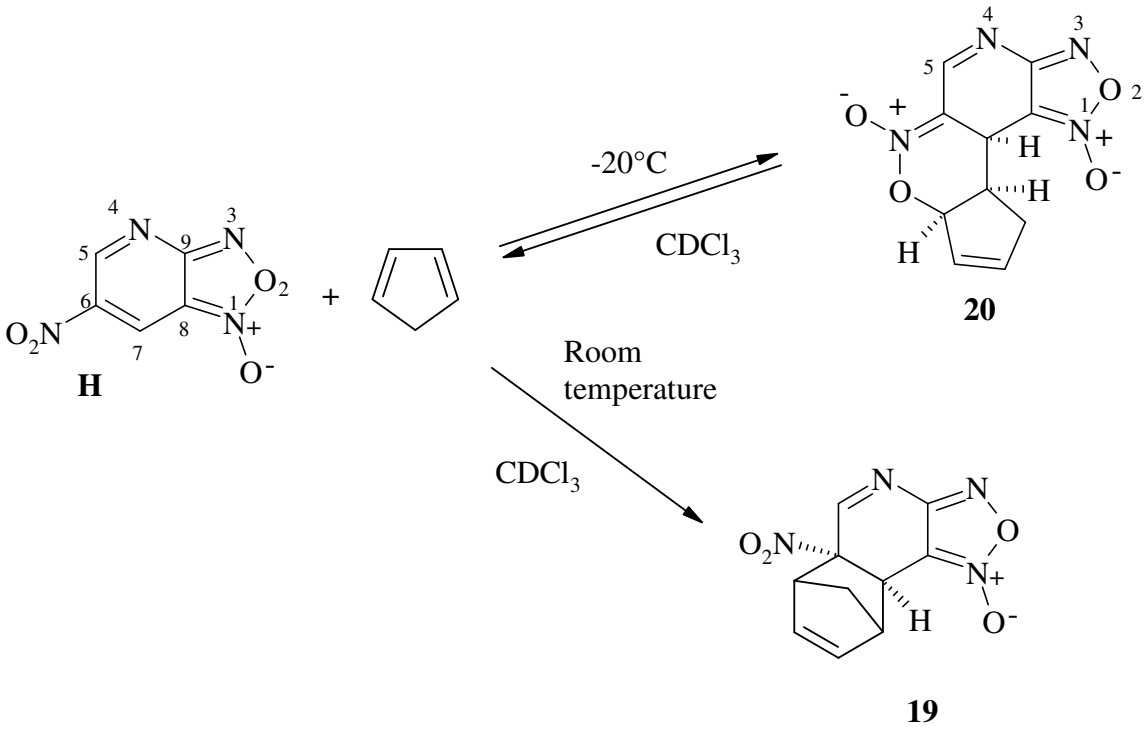
between 6.01 and 6.74 ppm and four deshielded signals characteristic of O–CH and N–CH type protons (H19 and H13: OCH; H10 and H16: NCH; see Scheme 9 for the numbering of the molecule **17**) between 4.88 and 5.67 ppm.

Similarly, it has been shown that the treatment of benzofuroxan **H** with an excess of cyclopentadiene is leading to the formation of the adduct **19**, resulting from a regio- and stereoselective addition of cyclopentadiene involving too the C6=C7 double bond of **H** as the dienophile component (Scheme 10).



Scheme 10. Reaction of benzofuroxan **H** with cyclopentadiene.

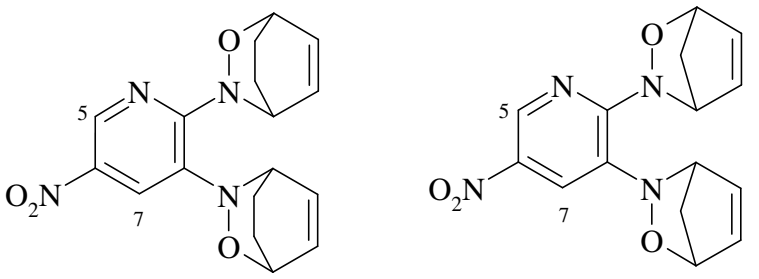
Carrying out the same experiment at low temperature (–20 °C) reveals the formation of the adduct **20**, this latter compound being the result of a competitive Diels-Alder reaction in which the aza molecule **H** now acts as a heterodiene through its O6=N6–C6=C7 fragment. Interestingly, this adduct becomes slowly converted to **19** when the temperature is allowed to rise. These observations show that **20** is the product of kinetic control, while **19** is the thermodynamically more stable product of the reaction (Scheme 11).[26]



Scheme 11. *In situ* generation of adducts **19** and **20**.

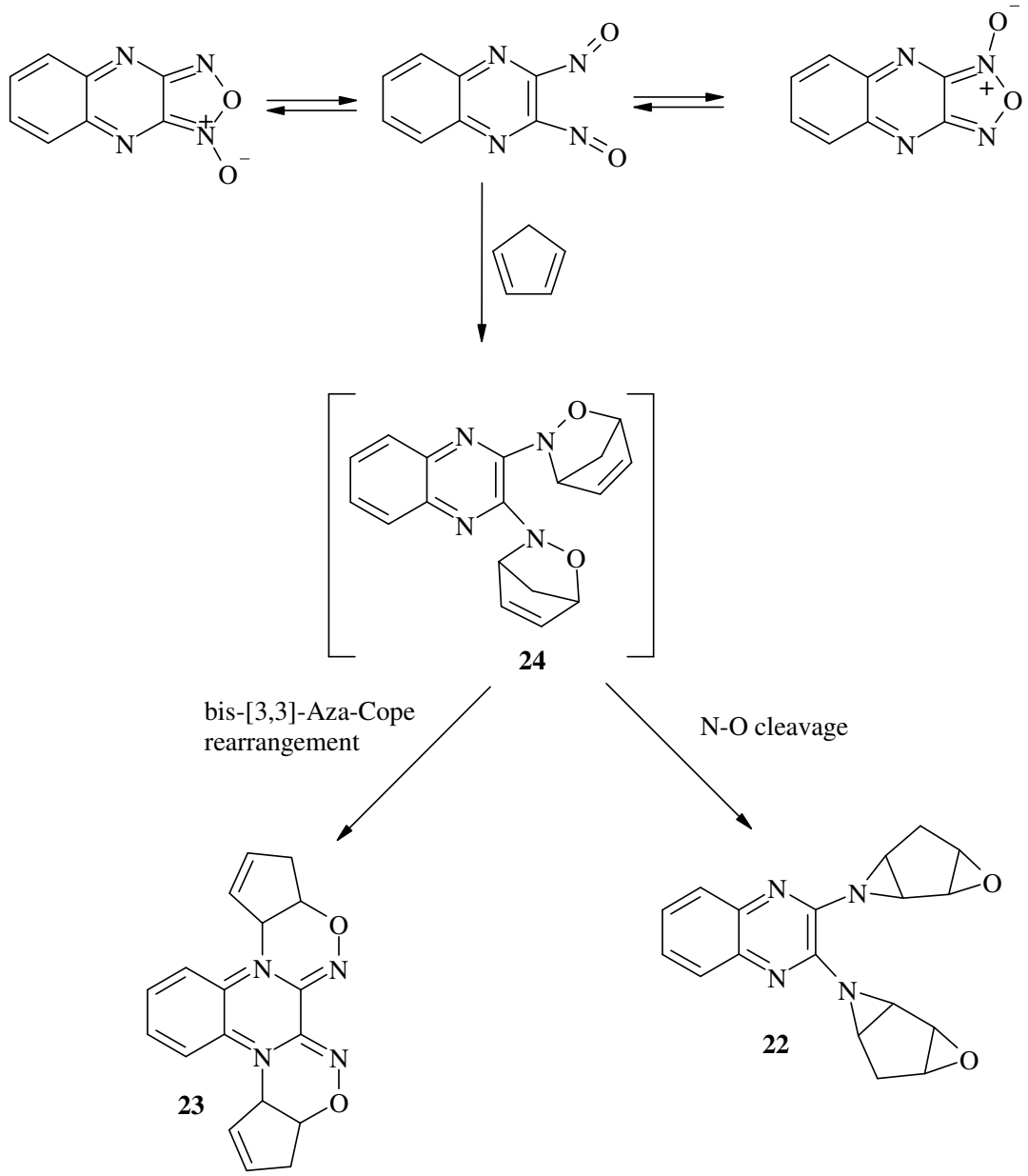
Also to be noted is that the reaction of **H** with cyclopentadiene at –20 °C gives rise to a minor product (5%) which can be identified as the Diels-Alder diadduct **21**. This adduct shows no decomposition on raising the temperature to room temperature and can be assigned to reaction of the *ortho*-dinitroso intermediate **18**

with the two N=O groups acting as dienophiles towards the cyclopentadiene molecule (see above). The two doublets observed at 8.72 (H5) and 7.86 ppm (H7), characteristic of the two protons pertaining to the pyridinyl moiety, are in total agreement with the structure of **21** (Figure 3).



17 **21**

Figure 3



Scheme 12. Indirect evidences of the intermediacy of diadduct **24**.

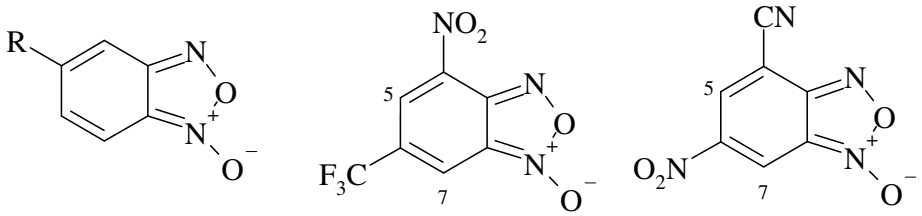
Some attention has to be paid to the influence of the size of the diene on the stability of the diadduct. When the reaction is carried out with cyclopentadiene, the diadduct **21** is obtained as a minor product, whereas the reaction with cyclohexa-1,3-diene leads to the compound **17** as the major product. The diadducts deriving from the addition of diene to the *ortho*-dinitrosoarenes are leading to the formation of two bicyclic moieties. The formation of these two fused rings in the final reaction product is going along with the appearance of steric hindrance and the size of the cyclic diene is noteworthy. Roughly, it is reasonable to assume that the steric strains are greater in the case of **21** (formation of two bicyclo[2.2.1]pentene type moieties) than in **17** (formation of two bicyclo[2.2.2]octene type moieties) being responsible that **21** could be of less stability than **17**.[26]

In 1994, Gallos *et al.* have reported a similar study. The reaction of the furazano[3,4-*b*]quinoxaline-1-oxide with the cyclopentadiene provides two compounds **22** and **23**, which are postulated resulting from the decomposition of the diadduct **24**, deriving from the addition of cyclopentadiene on the N=O double bonds of the *ortho*-dinitroso intermediate. Nevertheless, these authors have failed to isolate and characterize the diadduct **24** (Scheme 12) and to get direct evidence of the intermediacy of the *ortho*-dinitroarenes.

Even if in literature, many examples of benzofuroxan structures undergoing the tautomeric exchange have been reported, no firm Diels-Alder support for transient formation of the postulated *ortho*-dinitroso intermediate along the reaction coordinate has been obtained so far. The isolation and characterization of the diadducts **17** and **21** in a *thermal process at room temperature* (only photochemical evidences at low temperature have been reported in literature) are therefore of great relevance to the rearrangement shown in Scheme 4, especially because this equilibrium has been shown to be strongly shifted toward the 1-oxide tautomer in the case of benzofuroxan **H**.[27]

2.2. Extension of the trapping process to other benzofuroxans structures

Interestingly, this trapping has been extended to other benzofuroxans especially in the case of the heterocycles **8**, **B**, **F** and **J**. The reaction of these four substituted benzofuroxans with an excess of cyclohexa-1,3-diene leads to the formation of the diadducts **25–28**. As previously mentioned, the formation of these adducts can only be accounted for in terms of two NEDDA processes, in which the two N=O double bonds of the *ortho*-dinitroso intermediate play the role of the dienophile (Schemes 13 and 14).



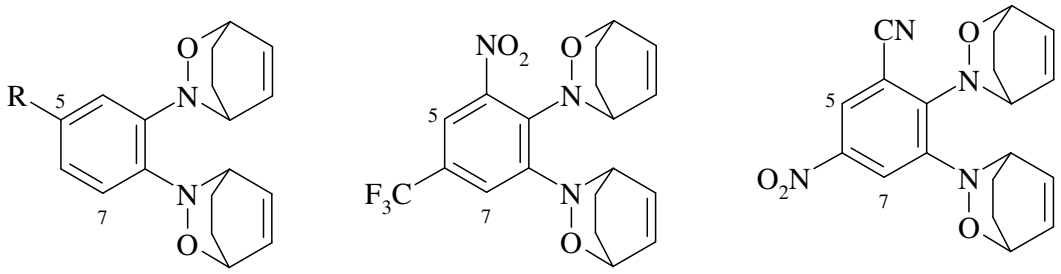
R = H, **8**
R = NO_2, **J**

B

F

Scheme 13. Structure of the benzofuroxans **8**, **B**, **F** and **J**.

These adducts are the sole products of the reaction in the case of **8** and **J**. However, in the case of **B** and **F**, they are obtained as the main compounds of the reaction together with a minor product. The reaction of 4-cyano-6-nitrobenzofuroxan **F** with cyclohexa-1,3-diene is leading to the formation and the characterization of the adduct **29** obtained in a 10% yield.

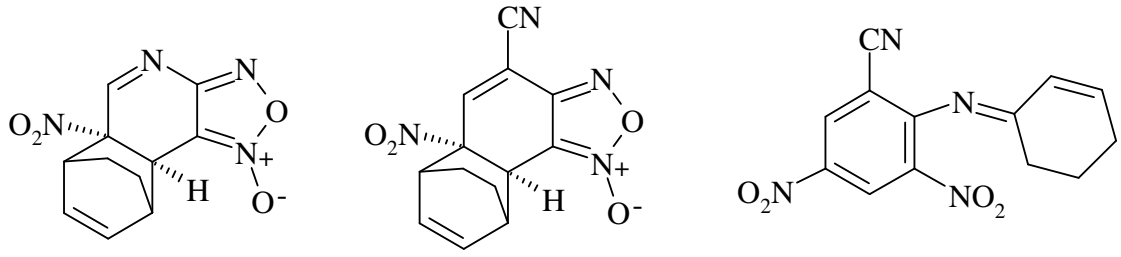


R = H, **25**
R = NO_2, **26**

27 **28**

Scheme 14. Structure of the diadducts **25–28**.

The structure of this adduct is reminiscent to that of **16** and its formation can be accounted for in terms of a NEDDA process, in which the C6=C7 double bond plays the role of the dienophile. The reaction of 4-nitro-6-trifluoromethyl-benzofuroxan **B** with cyclohexa-1,3-diene proceeds somewhat differently than that of **F** leading to the isolation of an unexpected compound **30**, whose formation will be extensively described in the third part of this review (Scheme 15). It will be shown that the formation of this highly substituted imine involves the addition of a molecule of cyclohexa-1,3-diene to the N3=C9–C8=N1 fragment of the furoxan ring acting as a heterodiene.

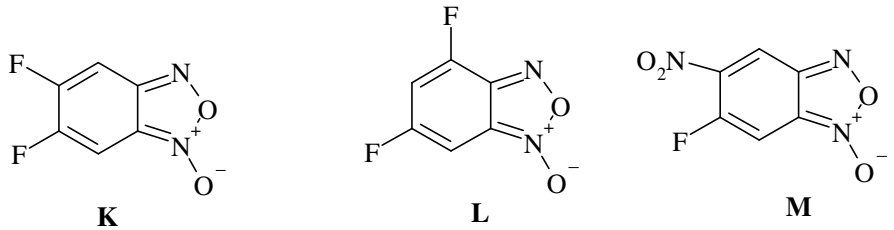


16 **29** **30**

Scheme 15. Structure of the adducts **16**, **29** and of the imine **30**.

2.3. A recent result: the case of 6-fluoro-5-nitrobenzofuroxan M

Fluoro- and difluorobenzofuroxan **K–M** (Scheme 16) have been extensively studied at the beginning of the 2000's. It has been shown that they react with nucleophiles as amines (through nucleophilic aromatic substitution) and that they exist as two tautomers interconverting through the intermediacy of the dinitroso compound.[28,29]

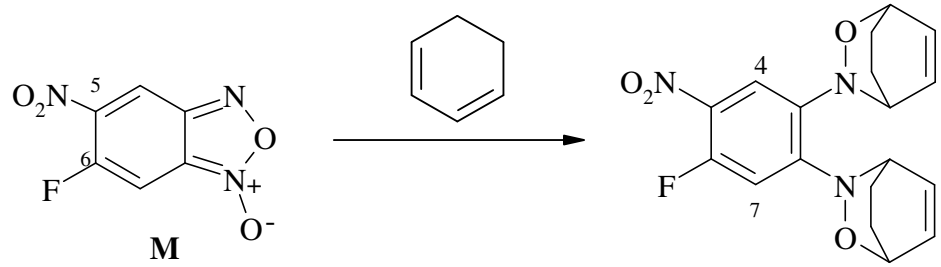


K **L** **M**

Scheme 16. Structure of the benzofuroxans **K–M**.

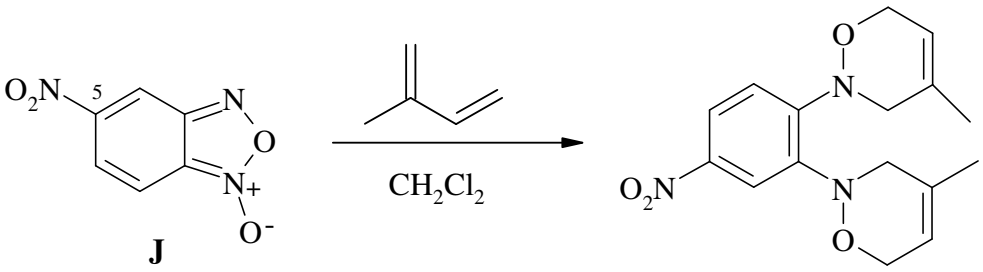
The reaction of 6-fluoro-5-nitrobenzofuroxan **M** with cyclohexa-1,3-diene is leading to the sole formation of the diadduct **31** arising from the addition of two molecules of cyclohexa-1,3-diene to the two

N=O fragments of the *ortho*-dinitroso intermediate. NMR spectra are in full agreement with this structure. The ^{1}H NMR spectra reveal the presence of two doublets pertaining to the two aromatic protons, H4 and H7, at 6.87 and 7.67 ppm, respectively. These two signals confirmed that the Diels-Alder reaction took place regioselectively at the furoxan ring (Scheme 17).



Scheme 17. Reaction of fluorobenzofuroxan **M** with cyclohexa-1,3-diene.

It has to be noted that the formation of this type of diadduct has only been observed in the reaction with cyclohexa-1,3-diene. This reactivity has not been observed in the Diels-Alder reaction with cyclopentadiene (except in the case of the reaction of **H** with cyclopentadiene at low temperature, *vide supra*) or with 2,3-dimethylbutadiene. Also to be noted is that only one example of formation of such diadduct in the reaction of isoprene with substituted benzofuroxans has been observed. The reaction of 5-nitrobenzofuroxan **J** with isoprene leads to the isolation of the diadduct **32**, whose formation can be accounted for in terms of NEDDA processes, in which the two N=O double bonds of the *ortho*-dinitroso intermediate play the role of the dienophile (Scheme 18). This adduct is unfortunately not very stable and we failed to get a suitable crystal for a radiocrystallographic study.



Scheme 18. Reaction of benzofuroxan **J** with isoprene.

It is very difficult to anticipate the formation of such diadducts. It appears that their formation is depending on the electronic effect and of the position of the substituents of the carbocyclic ring of the benzofuroxans and of the dienophilic partner. Theoretical calculations could be of great interest to understand the role of the substituent and of the structure of the diene in the reaction of the *ortho*-dinitroso intermediate with the diene.

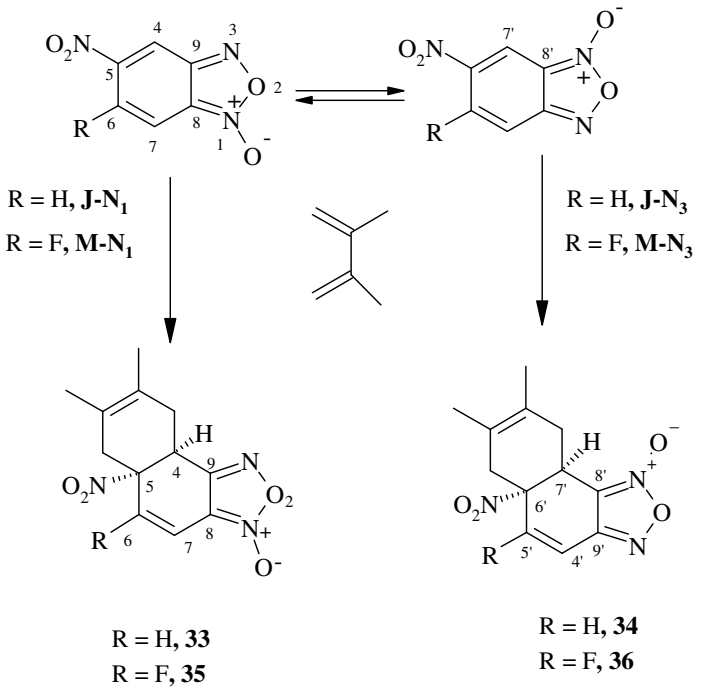
Our group has been the first group to bring direct evidences to support the formation of the postulated *ortho*-dinitroso intermediate and to show that this trapping not only involved mainly cyclohexa-1,3-diene but also isoprene and cyclopentadiene. The isolation of these diadducts has been observed and extended to 5 or 5,6 or 4,6 mono- or di-substituted benzofuroxans.

3. The 1-oxide/3-oxide interconversion: Diels-Alder reaction of both tautomers with isoprene and 2,3-dimethylbutadiene

3.1. Reaction of 5-nitrobenzofuroxan with 2,3-dimethylbutadiene

We have previously shown that the transformation between the 1- and 3-oxide structure proceeds *via ortho*-dinitrosobenzene as an intermediate, which has been trapped through the Diels-Alder reaction with cyclohexa-1,3-diene (*vide supra*). The 1-oxide/3-oxide interconversion occurs in substituted benzofuroxans. In this case, the amount of each tautomer is largely dependent on the nature and on the position of the substituent.

Treatment of 5-nitro-benzofuroxan **J** with a large excess of 2,3-dimethylbutadiene (5 eq.) at room temperature overnight led to the isolation of a yellow solid in a overall yield of 70%. A detailed analysis of the ^{1}H and ^{13}C NMR spectra of the product recorded in $CDCl_3$ indicates that it may be formulated as a mixture of two cycloadducts **33** and **34** in a 2/1 ratio. For example, the ^{13}C NMR spectra of the mixture reveal the presence of two signals around 88 ppm typical of a sp^3 carbon substituted by a NO_2 group. This leaves no doubt that the formation of **33** and **34** can be accounted for in terms of NEDDA processes, in which the C4=C5 double bond plays the role of the dienophile (Scheme 19, R=H). The ^{1}H NMR spectra also show the signals of two doublets at 6–7 ppm characteristic of ethylenic protons, confirming the isolation of ***mono***-adducts. Attempts to achieve the separation of these two adducts trough column chromatography have failed. The fact that these two adducts have very close polarity and that the Diels-Alder reactions, involving substituted benzofuroxans and dienes, are highly diastereoselective (only one diastereoisomer is always formed and isolated even in *in situ* reactions) is in favour of the formation of two isomers deriving from the position of the *N*-oxide functionality (see below) and not of the formation of two diastereoisomers.[12,13] ^{13}C NMR data, and especially the resonances of C8 and C8' (see numbering of the structures in Scheme 18), which are key elements in the structural assignment of **33** and **34**, are in full agreement with the structures of these compounds.



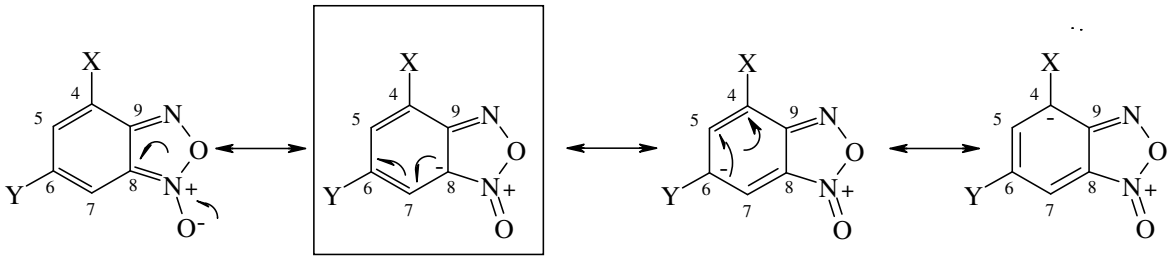
Scheme 19. Reaction of substituted 5-nitrobenzofuroxan **J** and **M** with 2,3-dimethylbutadiene: formation of the cycloadducts **33–36**.

The proportions of **J-N1** and **J-N3** have been found to be roughly 70% and 30%, respectively (see Scheme 5) and are in good correlation with the ratio of **33/34**, which is 2/1. This implies that the reaction with 2,3-dimethylbutadiene is very fast and that the amount of both tautomers remain unaffected by the Diels-Alder reaction.

To better understand the importance of the chemical shits of C8 and C9 and of the coupling constants involving these two carbons, in the structural assignment of these heterocycles, some information dealing with the NMR of substituted benzofuroxans are given below.[30]

The ^{13}C NMR spectra of benzofuroxans show some characteristic features. The complete ^{13}C NMR assignment of these compounds has been obtained using one- and two-dimensional NMR techniques including HMQC and HMBC experiments. So, the two resonances pertaining to C5 and C7 are readily determined while the resonances of the C9 and C8 appear to be the key features of the ^{13}C NMR spectra of benzofuroxans. With chemical shift of 145 and 115 ppm, respectively, the signals of C9 and C8 are quite independent of the position and of the nature of the substituent. The position of the signal pertaining to C8 with compare to that of C9 could be explained by the mesomeric effect of the *N*-oxide functionality.[30] This effect has been attributed to the presence of a partial negative charge on C8 resulting from a significant contribution of the second resonance form described in Scheme 20, while C9, more distant from the *N*-oxide function, remains unaffected or only slightly affected.[30]

HMBC spectra recorded for these compounds exhibited characteristic correlations. For example, two correlations between C9 (δ=145 ppm) and H7 (J_{C9H7}=5 Hz) and H5 (J_{C9H5}=7−9 Hz), respectively, can be observed while C8 (δ=115 ppm) is only correlated with H7 (J_{C8H7}=2−3 Hz).



Scheme 20. Resonance forms of substituted benzofuroxans: the effect of the *N*-oxide function.

Keeping in mind the aforementioned NMR features, two dimensional NMR experiments appear to be also a useful tool for the structural assignment of the adducts **33** and **34**. HMBC spectra (based on long range coupling) recorded for the mixture of cycloadducts **33** and **34** exhibited characteristic correlations. Three correlations between C8 (δ=109.0 ppm) and H4 (J_{C8H4}=3 Hz), H7 (J_{C8H7}=3 Hz) and H6 (J_{C8H6}=13 Hz), respectively, can be observed for **33**, while C9' (δ=150 ppm) is correlated with H4' ($J_{C9'H4'}$=2 Hz), H7' ($J_{C9'H7'}$=2 Hz) and H5' ($J_{C9'H5'}$=11 Hz) for **34**.

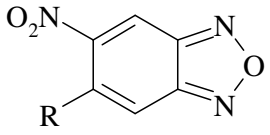
3.2. Reaction of 6-fluoro-5-nitrobenzofuroxan with 2,3-dimethylbutadiene

Similarly, the reaction of 6-fluoro-5-nitrobenzofuroxan **M** with 2,3-dimethylbutadiene is leading to the formation of two adducts **35** and **36** (70% yield) arising from the addition of 2,3-dimethylbutadiene to the nitro-activated double bond of both tautomers **M-N$_1$** and **M-N$_3$**. The determination of the structure of **35** and **36** has been made as described above. In this particular case, the couplings between the fluorine atom of the

carbocyclic ring and the various carbons and protons of the compounds **35** and **36** are helpful to assign unambiguously the chemical shifts (Scheme 19, R=F).

4. The reactivity of the benzofurazan N and O, analogues of J and M

In view of the potential importance of such a multifaceted reactivity as a new approach to synthesis in heterocyclic chemistry, we have looked at how one can modulate the Diels-Alder behaviour of benzofuroxans by eliminating the *N*-oxide functionality. So reactions with 2,3-dimethylbutadiene and cyclohexa-1,3-diene have been also performed with the benzofurazans **N** and **O** (Figure 4, Scheme 21).[28] In these compounds, the 1-oxide/3-oxide interconversion does not take place and the Diels-Alder reactivity is shown to be totally transferred to the carbocyclic ring of the heterocycles.

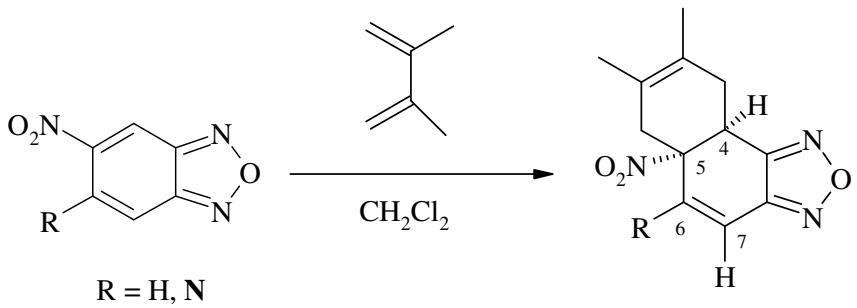


R = H, **N**
R = F, **O**

Figure 4

4.1. Reaction of N and O with 2,3-dimethylbutadiene

The treatment of **N** and **O** with an excess of 2,3-dimethylbutadiene afforded two mono-adducts **37** and **38** in their racemic form as a stable products of the reactions (Scheme 21). As major diagnostic feature for the occurrence of the monocondensation processes were the presence in the ^{1}H NMR spectra of a doublet at 6.74 ppm (J_{H7F}=13 Hz), characteristic of the olefinic-type proton H7 for **38** and of two doublets at 6.50 and 7.01 ppm (J_{H6H7}=9.8 Hz) for **37**, characterictic of H6 and H7, respectively. Also present in the ^{1}H NMR spectra are the pseudotriplets (δ=4.05 ppm for **37** and δ=4.45 ppm for **38**) assignable to the proton H4 bound to a deshielded sp^3 carbon. That the addition of the diene molecule occurred at the C4=C5 rather than C6=C7 double bond was unambiguously demonstrated by the following features of the ^{13}C spectra: (1) the presence of a resonance (δ=88.25 ppm for **37** and δ=90.05 ppm for **38**) assignable to the nitro substituted quaternary sp^3 carbon C5; (2) the presence in turn of a signal at δ=138.0 ppm for **37** and δ=161 ppm (doublet J_{C67F}=275 Hz) for **38** in agreement with the sp^2 carbon C6.



R = H, **N**
R = F, **O**

R = H, **37**
R = F, **38**

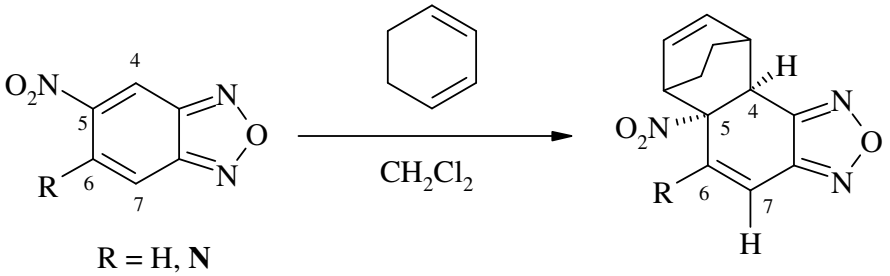
Scheme 21. Reaction of substituted nitrobenzofurazan **N** and **O** with 2,3-dimethylbutadiene.

The NMR data are consistent with the structures of **37** and **38**, which are resulting from a regioselective NEDDA condensation at the C4=C5 double bond. The structure of these adducts is in agreement with those reported in the literature by our group.[12,13]

Interestingly, contrasting with the situation which prevails in the benzofuroxan series, *i.e.* the formation of two adducts deriving from the position of the *N*-oxide functionality, the reaction of benzofurazans **N** and **O** is leading to the formation of only one adduct, **37** and **38**, respectively. This confirms the finding that the adducts **33** and **34** (or **35** and **36**) are not diastereoisomers but two adducts deriving from the position of the *N*-oxide functionality.

4.2. Reaction of N and O with cyclohexa-1,3-diene

The reaction of the benzofurazans **N** and **O** with cyclohexa-1,3-diene is leading to the formation of two adducts **39** and **40** as pale yellow solids in quantitative yields. The formation of these two compounds was accounted for in terms of Normal Electronic Diels-Alder (NEDDA) processes involving the nitro-activated C4=C5 double bond of the heterocycles as the dienophile contributor (Scheme 22). The structure of these two adducts agrees well with a detailed analysis of the ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$ as well as COSY and NOESY experiments. The structure of these adducts is also in agreement with those reported in the literature.[11]



R = H, **N**
R = F, **O**

R = H, **39**
R = F, **40**

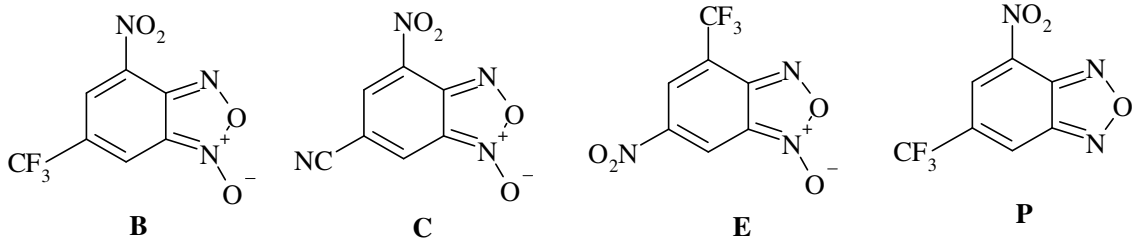
Scheme 22. Reaction of substituted nitrobenzofurazan **N** and **O** with cyclohexa-1,3-diene.

In view of these two last results, we have looked at how a slight structural modification can modulate the Diels-Alder behaviour of benzofuroxans by modifying the substitution pattern of the carbocyclic ring, removing the *N*-oxide functionality or varying the diene partner. The removal of the *N*-oxide is obviously going along with the fact that the 1-oxide/3-oxide tautomerism does not take place anymore and that the reaction of **N** and **O** with cyclohexa-1,3-diene is leading exclusively to cycloadducts involving the nitro-activated double bond C4=C5 confirming that the Diels-Alder reactivity of **N** and **O** is totally shifted to the carboxylic ring of the heterocycles.

5. The heterodienic behaviour of the N3=C9–C8=N1 system of the furoxan ring: an access to highly functionalized imines[31]

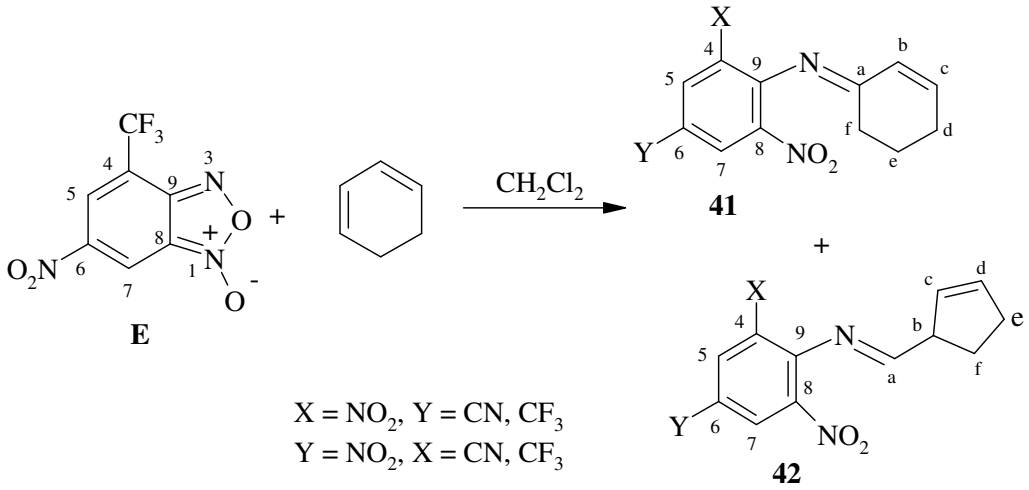
5.1. The reaction of benzofuroxans B, C and E with cyclohexa-1,3-diene

Here, we report on the discovery of another new Diels-Alder pathway that we have identified in the reaction of benzofuroxans **B**, **C** and **E** (Scheme 23) with cyclohexa-1,3-diene and isoprene. Structural evidences indicate that the N3=C9–C8=N1 fragment of the annelated ring of **B**, **C** and **E** acts as a heterodiene in these systems to give dinitroarylimines.



Scheme 23. Structure of benzofuroxans **B**, **C**, **E** and benzofurazan **P**.

Treatment of **E** with excess cyclohexa-1,3-diene at room temperature in CH_2Cl_2 takes place over one week to afford a mixture of the two imines **41** and **42** (see structures in Scheme 24).

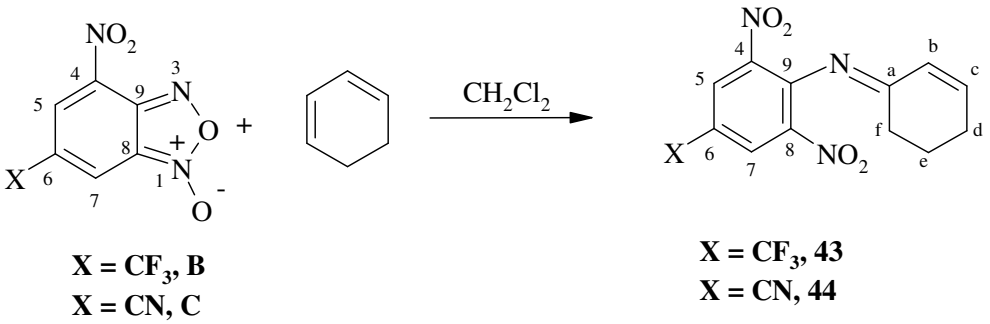


Scheme 24. Structure of the imines **41** and **42**.

Elemental analysis, mass spectrometric data as well as ^1H and ^{13}C NMR data fully agree with the proposed structures. Among other diagnostic features it is noteworthy that the proton and carbon resonances pertaining to the activated aromatic ring are very similar for **41** and **42**, a reflection of strong similarity of this moiety in these two molecules. In contrast, the imine fragments of **41** and **42** are characterized by quite different sets of carbons, two tertiary sp^2 carbons and one quaternary sp^2 carbon for **41** but two methylene carbons, one tertiary sp^3 carbon and three tertiary sp^2 carbons for **42**. A detailed analysis of ^1H NMR spectra reveals the presence of multiplet at 7.78 ppm characteristic of the olefinic proton Ha for the imine **42**. The greater deshielding of the ethylenic protons Hb and Hc in **41**, δ=6.13 ppm and δ=6.81 ppm, respectively, than for those of **42**, δ_{Hc}=6.07 ppm and δ_{Hd}=5.74 ppm is in full agreement with the conjugation of the two double bonds of the imine moiety in **41**.

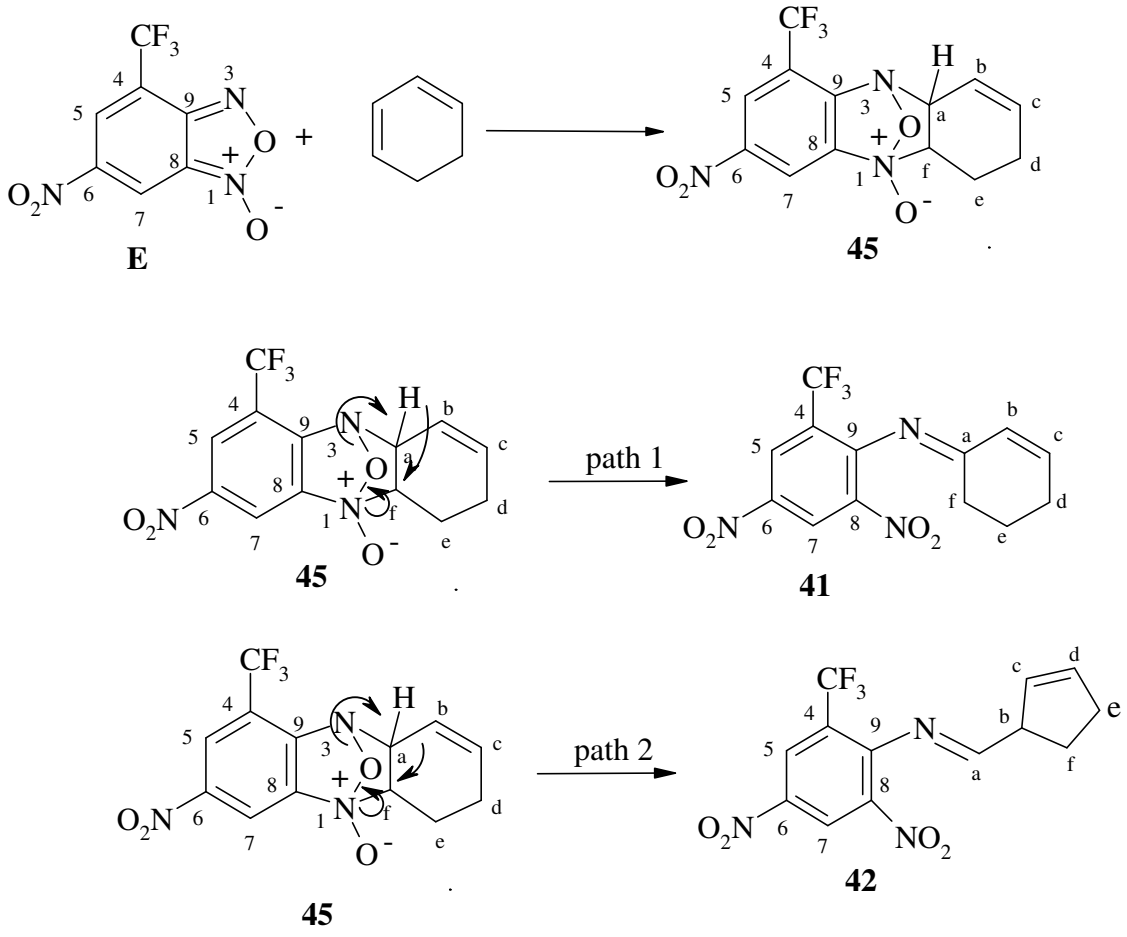
The reaction with the isomeric 4-nitro-6-trifluoromethylbenzofuroxan **B** with cylcohexadiene proceeds somewhat differently than that of **E**, giving rise to the imine **43** and the diadduct **27** in a 3/1 ratio. The formation of **27** has been already described (*cf.* paragraph 2.2.). Interestingly, the change of the position of the trifluoromethyl group on going from **B** to **E** is going along with the formation of a symmetrical imine (see the structure of **43** in Scheme 25). In accordance with the symmetry of this imine is the observation in the ^1H and ^{13}C NMR spectra of only signal for $H_{5,7}$ and $C_{5,7}$ at 8.37 ppm and 126.2 ppm, respectively. Similarly, the imine **44** has been isolated in a 30% yield in the reaction of 4-nitro-6-cyanobenzofuroxan **C** with cylcohexadiene giving ^1H and ^{13}C NMR spectra in full agreement with the structure of **44**. Also present

in the ^{1}H and ^{13}C NMR spectra are the unique singlet typical for $H_{5,7}$ and $C_{5,7}$ at 8.32 ppm and 129.5 ppm, respectively, confirming the symmetry of **44**. Surprisingly, the formation of the second isomer, *i.e.* the imine containing the five membered ring, has not been observed.



Scheme 25. Formation and structure of the imines **43** and **44**.

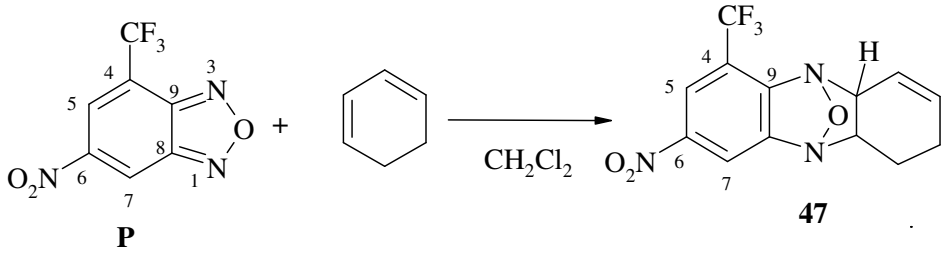
A reasonable mechanism can be envisioned to account for the formation of the imines **41** and **42**. This mechanism outlined in Scheme 26 involves the initial formation of the adduct **45** resulting from an inverse electron demand Diels-Alder condensation of a molecule of cyclohexa-1,3-diene to the N3=C9–C8=N1 fragment of the furoxan ring acting as a heterodiene. Structure **45** would not be stable, however being very prone to undergo a 1,2-hydride transfer (path 1) or a 1,2-alkyl group transfer (path 2) with the concomitant opening of the furoxan ring and breaking of the N1–Cf bond to give **41** and **42**.



Scheme 26. Mechanism of the formation of the imines **41** and **42**.

A second mechanism could be based on a possible nitrenoid reactivity of the nitrogen atom N3 of **B**, **C** and **E** with the initial formation of the aziridine **46** which will subsequently decompose to **41** and **42**. A significant feature in favour of the first mechanism is the isolation of the adduct **47** (Scheme 27) in removing the *N*-oxide functionality of **B** and looking at the reaction of 4-nitro-6-trifluoromethylbenzofurazan **P** (see structure of **P** in Scheme 23) with cyclohexa-1,3-diene.

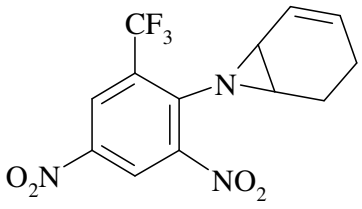
Since nitro-benzofuroxans and -benzofurazans behave in general similarly, we feel that the isolation of **47** is really a major argument favouring the mechanism described in Scheme 26.



P **47**

Scheme 27. Formation and structure of the adduct **47**.

In contrast, no evidence whatsoever could be obtained for the formation of **46**, despite the expected stabilization of the aziridine structure through conjugation of the nitrogen atom with the strongly electron deficient dinitrophenyl ring.



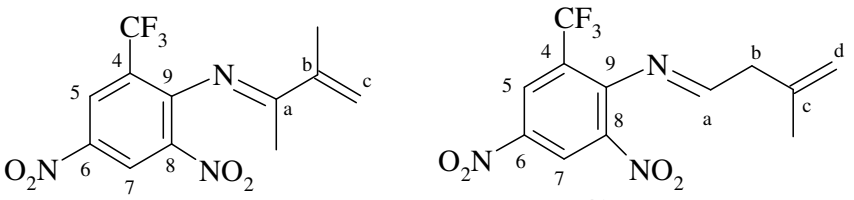
46

Scheme 28. Structure of the aziridine **46**.

The formation of the imines **41**–**44** represents a new reactivity pattern in the chemistry of nitrobenzofuroxans. The fact that the N3=C9–C8=N1 fragment of the furoxan ring seems to be capable to act as a heterodiene is a nice illustration that the behaviour of these heterocycles could be also related to that of azadienes.

5.2. The reaction of benzofuroxans C and E with isoprene

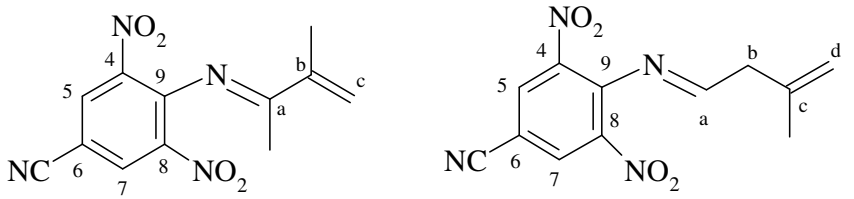
The treatment of **E** with isoprene at room temperature is leading to a mixture of two imines **48** and **49** (Scheme 29). The structural assignment has been made as above: (1) the NMR spectra pertaining to the aromatic ring remain unaffected on going from the imine deriving from cyclohexa-1,3-diene **41** and **42** to those deriving from isoprene **48** and **49** (δ_{H5}=8.70 ppm and δ_{H7}=8.99 ppm for **41**, δ_{H5}=8.73 ppm and δ_{H7}=9.05 ppm for **48**; δ_{C5}=126.1 ppm and δ_{C7}=124.3 ppm for **41**, δ_{C5}=126.3 ppm and δ_{C7}=124.5 ppm for **48**); (2) as reported in the paragraph 5.1., one of the two imines possesses two conjugated double bonds and this conjugation is going along with a greater deshielding of the ethylenic protons in **48** than in **49** (δ_{Hc}=5.78 and 5.88 ppm for **48** and δ_{Hd}=4.92 and 5.03 ppm for **49**); (3) two methyl groups are observed in the NMR spectra of the conjugated imine (δ_{CH3}=2.03 and 2.14 ppm for **48**) while only one methyl group (δ_{CH3}=1.87 ppm) together with a methylene group (δ_{CH2}=3.23 ppm) are observed for **49**.



48 **49**

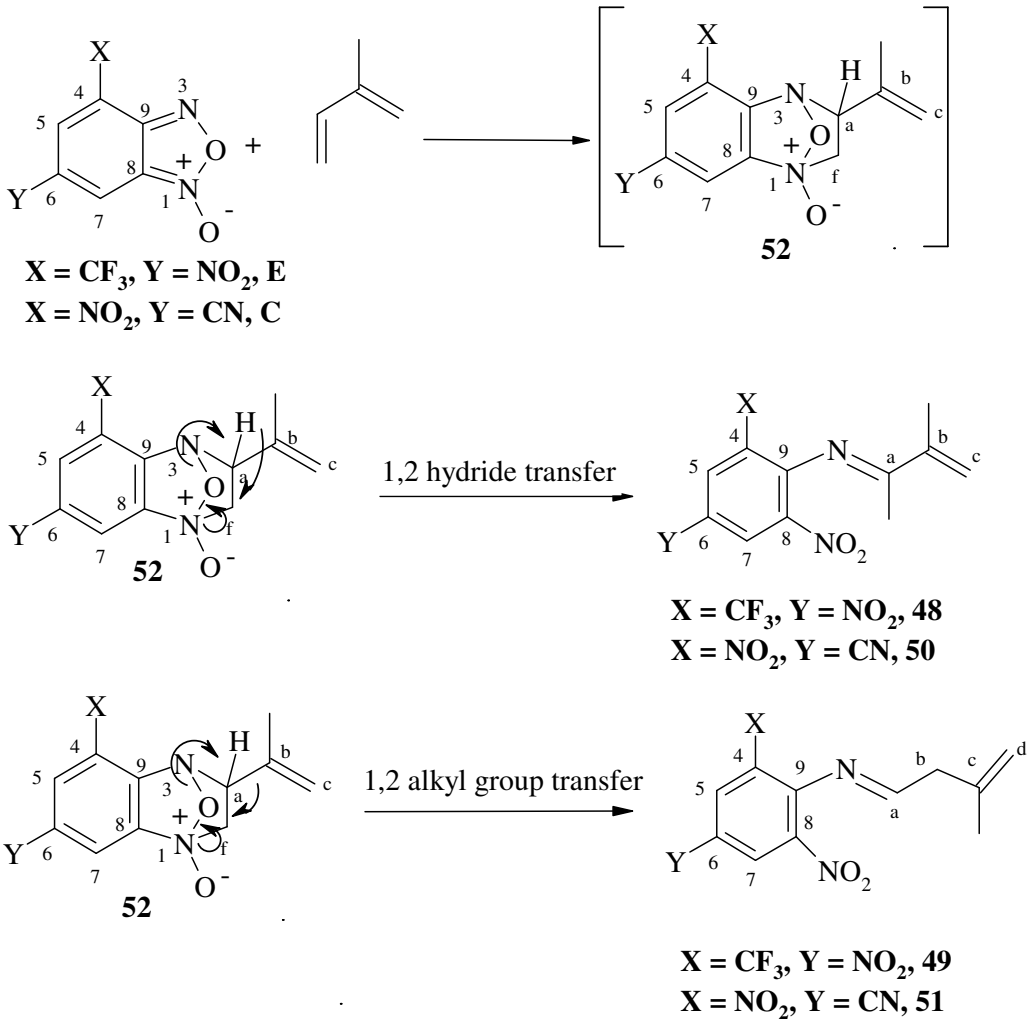
Scheme 29. Structure of the imines **48** and **49**.

The reaction of **C** with isoprene allows the isolation of two imines **50** and **51** differing from the previous ones by the position and the nature of the substituent. Due to the presence of the cyano group at the 6 position of the carbocyclic ring of **C**, the structure of compounds **50** and **51** is symmetrical (Scheme 30).



50 **51**

Scheme 30. Structure of the imines **50** and **51**.



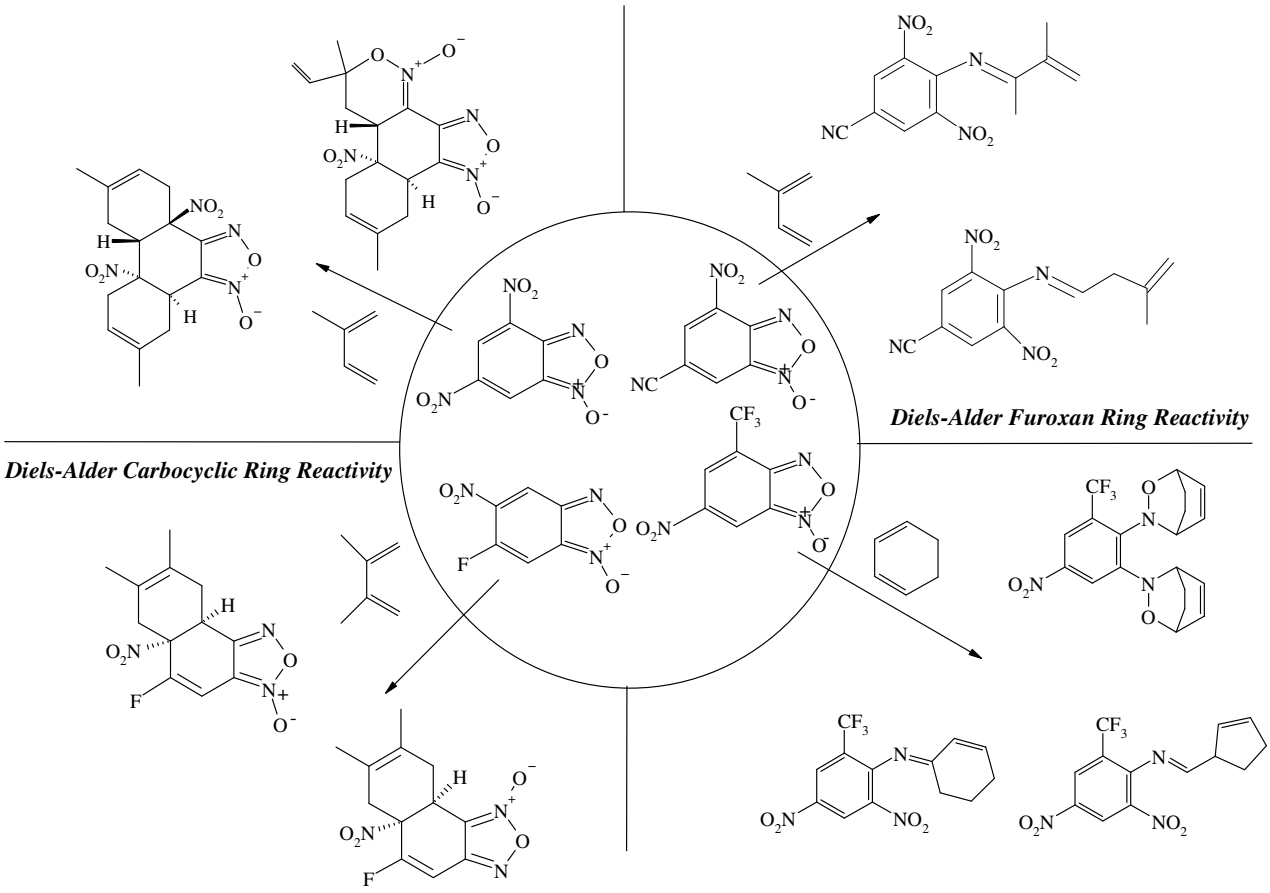
Scheme 31. Mechanism for the formation of the imines **48–51**.

A mechanism accounting for the formation of the imines **48–51** can be postulated on the basis of the mechanism described above in the reaction of benzofuroxans with cyclohexa-1,3-diene. The formation of the unstable adduct **52**, followed by the 1,2-hydride or 1,2-alkyl group transfer, is leading to the formation of **48–51** (Scheme 31).

Formation of these highly functionalized imines is of great interest since they are obtained in only one step, from the reaction between benzofuroxan (easy to synthesize) and isoprene or cyclohexa-1,3-diene (commercially available), in good yields. Unfortunately, this reactivity is restricted to nitrobenzofuroxans **B**, **C** and **E** and to their reaction with the two aforementioned dienes. For example, no reactivity of this type has been observed in the case of the reaction of **B**, **C** and **E** with cyclopentadiene or 2,3-dimethylbutadiene. Theoretical calculations could be a useful tool to rationalize the reactivity of the furoxan ring and need to be performed to:

*understand the nature and the position of the electron-withdrawing substituent borne by the carbocyclic ring of the benzofuroxan on the reactivity of the N3=C9–C8=N1 fragment of the furoxan ring.

*get structural criteria to extend this reactivity to other substituted benzofuroxans and dienophilic partners.



Scheme 32. Dual Diels-Alder reactivity of substituted benzofuroxans.

6. Conclusion

In this paper, we have shown that the Diels-Alder reactivity of nitrobenzofuroxans also involves the furoxan ring (*i.e.*, the five membered ring) and not only the carbocyclic ring of these heterocycles (Scheme 32, the upper and left part of this scheme is referring to reference 13). The trapping of *ortho*-dinitroso arenes

together with the reaction of the N3=C9−C8=N1 fragment of the furoxan ring with dienes are two examples illustrating this new reactivity. Even if in literature, many examples of benzofuroxan structures undergoing the tautomeric exchange (1-oxide/3-oxide) have been reported, no firm Diels-Alder support for transient formation of the postulated *ortho*-dinitroso intermediate along the reaction coordinate has been obtained so far. The isolation and characterization of the diadducts **17** and **21** in a *thermal process at room temperature* (only photochemical evidences at low temperature have been reported in literature) are therefore of great relevance to this interconversion shown in Scheme 4, especially because this equilibrium has been shown to be strongly shifted toward the 1-oxide tautomer in the case of benzofuroxan **H**. The fact that the N3=C9−C8=N1 fragment of the furoxan ring seems to be capable to act as a heterodiene to lead to the formation of highly functionalized imines is a nice illustration that the behaviour of these heterocycles could be also related to that of azadienes.

Acknowledgments

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APPROACHES TO THIAZOLE DIPEPTIDES FOR THE SYNTHESIS OF THIOPEPTIDE ANTIBIOTICS

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Abstract. *Here, we describe the chemical synthesis of thiazole dipeptides which are constituents of macrocyclic thiopeptide antibiotics. The synthetic methods for the assembly of thiazole dipeptides and their subsequent incorporation in oligopeptides are well-developed, often based on Hantzsch chemistry with thioamide precursors. In spite of interesting recent developments of milder reaction conditions, peptides with complex side chains are still hardly accessible. Current synthetic efforts focus on efficient methods for the synthesis of adequately protected dipeptides with mono- and dihydroxylated glutamate-related side chains next to the thiazole moiety and their incorporation into the macrocyclic thiopeptide antibiotics. The most challenging peptides contain these highly functionalized thiazole dipeptides not only linked at their α-amino and α-carboxy functionalities but also involving up to three functional groups of the amino acid side chain.*

Contents

1. Introduction

Thiazole peptides are formed by the enzymatic post-translational tailoring of peptides. The condensation of the mercaptyl side chain of cysteine and the neighbouring amide bond captures the two hydrophilic functional groups in a heterocyclic motif. The resulting overall improvement of biophysical properties transforms the polar peptide into a more drug-like heterocyclic compound. It is therefore not surprising that *"heterocycles are a recurring motif in Nature's medicinal chemistry toolbox"*,[1] being found in a multitude of peptides and polyketides of varying molecular weight and synthesized by different organisms.

Heterocyclic rings not only decrease the polarity of the peptide but also lock rotatable bonds of the peptide backbone within the aromatic ring. Hydrophobization and rigidity open up new possible modes of

action for the peptide which now can diffuse through membranes to reach cellular compartments which are otherwise hardly accessible to peptides. Therein, thiopeptides find their molecular targets which can be either metals, proteins, RNA or DNA, respectively. The increased stability against degradation by peptidases further improves the performance of thiopeptides as drugs.

While an amide bond between two amino acids is symbolized by the hyphen "-", we suggested the use of "<" to indicate the second linkage generated by the ring formation. A peptide precursor containing the Val-Cys dipeptide is thus transformed to the Val<Thz thiazole (Figures 1 and 2). Only the thiazole dipeptides which contain proteinogenic side chains are readily accessible along well-established synthetic protocols which can be even incorporated in solid phase peptide synthesis. Yet, the more complex mono- and dihydroxylated dipeptide thiazoles found in oligocyclic peptide antibiotics require sophisticated protecting group strategies not only for their assembly but also for the subsequent incorporation into the oligocyclic antibiotic. The synthesis of adequately protected dipeptide derivatives for the chemical synthesis of complex thiopeptides is the topic of this review. Figure 1 summarizes typical side chains and the problems associated with thiazole dipeptide synthesis. Major challenges are the number of stereocentres, the side chain functional group and the limited possibilities for up-scaling from sub-gram amounts to relevant amounts of orthogonally protected building blocks for the subsequent assembly of the thiopeptide antibiotic. This requests new chemical strategies which start from readily accessible educts along simple and robust preparation protocols towards various configurations and chain lengths. Extended side chains and artificial thiazole dipeptides analogs are of potential interest for Medicinal Chemistry.

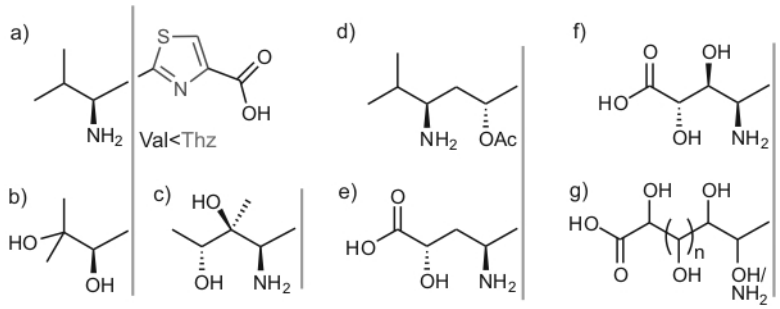


Figure 1. Side chains of increasing complexity as found in thiazole dipeptides. a) Several synthetic methods are available for the introduction of unpolar proteinogenic side chains like in the Val<Thz dipeptide which is constituent of the cyclopeptide patellamide. Further side chains b)–g) are shown without the Thz moiety (grey bar). b) Hectochlorin is a hydroxylated depsipeptide derivative of Val<Thz. Hydroxylated side chains are less readily accessible to chemical synthesis. c) (2*S*,3*S*,4*R*)-3,4-Dihydroxy-isoleucine<Thz is found in thiostrepton which is shown in Figure 3. d) Tubuvaline (Tuv) and e) (4*S*)-hydroxy-glutamate<Thz are components of the peptide antibiotics tubulysine and nosiheptide, respectively. Both are accessible *via* chiral pool approaches. f) The highly functionalized (2*S*,3*S*,4*S*)-3,4-dihydroxy-glutamate<Thz is found in nocathiacines and thiazomycines and was until recently not accessible by chemical synthesis. g) shows unnatural extended side chains.

1.1. Thiazole units in peptide natural products

1.1.1. Ribosomal thiazole formation

Figure 2 schematically shows the constitutive steps of thiazole formation in biosynthesis. The heterocycles originate from a dipeptide unit with any residue *N*-terminal to the amide bond and a Cys residue at the *C*-terminal position. Base activation of the side chain SH nucleophile at the binding site of a heterocylization catalyst (heterocyclase) is followed by attack the amide carbon, resulting in the tetrahedral

intermediate. A second basic residue triggers dehydration towards the thiazoline. Thiazoline motif widely occurs in peptide-derived natural products, from which the antibiotic bacitracin is among the most prominent ones, marketed for example as Nebacetin® (*Sandoz*) or Polyspectran® (*Alcon Pharma*, market volume 120 million USD).[2–4]

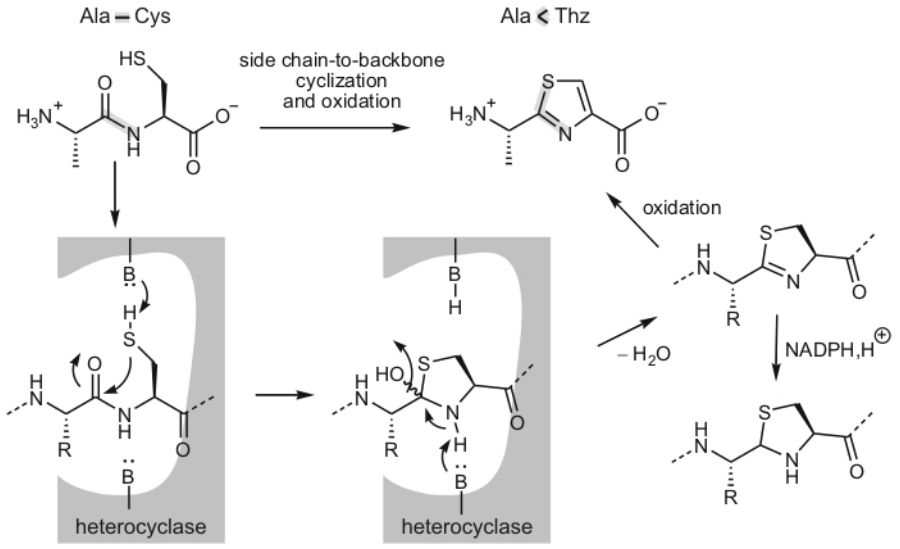


Figure 2. Biosynthesis of thiazole peptides. This enzyme-catalyzed reaction sequence is shown for an Ala-Cys dipeptide which is converted to an Ala<Thz dipeptide. Only the main intermediates of the biosynthetic side chain-to-backbone cyclization are drawn. The mercaptyl side chain Cys adds to the carbonyl of the *N*-terminal amide function and forms a thiazoline. At the active site of the enzyme (shown in grey), two basic side chains (B) trigger the nucleophilic attack of the side chain and the subsequent dehydration. Final reduction is rarely observed while the usual dehydrogenation yields the thiazole.

The semi-saturated thiazoline can be subjected to further enzymatic tailoring. The reduction to the thiazolidine motif is rarely observed, apparently due to ease of hydrolysis. The bacterial siderophore yersiniabactin is one of the few examples of natural products carrying such a saturated heterocycle.[5,6] Conversely, the oxidative transformation to thiazoles is observed out for the majority of thiazolines. This increases the stability of the heterocycle which is not inclined to hydrolysis anymore and it generates an aromatic motif within the peptide backbone. The thiazole dipeptide tubuvaline (Tuv) is essential for increase the activity of the linear tubulysin tetrapeptides[7] which are produced by two myxobacteria species and which are among the most cytotoxic peptides known to date.[8,9] In the past years, great effort has been spent on the synthesis of simplified analogs that for example lack the synthetically challenging Tuv aminal function.[10] The depsipeptide/polyketide hybrid hectochlorin which exhibits two identical thiazole units that are differently linked to the adjoining backbone.[11,12] By inducing actin hyperpolymerization, hectochlorin arrests cells at cytokinesis and thus inhibits the cell division process.

1.1.2. Thiopeptide antibiotics

The members of the class of thiopeptides show a considerably high level of structural complexity and perhaps exhibit the most striking examples of how ribosomally produced “standard” linear peptides are converted to microbiological warfare by ingenious combination of different post-translational modifications.[13–15] Figure 3 shows two representative examples of these heterocyclic peptides of high structural complexity. Thiostrepton (Figure 3 left) was the first known thiopeptide (discovered in 1955).[16] Instead of a simple loop, the peptide backbone forms a three-dimensional network connected by the

dehydropiperidine core. In addition to the 1,2-dihydroquinaldic acid moiety, the structure stands out by a Thr<Thz dipeptide which is not only linearly linked to the adjoining backbone but which serves as second core motif (highlighted). In addition, a highly functionalized (2*S*,3*S*)-dihydroxy-isoleucine<Thz dipeptide is present.

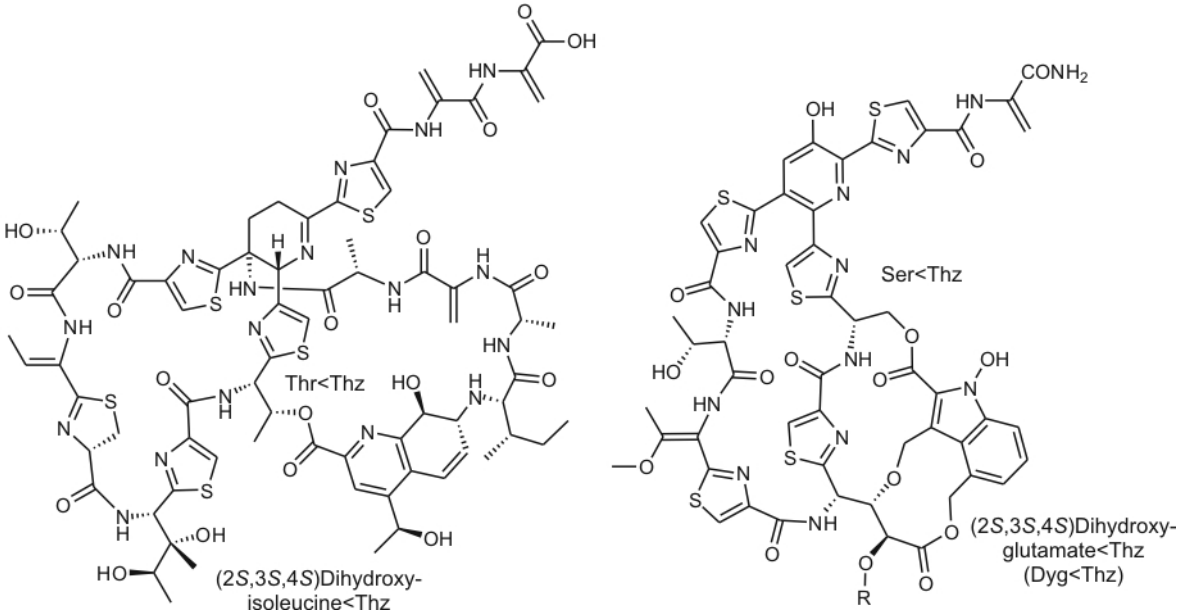


Figure 3. Thiopeptide antibiotics. The structure of thiostrepton is shown on the left. (2*S*,3*S*,4*R*)-3,4-Di-hydroxy-isoleucine<Thz is not substituted at the two hydroxyl groups. Nocathiacin I and thiazomycin on the right differ only in the type of glycosylation R. The dihydroxylated thiazole dipeptide is part of a network linked to the hydroxyindole side chain.

Several thiopeptide antibiotics contain a (hydroxy)pyridine or a partially reduced 6-membered nitrogen-containig ring and a Glu<Thz dipeptide, the latter being hydroxylated either in the 2- or the 3-position. Two representatives are the structurally similar nocathiacins[17] and thiazomycins[18] which represent the thiopeptides with the most complex backbone network comprising a 10-, a 15- and a 26-membered ring.[19] They also contain the most complex thiazole dipeptide known to date: a (2*S*,3*S*)-di-hydroxyglutamate (Dyg)<Thz which exhibits four linkages to a *N*-hydroxyindole and to the peptide backbone and which in addition serves as glycosylation site at 3-OH.

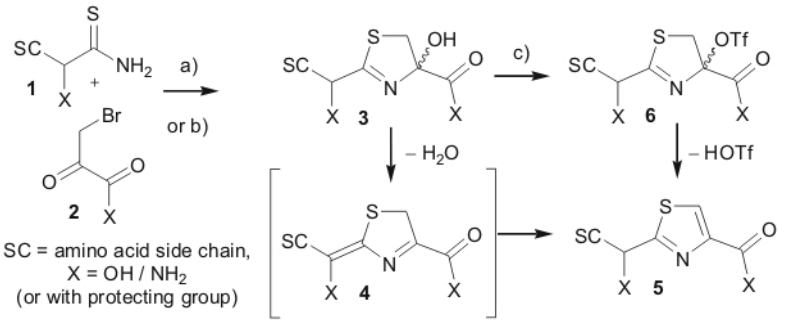
The structural and functional complexity of the thiopeptide antibiotics exhibits challenges for their chemical syntheses, and this is strikingly demonstrated by the fact that, in spite of the research spent effort, only seven of the approximatively eighty members of the thiopeptide class have so far succumbed to total synthesis.[15,20] In this context, the highly functionalized thiazole dipeptides, though being of small size, turned out to be especially difficult to be accessed, which served as motivation for the many synthetic works documented in the chemical literature. In order to generate a context with already accomplished work, chemical syntheses of thiazole dipeptides will be presented in the following.

2. Chemical thiazole synthesis: strategies and problems

2.1. Two-component reactions

The condensation reaction of a thioamide **1** and the α-bromocarbonyl compound **2** was discovered by Hantzsch[21] and exhibits the longest-known synthetic access to thiazoles dipeptides. With some modifications, it is still the most used reaction type for the synthesis of thiazole dipeptides (Scheme 1). In

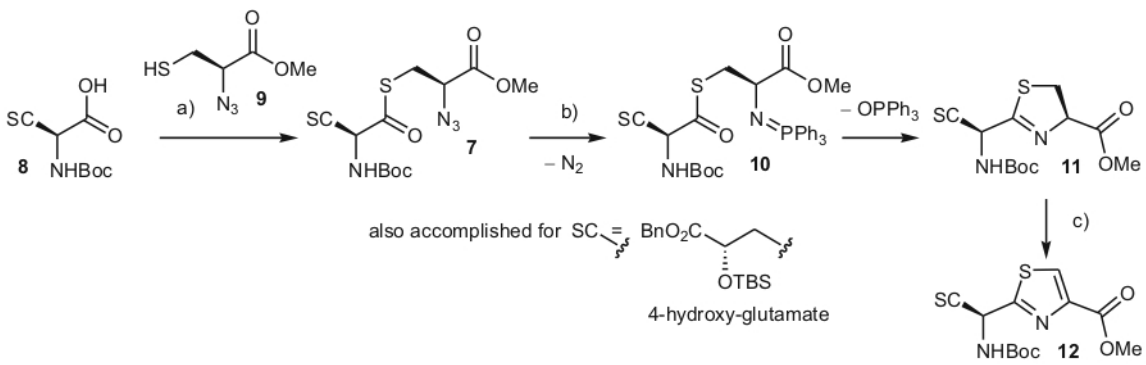
the first step, a primary amide is transferred to the corresponding thioamide **1** by using Lawessons's reagent.[22] Lawesson's reagent works well with protected dipeptides[23] but suffers from the effort of removing the phosphorus-containing by-products. The use of this toxic reagent and the potential formation of malodorous H_2S is problematic and not suitable for reactions on larger scale. In addition, the "classical" Hantzsch condensation procedure leads in the case of α-chiral thiazoles to a complete racemization of the product by elimination of the α-proton (**3** *via* **4** to **5**).[24] Therefore, modified reaction protocols were developed by Holzapfel *et al.*[25] and Myers *et al.*[26] which allow for the synthesis at room temperature. Under basic conditions (e), the hydroxythiazoline **3** can be isolated and subsequently be activated as triflate **6** which undergoes selective β-elimination and thus retains the stereochemistry at the α-position of the thiazole. Further modifications of the procedure by Nicolaou *et al.* led to a significant improvement of yields on larger reaction scales[27] and thus promoted the use of the Hantzsch synthesis within the scope of the landmark total synthesis of thiostrepton.[28,29]



Scheme 1. Thiazole syntheses employing the coupling of two components. Hantzsch synthesis and modified protocols according to Holzapfel, Myers and Nicolaou. Reagents and conditions: a) EtOH, reflux; b) $KHCO_3$, DME, 0 °C (Holzapfel)/ −40 to −20 °C (Myers)/ $NaHCO_3$, DME, rt (Nicolaou); c) Tf_2O, 2,6-lutidine, DME, 0 °C (Holzapfel)/ −40 to −20 °C (Myers)/ TFAA, Et_3N, Pyr, 0 °C (Nicolaou).

2.2. Cyclizations of linear precursors

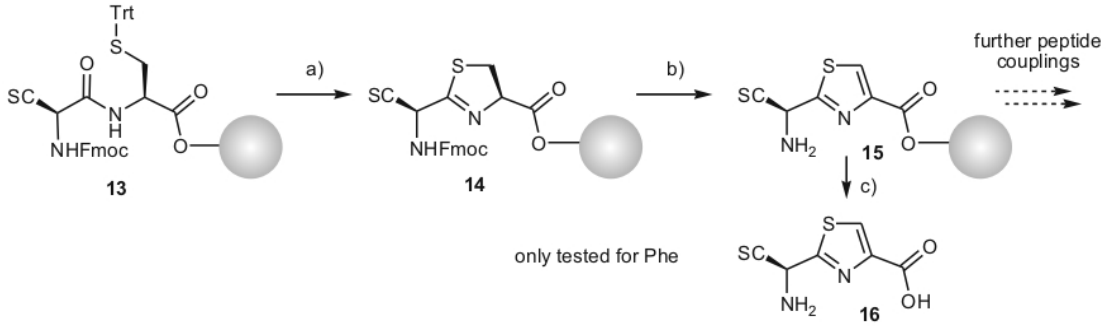
Over the past years, several strategies have been developed which allow for the construction of thiazole dipeptides under mild conditions. In all cases, the heterocycle is closed by nucleophilic attack of a sulfur functionality. In the efficient aza-Wittig based thiazole peptide synthesis developed by Arndt *et al.* (Scheme 2),[30] the sulfur is introduced by thioester formation (**7**) of an *N*-terminal amino acid **8** with an azidocysteine **9**.



Scheme 2. Thiazole formation of linear precursors in an aza-Wittig cyclization. This approach was applied for one of the few known syntheses of thiazole dipeptides with non-proteinogenic hydroxylated side chains. Reagents and conditions: a) DIC, DMAP, CH_2Cl_2, 0 °C to 20 °C; b) PPh_3, THF, −20 °C to rt; c) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C to 20 °C.

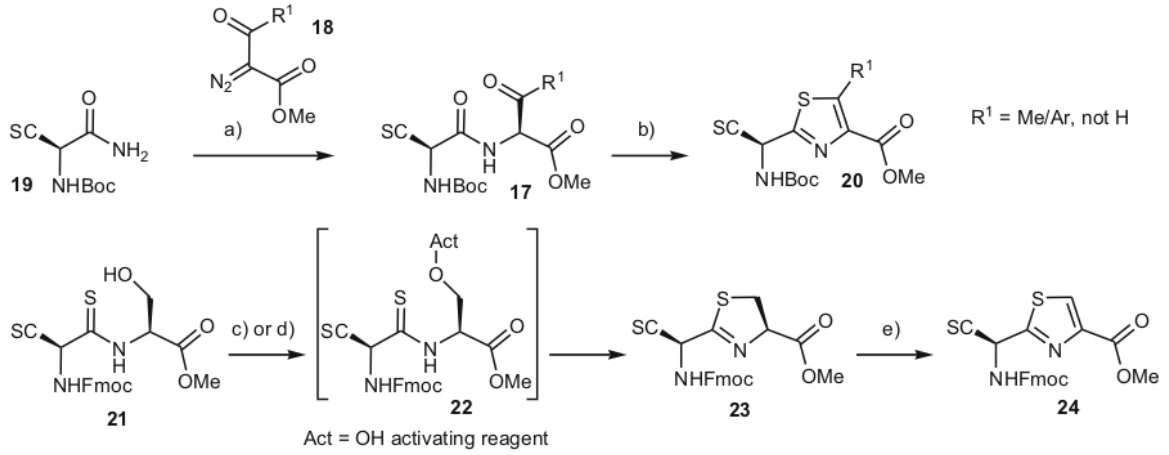
Upon addition of PPh_3, an iminophosphorane **10** is formed which reacts to the thiazoline which is oxidized to **12**. This strategy also proved suitable for the synthesis of bisthiazoles as for example present in bleomycin and was successfully utilized in synthetic studies towards nosiheptide.[31]

Kelly *et al.* described a biomimetic approach in which, similarly to thiazole biosynthesis, ring formation occurs in a pre-peptide **13** upon nucleophilic attack of the Xaa-Cys amide bond by the sulfur of the Cys side chain (Scheme 3).[32] In Kelly's synthesis, however, not the thiol but the amide is activated (with PPh_3) and also in this case a thiazoline **14** is obtained which is easily oxidized to the thiazole peptide **15**.[33] Kessler *et al.* demonstrated that this synthesis can be extended to solid phase-bound substrates with good overall yields.[34] After the thiazole **15** is obtained, the peptide chain can be further extended on solid phase or the deprotected Xaa<Thz dipeptide **16** can be cleaved from resin.



Scheme 3. Biomimetic approach by Kelly *et al.* which was established for solid phase peptide synthesis by Kessler *et al.*: Cys side chain-to-backbone cyclization triggered by amide activation. Reagents and conditions: a) PPh_3, Tf_2O, CH_2Cl_2, rt; b) $BrCCl_3$, DBU, CH_2Cl_2, rt; c) TFA/H_2O 95:5 (v/v), rt.

Other strategies exploit the activation of the side chain which is subsequently attacked by an *N*-terminally located thioamide (Scheme 4). In this context, Moody *et al.* described an efficient synthesis of α-acylamino ketones **17** by coupling of a rhodium carbenoid **18** with a primary amide **19** (Scheme 4).[35]



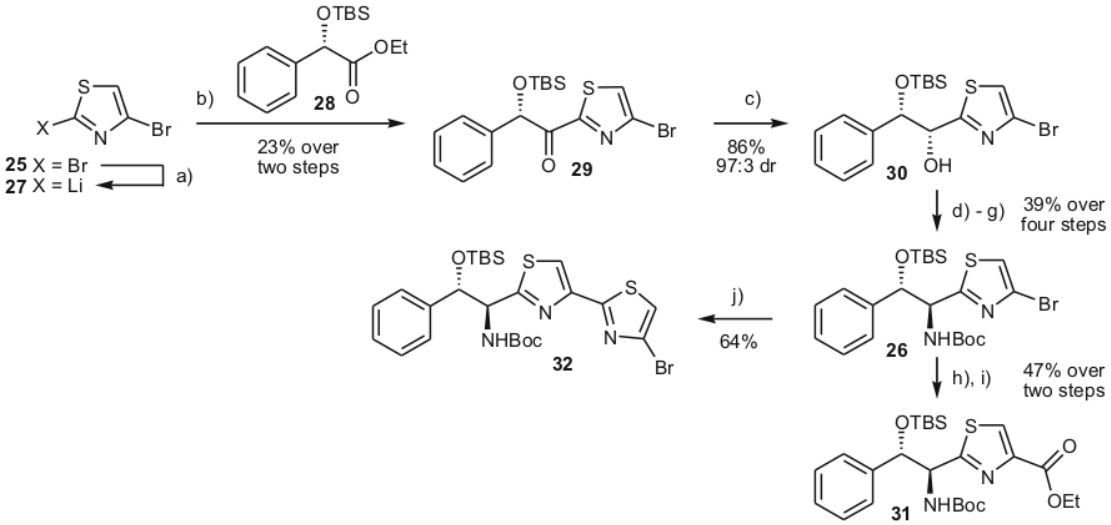
Scheme 4. Synthetic strategies which employ the intramolecular cyclization of thioamides to activated side chains: Rh carbene coupling yielding a dipeptide intermediate which an "activated" (oxidized) Thr side chain (top) and activation of the Ser hydroxy function with the Burgess reagent or DAST. Reagents and conditions: a) Rh_2Oct_4, CH_2Cl_2, reflux; b) Lawesson's reagent; THF, reflux; c) Burgess reagent, THF, reflux; d) DAST, CH_2Cl_2, −78 °C; e) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C.

The thiazole **20** then can be formed in one step with Lawesson's reagent.[36] This approach was successfully applied for the synthesis of the Asn<2-methyl-Thz unit present in the thiopeptide antibiotic

amythiamycin;[37] however, it is restricted to thiazoles with alkyl and phenyl substitutions (R^1) at position 5. The intramolecular nucleophilic attack by a thioamide can also be triggered in a Xaa-Ser dipeptide **21** if the Ser side chain hydroxyl function is adequately activated (**22**) and thus be turned into a leaving group. This can be accomplished with the Burgess reagent[38] or with DAST[39] and yields the thiazoline dipeptide **23**. This strategy was only applied for non-hydroxylated proteinogenic side chains (SC in **24**).

2.3. C–C couplings and multicomponent reactions

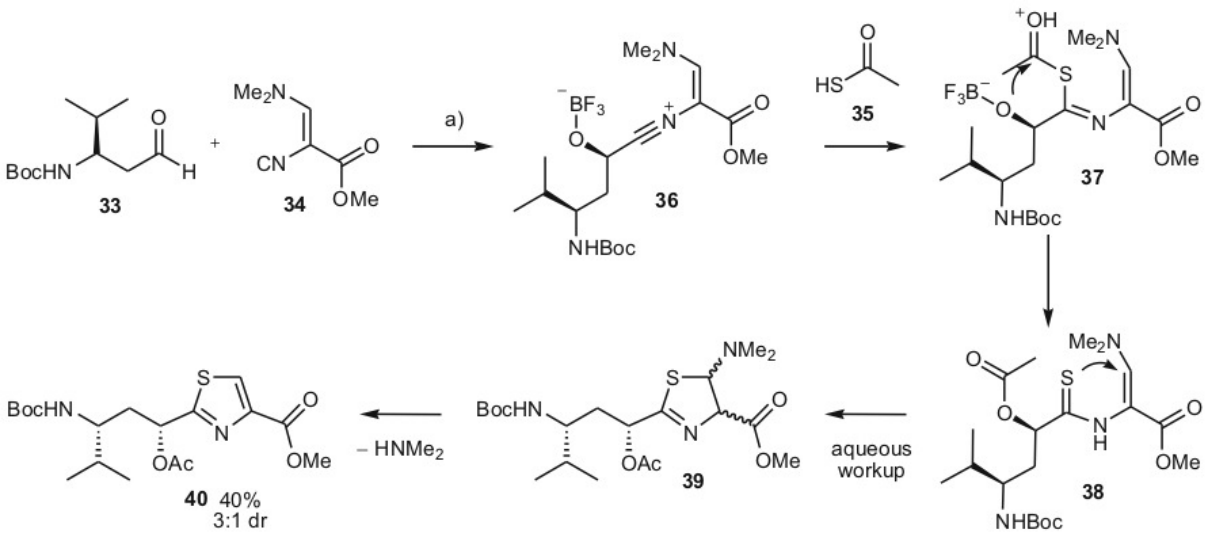
The methods described in the preceding two sections for the synthesis of Xaa<Thz dipeptides have in common the disadvantage that they are rather restricted to unpolar proteinogenic Xaa side chains. In order to be able to construct more complex thiazole units as they are present for example in the thiopeptides, further strategies were developed. One option which has been exploited for the incorporation of non-proteinogenic Xaa side chains is given by C–C couplings of lithiated thiazoles (Scheme 5). Yamanaka *et al.* described for the first time thiazole functionalizations by Pd-catalyzed couplings[40] and Bach *et al.* demonstrated that the different reactivity of 2,4-bromothiazole **25** can be utilized for the synthesis of the phenyl-serine<Thz scaffold **26** present in the GE2270 antibiotics.[41–43] The first metalation selectively occurs at position 2 (insertion of Mg or lithiation to **27**)[44] and treatment with the chiral pool mandelic acid ester **28** incorporates the first stereocentre, yielding the thiazolyl ketone **29**. Under Felkin-Anh control, reduction to the *threo* diol **30** takes place and a four-step O,N-exchange sequence yields the Boc-protected thiazolyl amine **26**. With the construction of the side chain completed, the adequate thiazole functionalization at can now be accomplished. By lithiation and carboxylation, the fully protected phenylserine<Thz dipeptide **31** is obtained. Alternatively, a *Negishi* coupling with a second Thz yields the bisthiazole **32** which was successfully used to accomplish the GE2270A total synthesis.[43]



Scheme 5. C–C couplings of lithiated thiazole a) synthesis of (2*S*,3*S*)-phenylserine dipeptides (present in the GE2270 antibiotics) by Bach *et al*. Reagents and conditions: a) *n*-BuLi, Et_2O, −78 °C; b) Et_2O, −78 °C; c) l-selectride, THF, −78 °C; d) MsCl, NEt_3, −78 °C; e) NaN_3, DMSO, 90 °C; f) PPh_3, H_2O, rt; g) Boc_2O, CH_2Cl_2, rt; h) *t*-BuLi, Et_2O, −78 °C, then solid CO_2; i) EtI, K_2CO_3, DMF; j) **25**, *t*-BuLi, $ZnCl_2$, −78 °C.

Tubuvaline (Tuv), a key part of the tubulysins, differs from the multitude of known Thz dipeptides by its nitrogen functionalization in the γ instead of the α-position of the side chain and by carrying an α-acyl group (Figure 1) and it has contributed to the difficulties associated with total syntheses of the

tubulysins.[9,45,46] In the first total synthesis of tubulysin derivates (Scheme 6), Dömling, Wessjohann *et al.* utilized a Lewis acid-catalyzed three-component coupling of an aldehyde **33**, a Schöllkopf isonitrile **34**[47] and a thiocarboxylic acid **35**.[48,49] After formation of the isonitrile adduct **36**, reaction with **35** yields the hetero anhydride **37** which, in analogy to the mechanism of the Passerini multicomponent reaction, undergoes transacylation towards **38**.[50] Upon aqueous workup, the acrylic acid is attacked by the thioamide to form **39** and elimination of dimethylamine finally yields the *C*- and *N*-terminally protected thiazole dipeptide **40** which is deprotected to Tuv after acidic removal of the Boc group and saponification of the methylester.

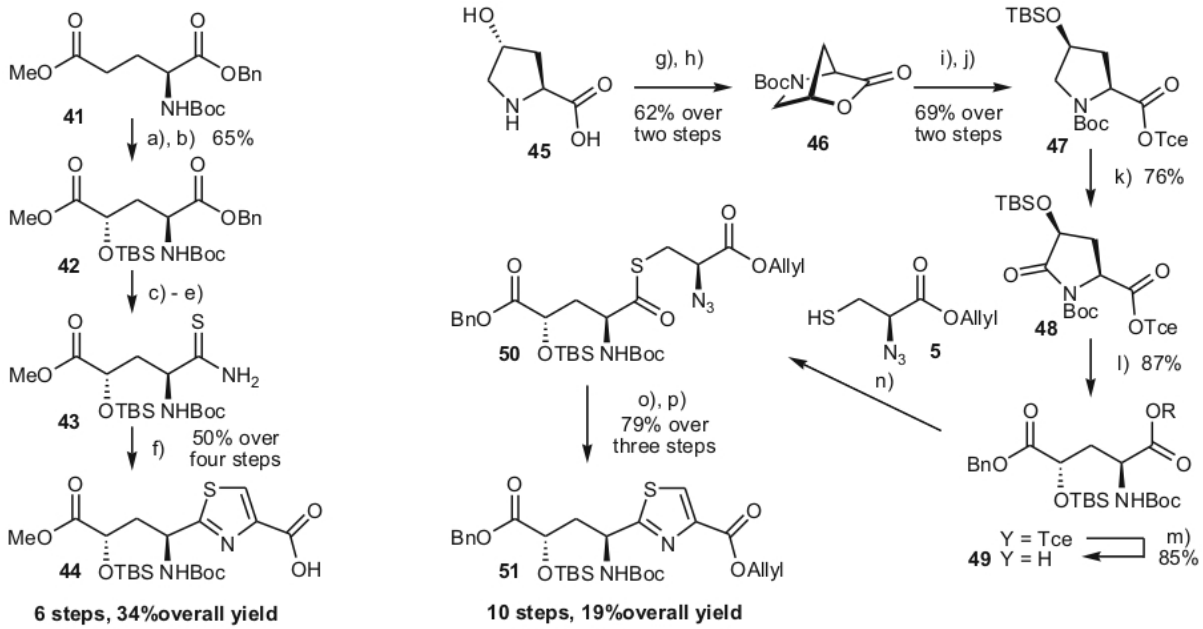


Scheme 6. Multicomponent reactions. Lewis acid-catalyzed three-component coupling of an isocyano acrylate, an aldehyde and a thiocarboxylic acid developed by Dömling and Wessjohann for the total synthesis of the tubuvaline unit present in the tubulysines. Reagents and conditions: a) THF, −78 °C to rt.

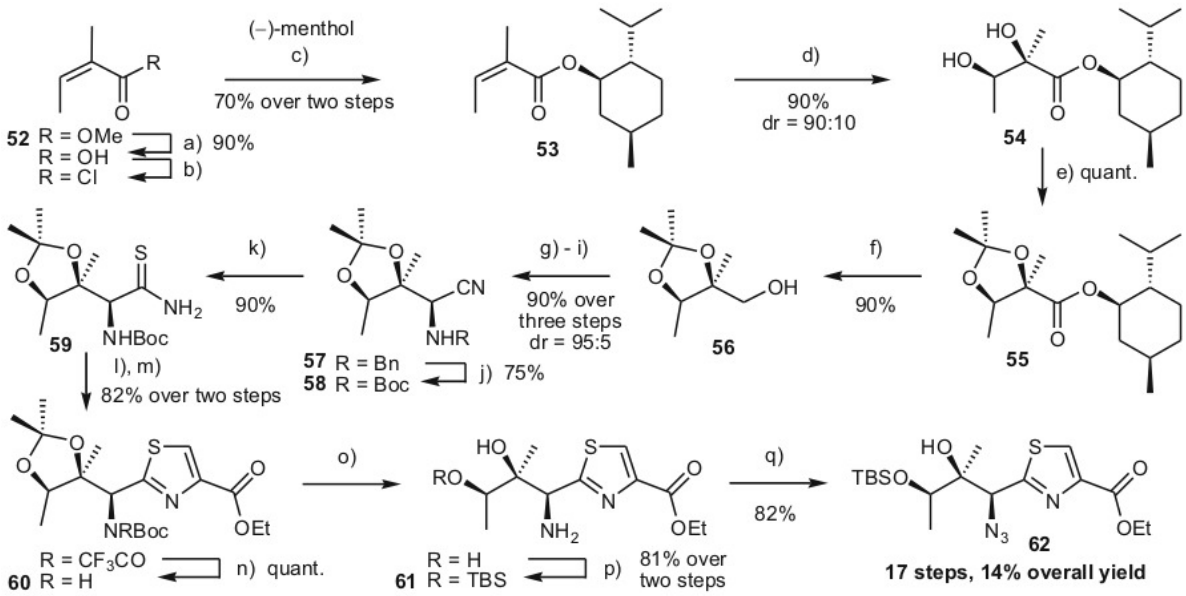
2.4. Total syntheses of Xaa<Thz dipeptides present in thiopeptide antibiotics

The difficulty to access to thiazole dipeptides with stereopure and highly functionalized non-proteinogenic side chains becomes especially apparent in the case of the few total syntheses of thiopeptides published so far and much effort has been spent on the construction of these units which in some examples also serve as core motifs, linking several backbone segments and a hydroxyindole with each other. The total synthesis of nosiheptide, which differs from thioazomycin by being not alkylated or glycosylated at the two hydroxyl groups of (2*S*,3*S*,4*S*)-3,4-dihydroxy-glutamate<Thz, is the subject of current research. Its 4-hydroxy-glutamate<Thz core dipeptide is accessible by two different strategies (Scheme 7). The synthesis by Moody *et al.*[51,52] starts with the protected Glu **41** and stereoselectively introduces the 4-hydroxy function using the Davis oxaziridine (a, b).[53,54] The benzyl ester of **42** is subsequently converted to the thioamide **43** which is transformed to the thiazole dipeptide **44** by Hantzsch condensation.

The alternative approach by Arndt *et al.*, in comparison, exhibits a longer sequence and a lower overall yield, yet it avoids the problems associated with the Hantzsch synthesis by a modern aza-Wittig mediated thiazole ring closure (Scheme 7). It utilizes the stereocentres of (2*S*,4*R*)-4-hydroxyproline **45** which is inverted in its configuration at position 4 *via* the lactone **46** and adequately protected (**47**). Oxidation at position 5 furnishes the lactam **48** which is opened and Tce-deprotected to yield the desired 4-hydroxy glutamic acid **49**. This reacts with the azidocysteine **9** to the thioester **50** and the synthesis is accomplished by the aza-Wittig reaction and oxidation of the thiazolidine to the thiazole **51**.



Scheme 7. Total syntheses of the (2*S*,4*S*)-4-hydroxy-glutamate<Thz dipeptide present in nosiheptide by Moody *et al.* (Hantzsch synthesis, left) and Arndt *et al.* (aza-Wittig thiazole formation, right). A total synthesis of nosiheptide has not been accomplished yet. Reagents and conditions: a) LHMDS, Davis oxaziridine, THF, −78 °C; b) TBSCl, imidazole, DMF, rt; c) Pd/C, H_2, MeOH, rt; d) Et_3N, EtO_2CCl, THF, rt; then NH_4OH, THF, rt; e) Lawesson's reagent, THF, reflux; f) $BrCH_2COCO_2Et$, $CaCO_3$, EtOH, rt; g) Boc_2O, K_2CO_3, 1,4-dioxane, 0 °C to rt; h) DIAD, PPh_3, THF, 0 °C; i) TceOH, NaH, THF, −78 °C; j) TBSCl, DMF, rt; k) $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$ 1:9:15 (v/v), 0 °C; l) BnOH, NaH, THF, −78 °C; m) Zn, THF, NaH_2PO_4, ultrasound, rt; n) EDC, HOBt, CH_2Cl_2, rt; o) PPh_3, THF, −20 °C to rt; p) $BrCCl_3$, DBU, CH_2Cl_2, rt.

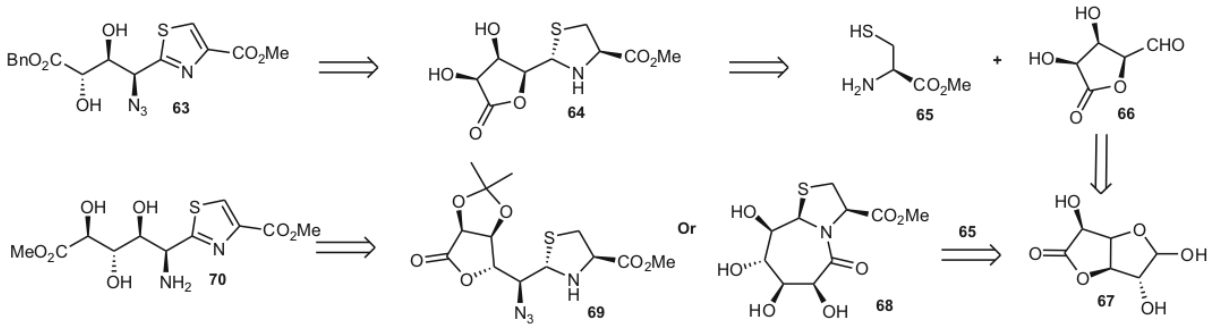


Scheme 8. Synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxy-isoleucine<Thz within the scope of thiostrepton total synthesis by Nicolaou *et al.* This substrate exhibits the most complex thiazole dipeptide which is accessible by chemical synthesis so far. Reagents and conditions: a) LiOH, MeOH/H2O 1:1 (v/v), reflux; b) KOH, $(COCl)_2$, Et_2O, DMF, rt; c) Et_2O, rt; d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1 (v/v), 0 °C; e) DMP, *p*-TsOH, rt; f) DIBAL-H, CH_2Cl_2, −78 °C; g) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; h) $BnHN_2$, $Yb(OTf)_3$, CH_2Cl_2, rt; i) TMSCN, CH_2Cl_2, rt; j) $Pd(OH)_2$, H_2, EtOAc, rt; then Boc_2O, EtOAc, rt; k) H_2S, Et_3N/EtOH/Pyr 1.7:1.7:1 (v/v), rt; l) $BrCH_2COCO_2Et$, $NaHCO_3$, DME, rt; m) Tf_2O, Pyr, 0 °C; n) NaOEt, EtOH, 0 °C; o) TFA/EtOH/ CH_2Cl_2, 0 °C to rt; p) TBSCl, Et_3N, CH_2Cl_2, 0 °C to rt; q) TfN_3, Et_3N, $CuSO_4$, MeOH/H_2O/ CH_2Cl_2 (3.3:1:1), rt.

A prerequisite of the total synthesis of thiostrepton by *Nicolaou et al.* [28,29,55,56] was the successful construction of the (2*S*,3*S*,4*R*)-3,4-dihydroxy-isoleucine<Thz, the most complex thiazole dipeptide which is accessible by artificial synthesis so far (Scheme 8).[57] Remarkably, the sequence starts with an achiral substrate, (*Z*)-2-methylbut-2-enoic acid methyl ester **52** which is converted to the chiral menthyl ester **53** and then bishydroxylated to the diol **54** with 90:10 diastereoselectivity. After diol protection, yielding the acetonide **55**, and reduction of the ester to the alcohol **56**, the chain is extended by one carbon and the third stereocentre is introduced. For this purpose, a one-pot procedure was carried out in which the alcohol is oxidized to the aldehyde that is reacted with benzylamine and the resulting imine is converted to the Strecker addition product **57**. The stereocontrol of the substrate thereby leads to the correct stereochemistry, as proven by X-ray crystallography.[57] After benzyl/Boc exchange, the nitrile **58** is converted to the thioamide **59** which is subjected to Hantzsch condensation. The use of Tf_2O for the dehydration to the thiazole leads to the TFA-protection of the Boc carbamate and the TFA-group has to be removed, which yields the dipeptide **60**. With the construction of the carbon skeleton completed, removal of the Boc group and exchange of the hydroxy protecting groups (**61**) as well as a diazo transfer[58] yielded the thiazole dipeptide **62**.

2.5. Sugar precursors of the dihydroxyglutamate side chain

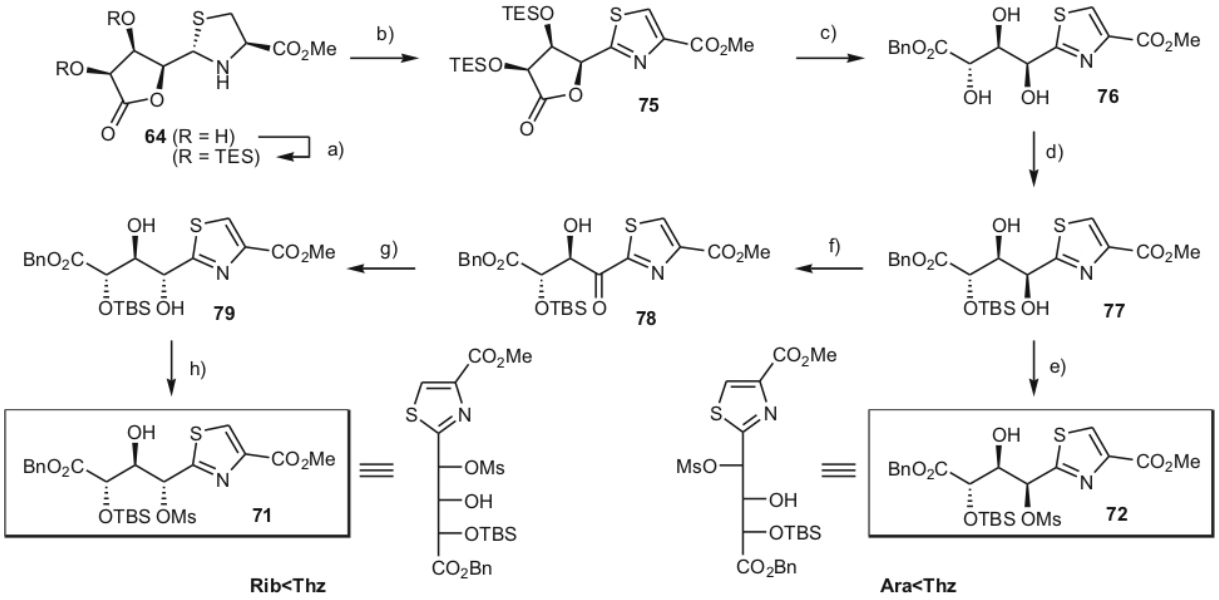
Another retrosynthetic approach towards hydroxylated thiazole dipeptides starts with the oxidation of the thiazolidine, thus making an uronic acid the key intermediate (Scheme 9).[59] Instead of creating the stereocentres of the side chain by chemical synthesis, sugar-based starting materials are versatile alternatives.[60] Potential advantages are a minimum of protecting groups when starting from unprotected sugars, the avoidance of malodorous and toxic thioxylation reagents and the availability of different sugar stereochemistries in such a chiral pool approach. The Dyg side chain in the Dyg<Thz unit has the stereochemistry of 2-deoxy-2-amino-*D*-arabinuronic acid. The work presented in this chapter describes the stereoselective synthesis of the Dyg<Thz dipeptide as well as of other highly functionalized derivatives.



Scheme 9. Retrosynthetic analysis of hydroxylated thiazole dipeptide to sugar precursors. The dihydroxylated Dyg<Thz dipeptide is obtained from a precursor lactone (**64**) which itself is formed from the condensation of the lactone of *D*-arabinuronic acid (**66**) and and *L*-cysteine methyl ester (**65**). By the condensation of *D*-glucuronolactone and (**65**) even longer sugar chains are accessible according to this strategy, leading to trihydroxy-homoglutamate<Thz dipeptides (**70**).

Scheme 9 shows the retrosynthetic analysis of a protected precursor (**63**) of the Dyg<Thz dipeptide. The azide opens the lactone ring of **64** by nucleophilic attack at the benzylic position. Compound **64** itself is accessible from the condensation of the commercially available educts *L*-cysteine (**65**) and the uronolactone **66**. Previous work describes the synthesis of the stereopure bicyclic thiazolidine lactams[61] as well as of the epimeric thiazolidine lactones,[62] which are directly accessible from condensation reactions of γ-*D*-glu-

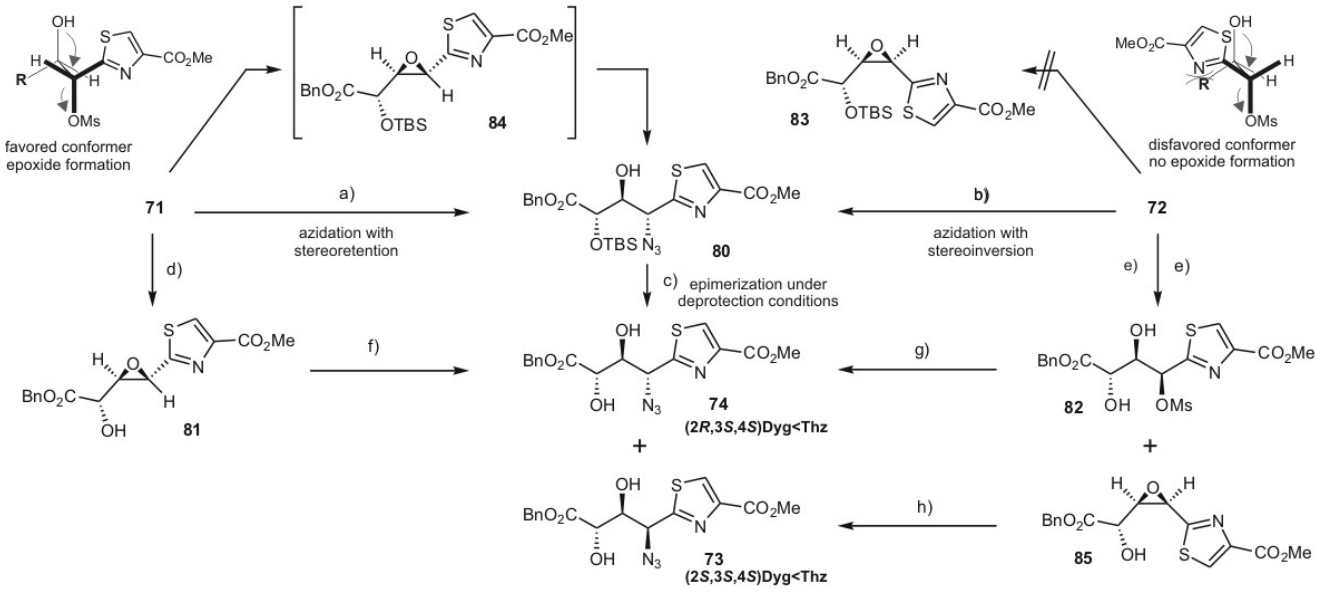
curonolactone **67** and *L*-cysteine **65** without protecting groups. The thermodynamic products of such reactions are the thiazolidine lactams which are isomers of the thiazolidine lactones obtained by kinetic reaction control. Cyclic and bicyclic starting materials minimize the number of protection and steps while maximizing the chemo-, stereo- and regioselectivity of the subsequent transformations like O/N-exchange and tailoring of the sugar chain. This approach gives access to chain-extended thiazole like **70**. Lactone **66** was obtained from **67** by periodate diol cleavage followed by condensation with **65**, yielding thiazolidine **64**. In the following, we describe the subsequent transformations of **64** towards activated depsipeptides **71** and **72** (Scheme 10) which are transformed to the Dyg<Thz dipeptide **73** and its α-epimer **74**, respectively (Scheme 11), as shown in the retrosynthesis in Scheme 8.



Scheme 10. Synthesis of the thiazole polyol **71** (Rib<Thz) in *D*-ribo (Rib) and of **72** (Ara<Thz) in *D*-arabino (Ara) configuration. The final products are also shown in the Fischer projection. Reagents and conditions: a) TESCl (2.4 equiv), imidazole (2.4 equiv), DMF, 0 °C to rt, 3 h; b) MnO_2 (20–25 equiv), toluene, 70 °C, 36–43 h, 33% over two steps; c) BnOH, CSA (0.05 equiv), 50 °C, 67 h, 81%; d) TBSCl (1.2 equiv), imidazole (1.2 equiv), DMF, rt, 18 h, 74% (plus 16% starting material re-isolated); e) MsCl (1.0 equiv), anhydrous pyridine, 0 °C to rt, 13 h, 48% (plus 23% starting material and 20% dimesylate isolated); f) IBX (5.0 equiv), EtOAc, 80 °C, 1.5 h, 29% (plus 53% starting material reisolated); g) BF_3:Et_2O (2.2 equiv), Bu_3SnH (1.2–1.0 equiv), anhydrous THF, −78 °C to rt, 32 h, 75%, dr>99:1; h) MsCl (1.5–1.0 equiv), DMAP (cat.), anhydrous pyridine, 0 °C to rt, 17 h, 73% (plus 25% dimesylate).

The strategic bottleneck of a thiazole synthesis from a hydroxylated thiazolidine precursor is to carry out the oxidative dehydrogenation to the thiazole by avoiding hydrolysis and minimizing oxidative side reactions like diol cleavage, benzylic oxidations and other degradation reactions. Activated MnO_2 has by far been used most often as oxidant to generate thiazoles,[63,64] although it is known to generally reduce the yields due to these side reactions.[65–67] In order to make this oxidation applicable to the highly functionalized thiazolidine lactone **64**, its hydroxyl functions had to be protected appropriately and silyl ethers proved sufficiently stable to the MnO_2 oxidation. Reaction of the diol **64** with TES chloride and imidazole in DMF yielded the bis(-triethylsilyl) (TES) ether, which was directly subjected to oxidation with excess MnO_2 in toluene at 70 °C, yielding the desired TES-protected thiazole lactone **75** in 33% yield over two steps on a multigram scale. In order to access the α-position of the later amino acid side chain, the lactone was opened in the following step using benzyl alcohol as both reagent and solvent with 0.05 equiv of camphor sulfonic

acid at 50 °C. Under these conditions, the thiazole triol **76** with orthogonally protected carboxyl functions precipitates from the reaction mixture and it was isolated in good purity and in 81% yield by filtration. With the *D*-arabino configuration of the triol chain, thiazole **76** already represents the 2-oxo analog of the naturally occuring (1*S*,2*S*,3*S*)Dyg<Thz core motif and was accessible from γ-*D*-glucuronolactone (**67**) and *L*-cysteine methyl ester (**65**) in five linear steps with 14.2% overall yield, yet on the multigram scale. The reaction sequence requires only one chromatographic purification (after the oxidation step) and no anhydrous solvents or inert gas. The desired nitrogen functionality at position 1 could not be installed with all three hydroxyl groups unprotected. Attempts to maintain the silyl ethers upon lactone opening (in this case, the more stable TBS group was chosen) were unsuccessful as protecting group migration occurred. However, the 3-hydroxyl function of the triol **76** was protected selectively as *tert*-butyldimethyl silyl (TBS) ether **77** in 74% yield. Treatment with mesyl chloride in pyridine finally allowed to selectively activate the 1-hydroxy function as mesylate **72** in 62% yield b.r.s.m. In addition to the selective activation, we also sought to selectively invert the stereocentre at position 1 in order to obtain both epimers of the Dyg<Thz dipeptide as well as of its depsidipeptide analog. Since $KMnO_4$, which had been successfully used for analogous oxidations of sugar substrates,[68] led to diol cleavage in the case of thiazole **77**, the authors investigated the use of IBX in EtOAc.[69] Under optimized reaction conditions (5.0 equiv IBX, 80 °C, 1.5 hours), the extent of decomposition was minimized and 62% b.r.s.m. of the ketone **78** were obtained. Reduction with Bu_3SnH in the presence of $BF_3 \cdot OEt_2$ finally afforded the thiazole triol **79** with *D*-ribose (Rib) configuration in 75% yield and >99:1 diastereoselectivity. Analogously to the 1-epimeric triol **77**, compound **79** was subjected to selective activation of the 1-hydroxyl, yielding 73% of the mesylate **71**. O/N-exchange reactions were investigated with both mesylates **72** and **71** (Scheme 11).



Scheme 11. O/N-exchange reactions and neighbouring group effects in thiazole units with *D*-ribo (left) and *D*-arabino configuration (right). Reagents and conditions: a) NaN_3 (1.5 equiv), anhydrous DMF, 85 °C, 3.5 h; b) NaN_3 (1.5 equiv), DMF (abs), 85 °C, 2.5 h, 19%; c) H_2SiF_6 (2.0 equiv), acetonitrile, rt, 24 h, 13% of **73**8 and 12% of **74** (over two steps from **72**); d) TBAF (1.3 equiv), anhydrous THF, 0 °C, 45 min, 42%; e) TBAF (1.3 equiv), anhydrous THF, 0 °C, 1.5 h, 21%; of **82** and 23% of **85**; f) NaN_3 (5.0 equiv), CSA (cat.), anhydrous DMF, 70 °C, 4 h, >95% conversion (NMR); g) NaN_3 (3.0 equiv), anhydrous DMF, 85 °C, 2 h, 70%; h) NaN_3 (5.0 equiv), DMSO, *p*-TosOH·H_2O (cat.), 70 °C, 9 h, >95% conversion (NMR), isolated yield 16%. R=CH(OTBS)–CO_2Bn.

Under identical reaction conditions (3.0 equiv NaN_3 in DMF at 85 °C), the same azide main product was obtained from both **71** (a) and **72** (b), respectively, which was later identified as azide **80**. As some TBS group migration had occurred, the silyl ethers were deprotected with hexafluoro silicic acid.

However, this resulted in racemization of the stereocentre at position 1, yielding a 1:1 mixture of the Dyg<Thz epimers **73** and **74** in an overall yield of 25% over both steps. In order to overcome the low yields, the azide exchange was performed with TBS-deprotected substrates. The less steric congestion associated with the removal of the bulky TBS group had also significantly increased the yield of azide product in the total synthesis of the GE2270 thiopeptides.[70] The mechanism of azide introduction is also included in Scheme 11. Epoxide intermediates allow for the introduction of substituents by retention of configuration (double inversion). Yet, the efficiency of epoxide formation strongly depends on the proper antiperiplanar alignment of alcohol nucleophile and the leaving group mesylate. Consequently, **71** forms **80** with retention of configuration either along the characterized epoxide **81** or *via* the transient intermediate **84**. Analogous intermediates play a role in the formation of **73** or **74** from **72** along epoxides **83** or **85**, respectively. The reaction conditions and the protecting group pattern influence allow for a differentiation between the different reaction pathways.

Two direct precursors of Dyg<Thz are available. Further syntheses towards chain-extended homologs according to the strategy of Scheme 8 are described in literature.[59]

3. Conclusion

Current synthetic methods allow the incorporation of Xaa<Thz dipeptides in oligopeptides. More complicated hydroxylated side chains are accessible although with much larger effort. The synthesis of Dyg<Thz peptides with complementary protecting groups lays the fundament for the assembly of oligocyclic thiopeptide antibiotics and derivatives thereof. This stereoselective synthesis of highly functionalized Xaa<Thz depsidipeptides and dipeptides relies on the condensation of an uronic acid and cysteine. Assembling the carbon skeleton already in the first step avoids tedious multi-step protection and deprotection protocols. The methods described above yield peptidic thiazole motifs that are present in thiopeptide antibiotics and that have not been available by other methods so far. This includes the Dyg<Thz unit, which is an essential core motif of the nocathiacin and thiazomycin antibiotics.

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5-HETARYL-PYRIMIDINE-2,4(1*H*,3*H*)-DIONES: SYNTHESIS AND FUNCTIONALIZATION

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Abstract. *In this part, a number of synthetic methods for the preparation of 5-hetaryl-derivatives of uracil and cytosine and their applications are described. Due to the well-established antiviral and antitumor activity of several 5-substituted uracil derivatives an increasing interest in analogues of uracil and cytosine having more complicated substituents is observed. There is a variety of reactions used for the construction of the heterocyclic system attached to the uracil ring i.e. condensation, ANRORC, Suzuki-Miyaura, Stille and Negishi cross coupling or 1,3-dipolar and Diels-Alder cycloaddition which were developed in the past few decades.*

Contents

1. Introduction

1.1. Uracil and cytosine

Uracil, thymine and cytosine belong to the family of pyrimidine nucleobases being components of the nucleosides. In the nucleosides, the nucleobase is connected *via* C–N glycosidic bond formed between an

anomeric carbon atom of D-ribofuranose (or 2-deoxy-D-ribofuranose) and the nitrogen atom ^{1}N of the pyrimidine ring. In the natural nucleosides, this bond has β-configuration. The nucleosides are building blocks for the nucleic acids. In nucleic acids, the particular nucleosides are linked by phosphate ester bond created between the 3'-OH group of the one nucleosides and 5'-OH group of the sequent one. According to the IUPAC, the nucleobases and related nucleotides are abbreviated as follows: uridine (**U**), thymidine (**T**) and cytidine (**C**) (or 2-deoxycytidine, **dC**) (Figure 1). Uracil is a constituent of RNA, thymine is present in DNA whereas cytosine is present in both nucleic acids: RNA and DNA. Uracil can be considered as a parent pyrimidine compound. Amination of uridine on carbon C-4 of the uracil ring converts it into cytidine. This reaction is reversible under physiological conditions. The transformation of uridine into thymidine involves thymidylate synthase and ^{5}N,^{10}N-methylene tetrahydrofolate as a donor of methylene group.

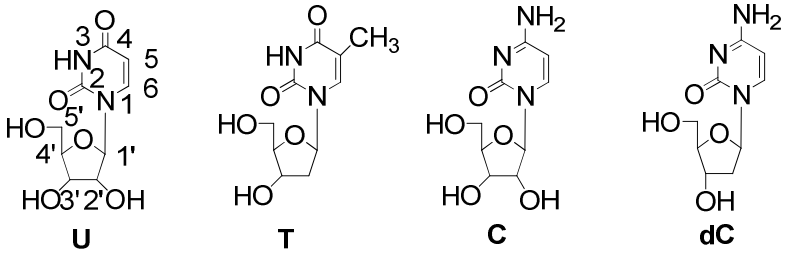


Figure 1

1.2. Biological activity

C-5 substituted uracil and cytosine derivatives and their nucleosides play an important role in antitumor, antiviral and antifungal therapy. This group comprises such compounds as: 5-iodo-2'-deoxyuridine (*Idoxouridine*, IUrd) (**1**), 5-trifluoromethyl-2'-deoxyuridine (*Trifluridine*) (**2**), 5-(*E*)-(2-bromovinyl)-2'-deoxyuridine (*Brivudine*, BrVUrd) (**3**) 2',3'-dideoxycytidine (*Zalcitabine*) (**4**), 5-fluoro-2'-deoxyuridine (*Fluridine*, FUrd) (**5**) and 5-fluorocitosine (*Flucytosine*) (**6**) (Figure 2).[1–3]

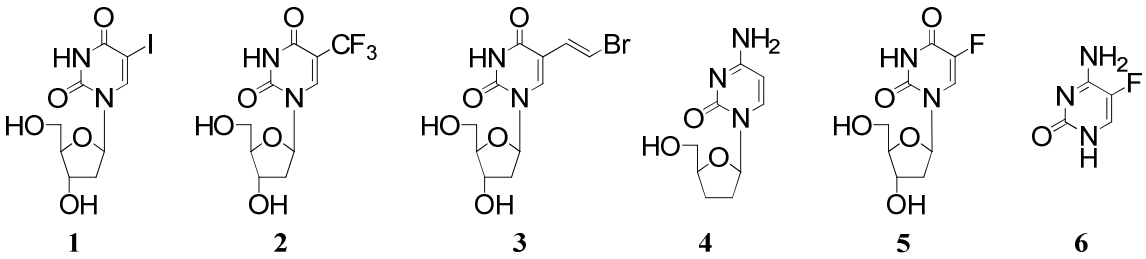
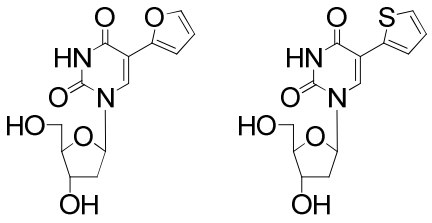


Figure 2

The activity of those compounds depends on their ability to be phosphorylated by virus or host cell, incorporation of metabolites to viral DNA strand and blocking a target enzyme. For instance, compounds **1**, **2** and **3** (anti-herpes activity), after conversion to its 5'-*O*-triphosphate, inhibit DNA polymerase preventing its viral replication. Reverse transcriptase is another drug target enzyme and it is inhibited by 5'-*O*-triphosphate of **4** (anti HIV-1 and HIV-2 activity). The absence of 3'-OH group in the newly built DNA strand causes its termination. 5'-*O*-Monophosphate of **5** deactivates the thymidylate synthase, as a result of impossibility to convert this metabolite into thymidine analogue because of the presence of fluorine atom. Compound **6** exhibits antifungal activity against *Candida* and *Cryptococcus*. After entering the drug to the fungal cell, cytosine deaminase alters **6** to 5-fluorouracil which is an active metabolite of the drug.[1–3]

The substituents are commonly introduced on C-5 carbon of uracil and cytosine moiety because this position is not involved into base-pairing of DNA. Goodchild and his co-workers studied a structure activity relationship against *herpes simplex virus type 1* (HSV-1) of over 30 olefinic 5-substituted deoxyuridines. Their research established a few features which define the best C-5 substituent. It should be: unsaturated, conjugated with pyrimidine ring, not longer than four carbon atoms, have (*E*) stereochemistry and possess a hydrophobic, electronegative function.[4] Some of 5-aryl-derivatives seem to follow the structural restrictions mentioned above. The Herdewijn group synthesized and evaluated biological activity for 5-hetaryl-2'-deoxyuridines. The most promising compounds are 5-(furan-2-yl)-2'-deoxyuridine (**7**) and 5-(thien-2-yl)-2'-deoxyuridine (**8**) (Figure 3). They marked activity against HSV-1, *varicella zoster virus* (VZV) and *vaccinia virus* (VV). The mechanism of their action is similar to the previously quoted active compounds.[5,6]



7 **8**

Figure 3

2. Methods of synthesis

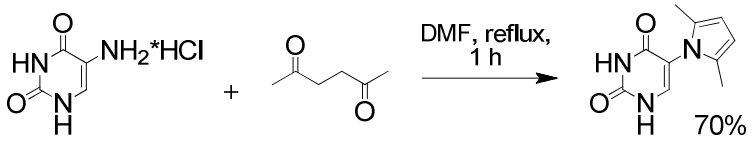
2.1. Historical review

The first experiments on 5-hetaryluracil derivatives synthesis were reported in the early 60's. Throughout the next three decades almost all these derivatives were obtained by condensation reactions. The condensation methods have two main disadvantages, namely a limited range of the obtained hetaryl rings (imidazoles, pyrroles, thioazoles) and usually low or moderate yields. Development of organic chemistry synthesis and new achievements in the catalysis resulted in elaboration of cross-coupling reactions (*i.e.*, Suzuki-Miyaura, Stille, Negishi). These palladium-assisted reactions gave an opportunity to create a huge variety of hetaryl derivatives in good or excellent yields. The important advantages of those coupling reactions are conditions compatible with many functional groups, for example amino or hydroxyl ones. The other strategy for the construction of heterocyclic ring involves 1,3-dipolar cycloadditon reactions. Although the cycloaddition reaction gives a possibility to get a broad scope of heterocycles, almost all of the preparations using this strategy gave triazoles, isoxazoles or 1,2,4-oxadiazoles derivatives.

2.2. Condensation

2.2.1. Classical condensation

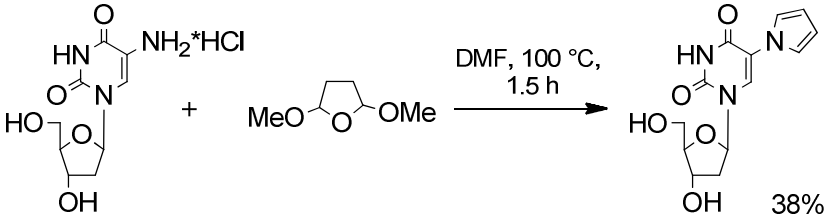
One of the first synthesis of 5-hetaryluracil described by Miller and Bambury was focused on a creation of pyrrole ring according to the Paal-Knorr[7] synthesis. They obtained 1-substituted-2,5-dimethylpyrroles during the condensation of primary amine or its hydrochloride with 2,5-hexanodione (**10**) (Scheme 1). In order to synthesize 5-(2,5-dimethylpyrrol-1-yl)-uracil (**11**), 5-aminouracil hydrochloride (**9**) was used. The reaction was conducted in boiling *N,N*-dimethylformamide (DMF) for 1 hour in 70% yield.[8]



9 **10** **11**

Scheme 1

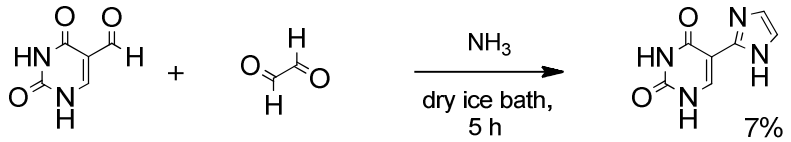
The similar reaction was applied to obtain 5-pyrrol-1-yl-2'-deoxyuridine (**14**). The pyrrole ring was formed during cyclization of a hydrochloric salt of 5-amino-2'-deoxyuridine (**12**) and 2,5-methoxy-tetrahydrofuran (**13**) (the Clauson-Kaas synthesis).[9] The first stage or the reaction is acidic hydrolysis of 2,5-dialkoxytetrahydrofuran derivative to succinaldehyde and then the Paal-Knorr reaction pathway continues. Because of the deactivation of amine group, the reaction was carried out at 100 °C using DMF as a solvent (Scheme 2).[3]



12 **13** **14**

Scheme 2

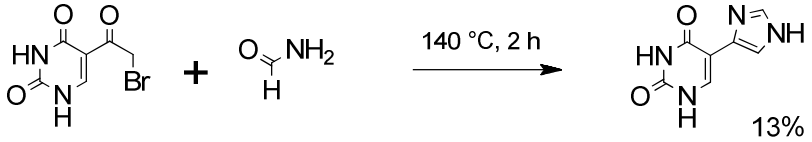
Ressner *et al.* described the methods for the synthesis of two different substituted imidazolyl derivatives of uracil. The first one, 5-(imidazol-2-yl)-uracil (**17**), was obtained in a poor yield *via* the Debus-Radziszewski reaction from 5-formyluracil (**15**), glyoxal (**16**) and ammonia. In the first step, ammonia and diketone form diimine which condenses in the next step with an aldehyde derivative (Scheme 3).[10]



15 **16** **17**

Scheme 3

When 5-bromoacetyluracil (**18**) was heated in freshly distilled formamide (**19**) at 140 °C for two hours 5-(imidazol-4-yl)uracil (**20**) was gained (Scheme 4).[10]

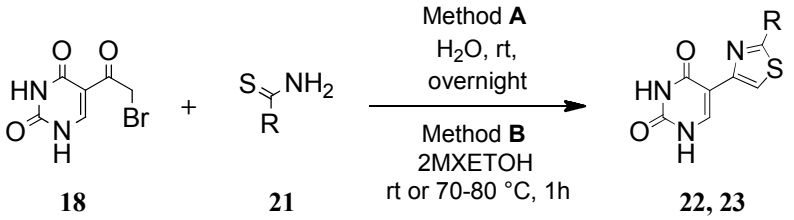


18 **19** **20**

Scheme 4

Treating the same starting compound **18** with thioamides or thioureas (the Hantzsch reaction[9]), another group of title compounds, thiazoles, can be obtained. 5-(2-Aminothiazol-4-yl)uracil hydrobromide (**22**) was obtained by two different methods: A) stirring overnight at room temperature in water or B) heating in

2-methoxyethanol (2MXETOH) at 70–80 °C for one hour. The method B was also used for the synthesis of 5-(2-methylthiazol-4-yl)uracil (**23**) (Scheme 5).[10,11]

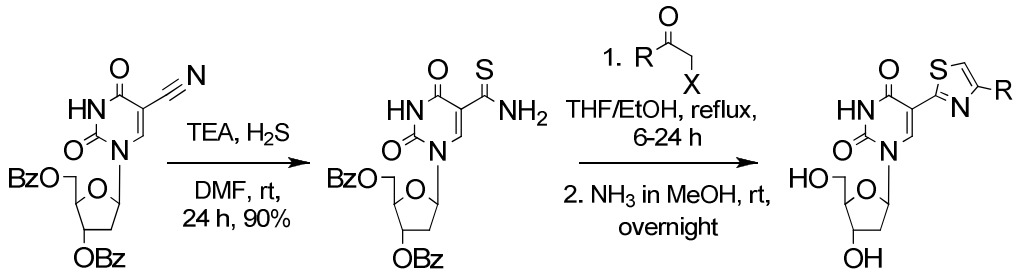


18 **21** **22, 23**

No	R	Method	Yield
22	NH_2*HBr	A	89
22	NH_2*HBr	B	87
23	CH_3	B	87

Scheme 5

Using an inverse approach uracil derivative as a thioamide, a few other thiazoles were produced. 2',5'-Dibenzoyl-5-cyanuridine (**24**) was a starting compound which, after saturation with hydrogen sulphide, was transformed into the before mentioned thioamide **25**. The reaction with α-halogen aldehydes or ketones gave the new thiazol-2-yl uridine derivatives (**26–28**). Deprotection of the sugar moiety was provided by ammonia in methanol (Scheme 6).[3]

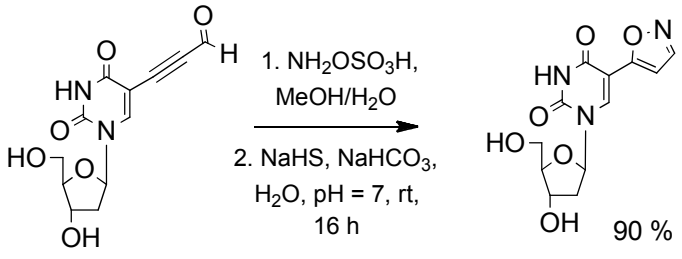


24 **25** **26-28**

No	X, R	Yield
26	Cl, H	36
27	Br, Ph	62
28	Cl, CH_3	58

Scheme 6

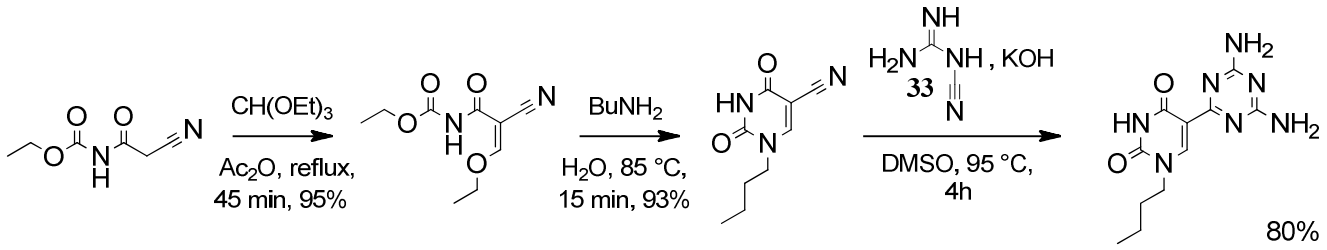
Wigerinck *et al.* attempted to obtain an isothiazole ring on carbon C-5 in uridine applying conditions from the literature.[12] Surprisingly, they obtained an isoxazole ring instead of the desired isothiazole. The reaction was repeated in different pH's (4, 7, 10) but the main product (**30**) remained the same (Scheme 7).[13]



29 **30**

Scheme 7

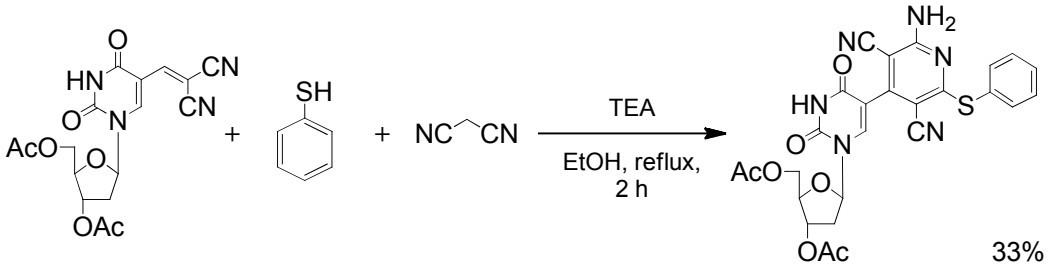
Not only a 5-membered ring could be formed during condensation. In the reaction of 5-cyanouracil derivative with *N*-cyanoguanidine, 5-(4,6-diamino-1,3,5-triazin-2-yl)-1-butyluracil (**34**) was obtained. The synthesis consisted of three steps: condensation of *N*-cyanoacetylurethane (**31**) with triethylorthoformate followed by the addition of butylamine and the ring closure to 5-cyanouracil derivative (**32**) which was further condensed with *N*-cyanoguanidine (**33**) (Scheme 8).[14]



31 **32** **34**

Scheme 8

Also, the condensation of three components, benzylidenemalononitrile (**35**), thiophenol (**36**) and malononitrile (**37**), resulted in the formation of nucleoside substituted by pyridine ring on carbon C-5 of uridine moiety. The yield of obtained product **38** was low because of the by-products formation (Scheme 9).[15]

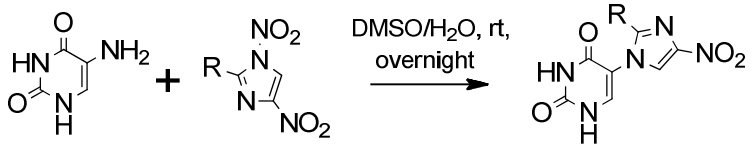


35 **36** **37** **38**

Scheme 9

2.2.2. *ANRORC*

ANRORC is an acronym of reaction consisting of three stages: ***A***ddition of ***N***ucleophile, ***R***ing ***O***pening and ***R***ing ***C***losure. An addition of nucleophile to activated heterocycle leads to opening its ring to acyclic form followed by subsequent ring closure and formation of a new heterocycle. Literature provides only one example of 5-hetaryluracils synthesis according to the *ANRORC* mechanism. 5-Aminouracil (**39**), acting as nucleophile, attacks 1,4-dinitroimidazole (**40**) derivative. After the ring closure stage, an imidazole ring was incorporated as the uracil substituent with a simultaneous elimination of unstable nitroamine (NH_2NO_2) molecule. The reaction conditions are depicted below (Scheme 10).[16,17]



39 **40** **41, 42**

Scheme 10

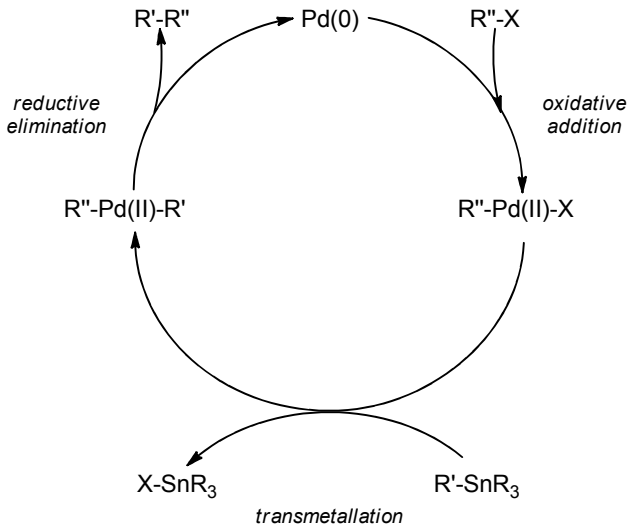
No	R	Yield
41	H	89
42	CH_3	74

2.3. Metal-assisted reactions

2.3.1. Stille cross-coupling reaction

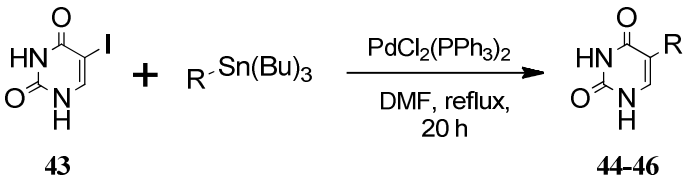
The reagents applied in Stille cross-coupling reaction are: organostannanes $R_3Sn–R'$, where R could be alkyl or rarely aryl substituent and organic halides R''X (X=chlorides, bromides, iodides) or other compounds possessing good leaving group (*i.e.*, triflates). There are two types of Pd catalysts employed in

the Stille reaction: Pd(0) like $Pd(PPh_3)_4$ or Pd(II) like $PdCl_2(PPh_3)_2$. Solvents like DMF, DMSO, THF or dioxane and elevated temperature are the preferred conditions in the syntheses. The presence of Ag_2O as a co-catalyst improves the efficiency due to its influence on the transmetallation stage.[18] One of the greatest advantages of this reaction is a reflection of quite good stability of organostannanes and versatility of conditions for a wide range of functional groups. The discouraging facts are toxicity of the reagents and organometallic impurities in the obtained products making the biological research difficult or even impossible. The catalyst cycle is presented above on Scheme 11.



Scheme 11

Peters *et al.* reported one of the first attempts to obtain 5-hetaryluracils during Stille cross-coupling of 5-iodouracil (**43**) and some aryltributylstannanes in boiling dimethylformamide (DMF) using $PdCl_2(PPh_3)_2$ as catalyst (Scheme 12). The employ of 5-bromouracil instead of iodide did not give the desired products. Among the stannanes used, the least reactive appeared to be pyridyl derivatives and among the three possible isomers, only 5-(pyridin-3-yl)uracil (**46**) was obtained.[19]



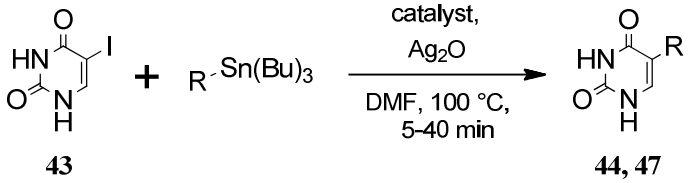
43 **44-46**

No	R	Yield
44		37
45		45
46		25

Scheme 12

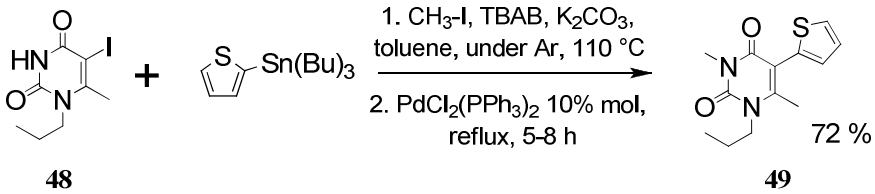
Gronowitz and his research group reported that the addition of Ag_2O as co-catalyst increased reactivity of substrates. The higher yields and shorter reaction times were observed during synthesis of 5-(pyridine-2-yl)uracil (**47**) which was not even formed in the previous attempts (Scheme 13). It is suspected that Ag(I) facilitates the transmetallation stage that leads to higher yield.[20]

Another modified nucleobase was obtained during a two-step synthesis. The first stage was the protection of ^{3}N nitrogen atom in uracil moiety by treatment of starting compound **48** with methyl iodide, tetra-*n*-butylammonium bromide and potassium bicarbonate in toluene. In the next step, Stille coupling was performed employing $PdCl_2(PPh_3)_2$ as catalyst. The final product **49** was formed in 72% yield (Scheme 14).[21]



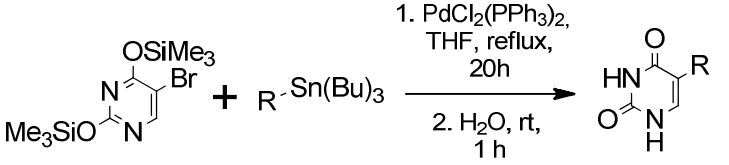
No	catalyst	X, R	Yield
44	$Pd(PPh_3)_4$		18
47	$PdCl_2(PPh_3)_2$		68
47	$Pd(PPh_3)_4$		51

Scheme 13



Scheme 14

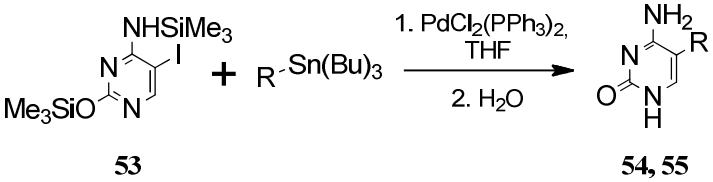
The more effective way for the synthesis of the title compounds employs 5-bromo-2,4-ditrimethylsilyloxypyrimidine (**50**) as the starting material. The reactions were conducted in boiling tetrahydrofuran (THF) using $PdCl_2(PPh_3)_2$ as a catalyst. In the case of products **46** and **47**, the reactions were carried out in the absence of solvent at 80 °C. The deprotection of silyl groups was performed upon aqueous hydrolysis (Scheme 15).[19]



No	R	Yield	No	R	Yield
44		37	47		49
45		39	51		34
46		50	52		44

Scheme 15

When the same coupling conditions were applied for a silylated cytosine derivative, the products were isolated in low yields (18%) (Scheme 16). Changing solvent to dimethylsulfoxide (DMSO) slightly increased yields of the isolated compounds.[22]

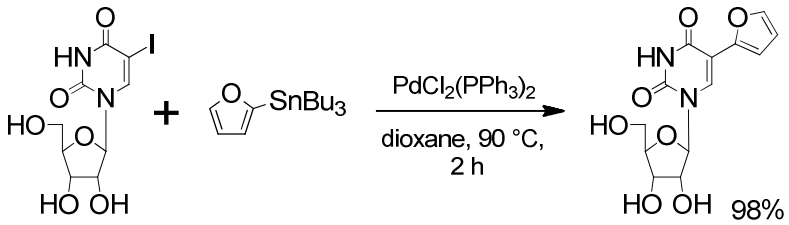


No	R	Yield
54		18
55		18

Scheme 16

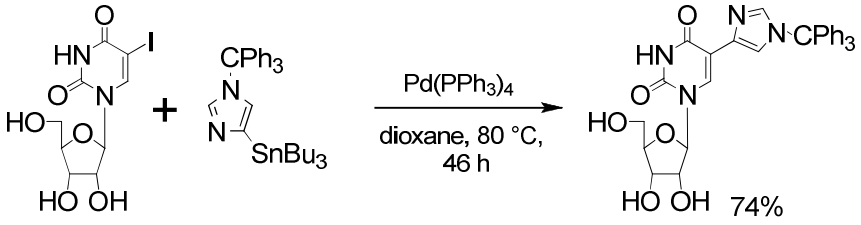
Stille cross-coupling is also applicable for modification of both unprotected and protected nucleosides. For instance, 5-iodouridine (**56**) was coupled with 2-(tributylstannyl)furan (**57**) in boiling dioxane in the presence of $PdCl_2(PPh_3)_2$ (Scheme 17). Product (**58**) was obtained in an almost quantitative yield (98%).[23]

Another example of the synthesis of modified uridine using the same starting compound **56** and conditions was a reaction with 4-tributylstannylimidazole derivative (**59**) (Scheme 18). $Pd(PPh_3)_4$ gave slightly higher yields and purer products in comparison with $PdCl_2(Ph_3P)_2$.[24]



56 **57** **58**

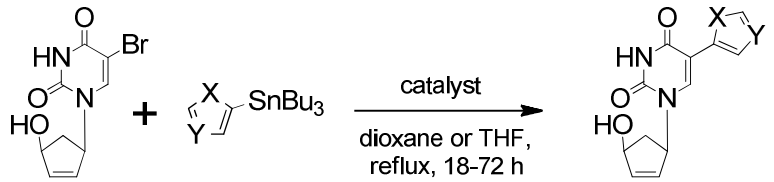
Scheme 17



56 **59** **60**

Scheme 18

The carbocyclic nucleosides modified by thiophene, furan or thiazole ring were obtained in the reaction in dioxane or THF. Both catalysts [$PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$] provided high yields of products, but in the case of thiazole, $Pd(PPh_3)_4$ was more efficient (Scheme 19).[25,26]

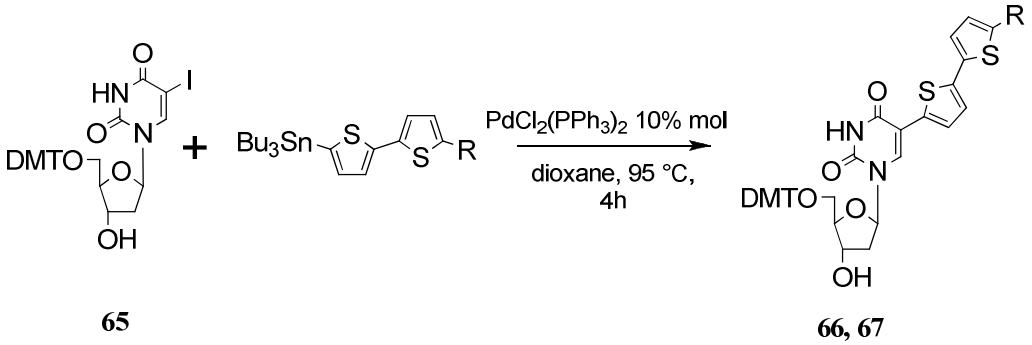


61 **62-64**

No	X, Y	Catalyst	Yield
62	S, C	$PdCl_2(PPh_3)_2$	89
63	O, C	$PdCl_2(PPh_3)_2$	89
64	S, N	$Pd(PPh_3)_4$	68

Scheme 19

The oligothiophene derivatives of 2'-deoxyuridine were obtained during the coupling of the bi- or terthiophene tributhylstannane with 5-iodo-5'-*O*-(4,4'-dimethoxytrityl)-2'-deoxyuridine derivative (**65**) (Scheme 20). The coupling with a longer oligothiophene was less effective than with the shorter one due to its lower reactivity.[27]



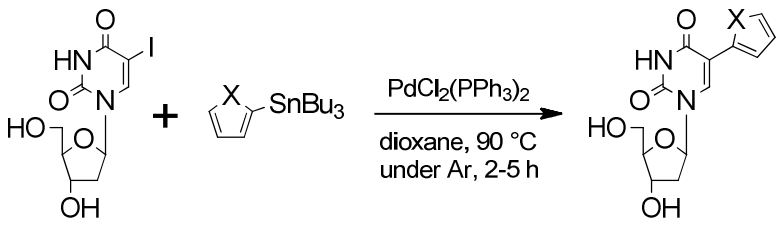
65 **66, 67**

No	X, R	Yield
66	H	97
67		40

Scheme 20

A use of 5-iodo-2′-deoxyuridine (**68**) or its 3′,5′-ditoluoyl-protected analogue (**69**) in a coupling with stannylated heterocycles gave a set of modified pyrimidine nucleosides. The syntheses were conducted in

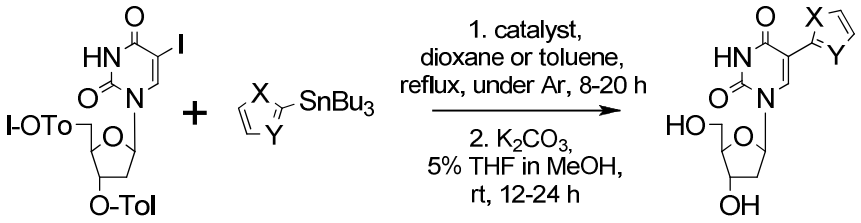
dioxane or toluene using $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ as a catalyst. Toluoyl groups were removed in the reaction with K_2CO_3 in 5% THF/MeOH (Schemes 21 and 22).[28]



68 **7, 8**

No	X	Yield
7	O	94
8	S	53

Scheme 21

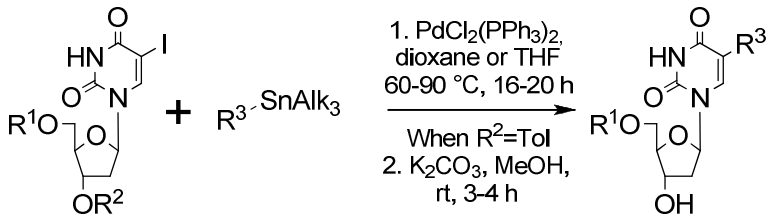


69 **26, 70**

No	X, Y	Catalyst	Yield
26	S, N	$PdCl_2(PPh_3)_2$	34
70	O, N	$Pd(PPh_3)_4$	10

Scheme 22

Direct coupling of unprotected 5-iodo-2'-deoxyuridine with pyridine-2-yl trimethylstannane in the presence of $PdCl_2(Ph_3P)_2$ gave 5-(pyridin-2-yl)-2'-deoxyuridine (**72**). The same synthetic pathway was unsuccessful for other stannanes (thien-2-yl- or thiazol-2-yl) because reduction to 2'-deoxyuridine was observed as the main process. However, protection of the hydroxyl group in sugar moiety made the cross-coupling possible and after removal of toluoyl groups (Tol) by potassium carbonate (K_2CO_3) in methanol, other products (**73** and **8**) were formed (Scheme 23).[18]

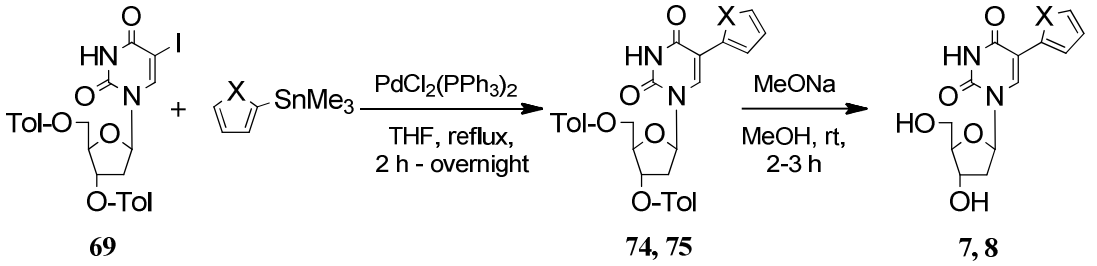


68, 69, 71 **72, 73, 8**

No	R^1	R^2	Alk	R^3	Yield
68	H	H	Me		
69	Tol	Tol	n-Bu		
71	DMT	Tol	Me		
72	H	H			83
73	DMT	H			81
8	H	H			31

Scheme 23

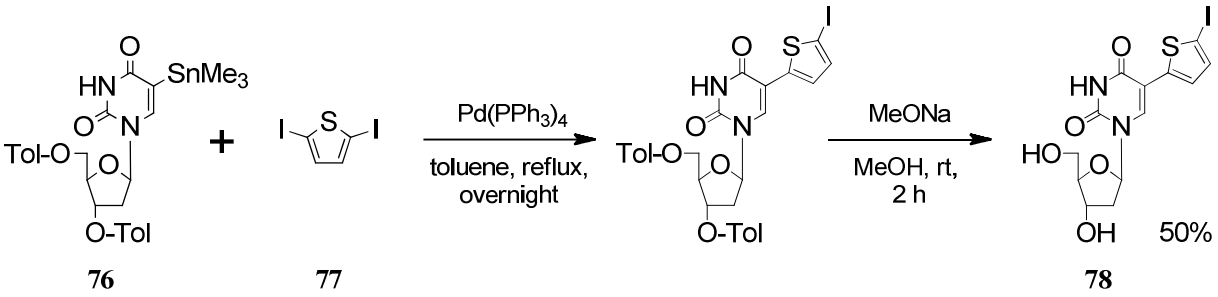
Wigerinck and his co-workers demonstrated that using a coordinating solvents like dioxane or THF accompanied by $PdCl_2(PPh_3)_2$ as catalyst causes reduction of 5-iodo-2'-deoxyuridine to 2'-deoxyuridine. Therefore when non-coordinating solvent like toluene and $Pd(PPh_3)_4$ were used, the reduction product was not observed. The unprotected nucleosides (**7** and **8**) were obtained from **74** and **75** by treatment with sodium methoxide in methanol (Scheme 24).[5]



No	X	Yield
74	O	73
75	S	87
7	O	85
8	S	93

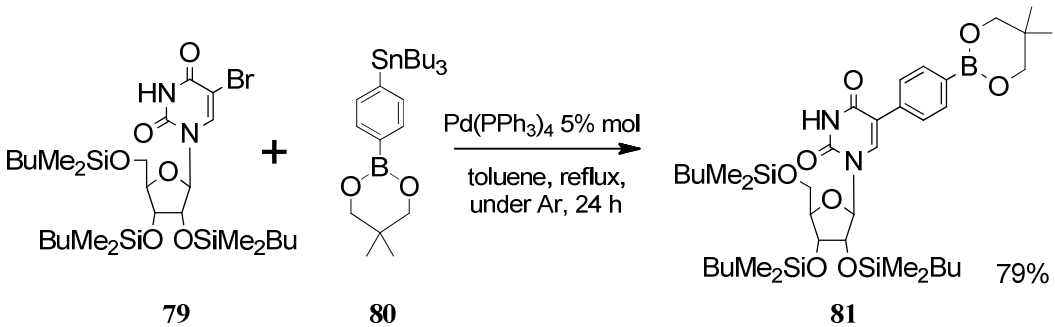
Scheme 24

There is also a possibility to use an inverse version of Stille reaction where a nucleoside possesses trimethylstannyl functional group (**76**). Coupling with 2,5-diiodothiophene (**77**) was accomplished under standard conditions (boiling toluene and $Pd(PPh_3)_4$ as catalyst). After subsequent hydrolysis with sodium methoxide in methanol the nucleoside **78** was formed (Scheme 25). The additional iodine substituent could be engaged in another cross-coupling reaction.[13]



Scheme 25

Very interesting investigations were reported by Yamamoto and co-workers. They coupled protected 5-bromouridine (**79**) with an aryl compound bearing tributylstannyl and boronate substituents. Both groups were active in palladium-assisted coupling, thus two reaction pathways were possible. The research results proved a larger affinity of **80** to Stille coupling under the applied conditions (Scheme 26).[29]

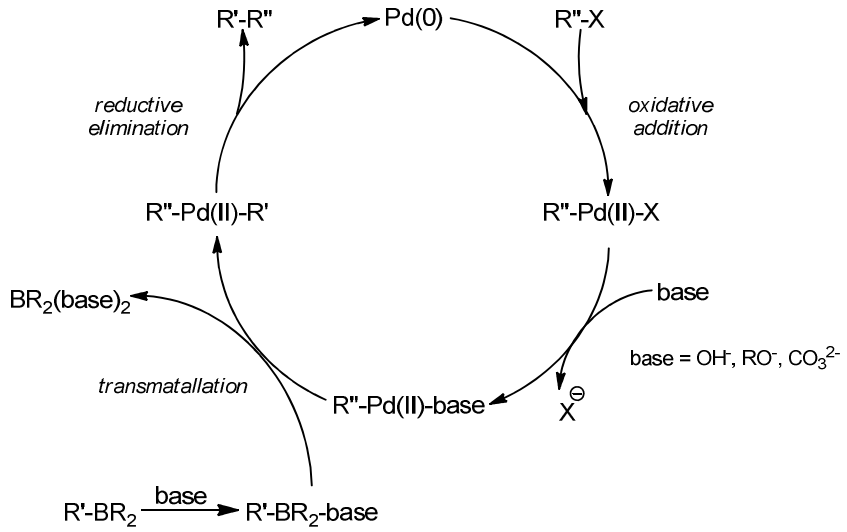


Scheme 26

2.3.2. Suzuki-Miyaura cross-coupling reaction

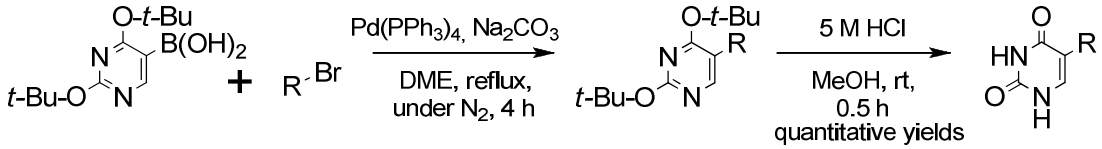
Another efficient method of arylation is Suzuki-Miyaura cross-coupling. This reaction employs organic halides and arylboronic acids or esters as reagents. In contrast to the Stille coupling, the borane derivatives are non-toxic; this fact facilitates thereof biological or medicinal investigation.[30] The standard reaction conditions are: weak basic environment, presence of palladium catalysts *i.e.*, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$, polar solvents including water and elevated temperature. The role of used bases

(Na_2CO_3, K_2CO_3 or Cs_2CO_3) is to activate arylboronic acid or its ester. The huge advantage of this reaction is its tolerance to some unprotected functional groups.[31] The catalysis cycle is presented below on Scheme 27.

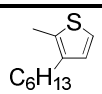
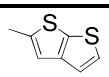
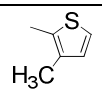
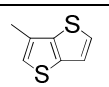
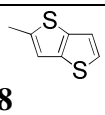
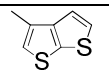


Scheme 27

Peters and co-workers made a substantial contribution to the progress in the field of cross-coupling reactions including the Suzuki's type. They obtained a broad range of 5-hetaryluracils involving 5- and 6-membered ring or even bicyclic substituents. They employed 2,4-di-*tert*-butoxy-5-pyrimidineboronic acid (**82**) as a starting compound and coupled it with arylhalides in the presence of $Pd(PPh_3)_4$ and dimethoxyethane (DME) as solvent. The obtained products **83–94** were transformed into their unprotected uracil analogues during acidic hydrolysis by a mixture of hydrochloric acid in methanol. The yields of obtained products were almost quantitative (Scheme 28). The uracil derivatives containing nitrogen atom in their heterocyclic ring precipitated out as hydrochlorides salts but trials to furnish free bases were unsuccessful. This was probably caused by excellent solubility of uracils in aqueous basic solutions. Surprisingly, during recrystallization from methanol, thiazol-2-yl derivatives precipitated as free bases.[19]



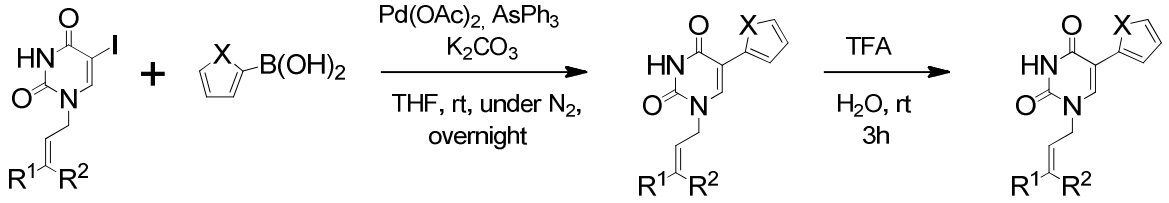
82 **83-94**

No	R	Yield	No	R	Yield	No	R	Yield	No	R	Yield
83		49	86		60	89		61	92		60
84		49	87		69	90		62	93		55
85		62	88		70	91		57	94		40

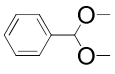
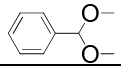
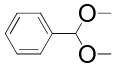
Scheme 28

The acycloalkenyl nucleosides were obtained in the reaction of iodinated uracil derivative with thiophene or furan boronic acid in the presence of $Pd(OAc)_2$ and triphenylarsine ($AsPh_3$) as an additional

ligand. Potassium carbonate was used as a base and the reaction was carried out at room temperature in THF solution. The hydroxyl groups in alkenyl chain were protected by two different ketones (acetone or cyclohexanone) creating cyclic acetals. After coupling, the acidic deprotection with trifluoracetic acid (TFA) in water was conducted. The yields of deprotected products **101–104** were approximately quantitative (Scheme 29).[32]

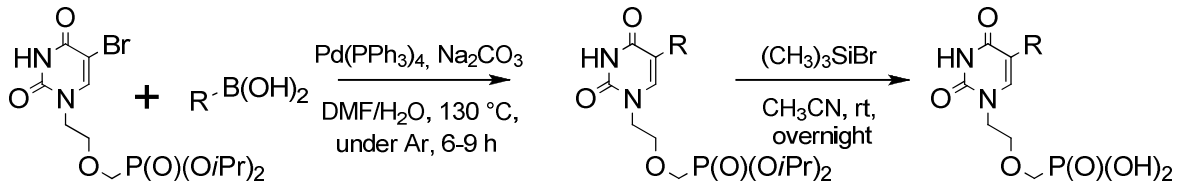


95, 96 **97-100** **101-104**

No	R^1	R^2	No	R^1	R^2	X	Yield	No	R^1	R^2	X	Yield
95		H	97		H	O	94	101		H	O	93
			98		H	S	68	102		H	S	90
96			99			O	75	103	HO–	HO–	O	96
			100			S	76	104	HO–	HO–	S	93

Scheme 29

Pomeisl's research group applied Suzuki coupling for the synthesis of 5-hetaryluracil acyclic nucleosides phosphonates. They developed a method for the formation of two kinds of phosphonates. In the first case, 5-bromouracil derivatives and a number or heteroaryl boronic acids were coupled. The reactions were conducted in a mixture of DMF:H_2O as solvent system in the presence of Na_2CO_3 and catalyzed by $Pd(PPh_3)_4$ at 130 °C. Using bromotrimethylsilane followed by hydrolysis allowed to obtain final products **110–113** in moderate yields (Scheme 30).[30]

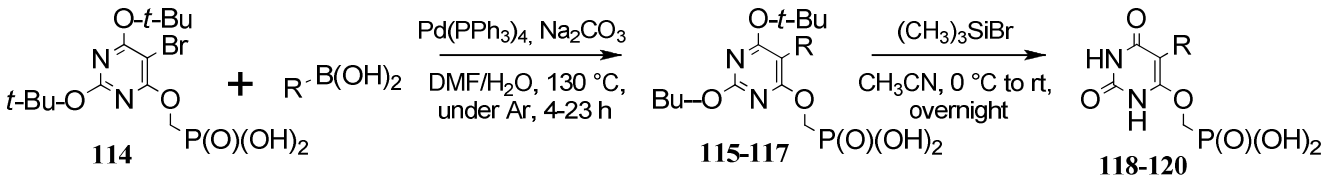


105 **106-109** **110-113**

No	R	Yield	No	R	Yield
106		24	110		75
107		44	111		59
108		24	112		72
109		38	113		78

Scheme 30

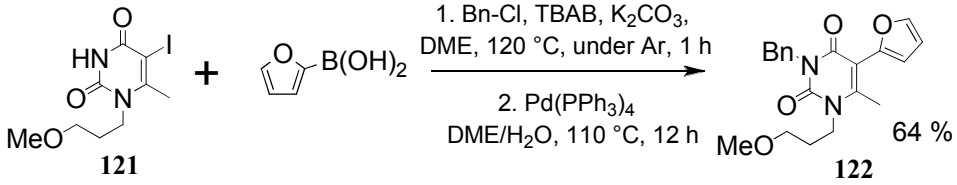
The same conditions were applied for the synthesis of previously mentioned phosphonates of other type (Scheme 31). In comparison of these two groups, the C-6 phosphonates were isolated in higher yields than the corresponding ^{1}N analogues.[33]



No	R	Yield	No	R	Yield
115		45	118		33
116		78	119		29
117		43	120		57

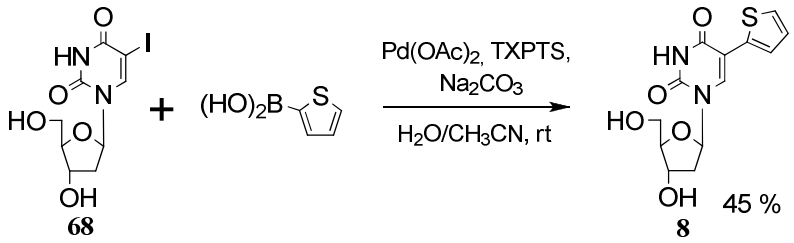
Scheme 31

Another acyclic nucleoside was obtained in a two-step synthesis. The first stage was protection of ^{3}N nitrogen atom in the uracil moiety by treatment of the starting compound with benzyl chloride, tetra-*n*-butylammonium bromide and potassium bicarbonate in DME. In the next step, an appropriate coupling was performed in the mixture of DME and water using $Pd(PPh_3)_4$ as catalyst. The final product **122** was formed in 64% yield (Scheme 32).[21]



Scheme 32

It is believed that homogeneous conditions of cross-coupling reaction are more efficient way for the synthesis of unprotected 5-hetaryl nucleosides. The employ of a mixture of solvents like water and acetonitrile, $Pd(OAc)_2$ as a water soluble catalyst and tri-(4,6-dimethyl-3-sulfonatophenyl)phosphine trisodium salt (TXPTS) gave the desired product **8** in 45% yield (Scheme 33).[34] However, the same final product **8** was obtained in a better yield in the previously described Stille reaction[5,28] (93% and 53%, respectively).

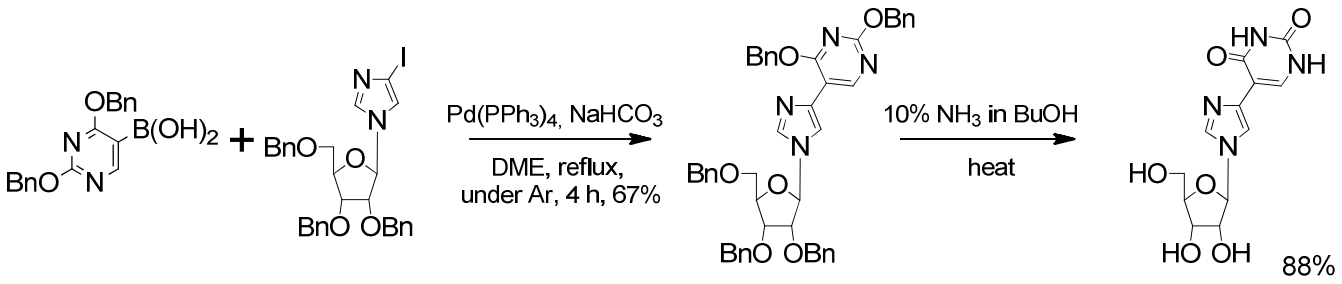


Scheme 33

The other compound, an imidazole nucleoside derivative, was prepared in reaction of 4-iodoimidazole derivative (**124**) with 2,4-dibenzyloxy-5-pyrimidineboronic acid (**123**) under standard coupling conditions. All benzyl protected groups were removed by 10% ammonia in butanol while heating. The product **125** was formed in 88% yield (Scheme 34).[35]

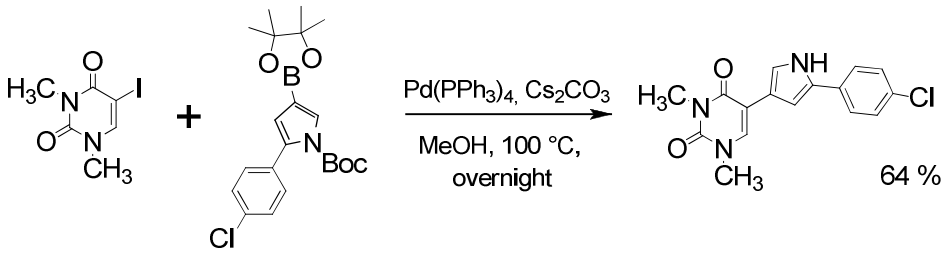
An effective one-pot synthesis was also described. In a single procedur, three different reactions were conducted. First stage included Masuda borylation where $Pd(PPh_3)_4$ was employed as the catalyst. The same

portion of palladium complex catalyzed the next stage which is the actual Suzuki coupling. During this reaction, Cs_2CO_3 was used as a boronic ester activator and this reagent in methanolic solution was also applied in the last stage of synthesis - deprotection of Boc group. The final product (**127**) was obtained in 64% yield (Scheme 35).[36]



123 **124** **125**

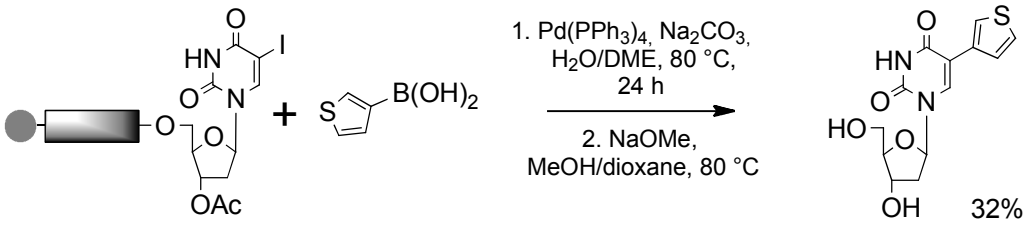
Scheme 34



126 **127**

Scheme 35

The Suzuki-Miyaura cross-coupling is also applicable in a solid support synthesis. 5-Iodo-2'-deoxy-uridine (**128**) was attached to polystyrene resin and reacted with thien-3-ylboronic acid under optimized conditions. Standard cleavage of the resin was carried out by sodium methoxide in the mixture of methanol and dioxane at elevated temperature. The yield of desired product **129** (after five steps) was 32% (Scheme 36).[37]

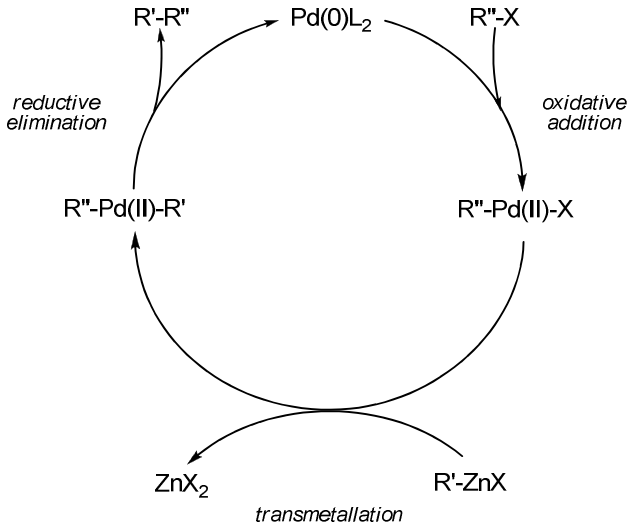


128 **129**

Scheme 36

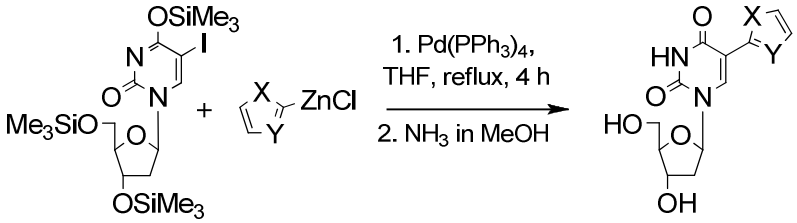
2.3.3. Negishi coupling

Negishi reaction is another type of metal-assisted cross-coupling. The reactants used in this reaction are: organozinc compounds (R'−ZnX), organic halides (R''−X) like chlorides, bromides or iodides and palladium or nickel complexes employed as catalysts. The largest disadvantage of this reaction is an obligation of strictly anhydrous conditions that makes the workup procedures problematic and, in comparison with trialkylaryl stannanes and boronic compounds, zinc salts are the least stable reagents.[5] The catalyst cycle is presented on Scheme 37.



Scheme 37

The reaction between trimethylsilylated 5-iodo-2'-deoxyuridine (**130**) and $ZnCl^+$ salts of the heterocycles in boiling THF, in the presence of $Pd(PPh_3)_4$ as catalyst, allowed to obtain the thiazol-2-yl and *N*-methylimidazol-2-yl derivatives of 2'-deoxyuridine in moderate yields. This strategy was not successful in attempts of the synthesis of isoxazole, 2-(trimethylsilyl)thiazole, furan and *N*-{[(2-trimethylsilyl)ethoxy]methyl}imidazole derivatives due to very poor yields (less than 10%). Trimethylsilyl groups were cleaved in the reaction with methanolic solution of ammonia (Scheme 38).[5]

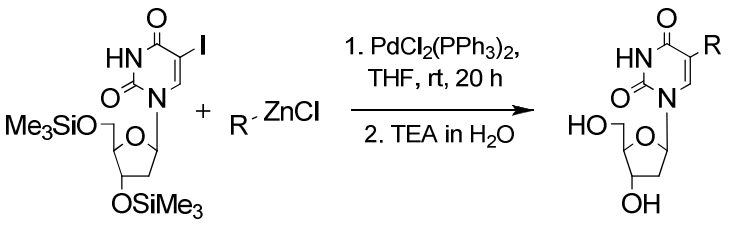


130 **26, 131**

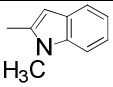
No	X, Y	Yield
26	N, S	48
131	N, N-Me	64

Scheme 38

Similar conditions were used in a direct coupling of silylated 5-iodo-2'-deoxyuridine with some organozinc heterocycles. Deprotection of silyl groups was performed by hydrolysis in aqueous solution of triethylamine. The yields of obtained products (**8**, **133**, **134**) were from low to moderate (8–39%) (Scheme 39).[38]



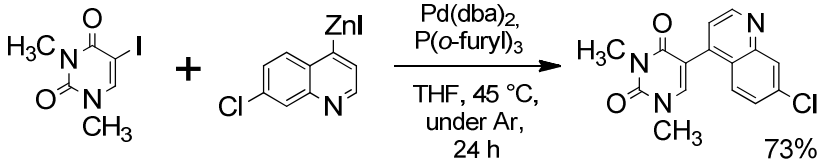
132 **8, 133, 134**

No	R	Yield
8		15
133		39
134		8

Scheme 39

In another approach of the synthesis of 5-hetaryluracil derivative under cross-coupling reaction conditions, the palladium catalyst was generated *in situ* from bis(dibenzylideneacetone)palladium(0)

(Pd(dba)$_2$) and P(*O*-furyl)$_3$. This strategy gave the satisfactory result: in fact, the desired product **135** was obtained in good yield (Scheme 40).[39]

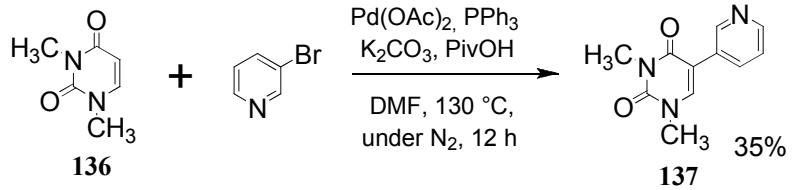


126 **135**

Scheme 40

2.3.4. Direct arylation reaction

Direct C–H arylations is an alternative to the cross-couplings reactions. Similarly to the other metal-assisted reactions palladium complexes are the most versatile catalysts. The syntheses can be performed in the presence or absence of Cu(I) salts. The Cu-free reactions proceed by a concerted metallation-deprotonation (CMD) mechanism.[40] K. H. Kim *et al.* reported a reaction of 1,3-dimethyluracil (**136**) with 3-bromopyridine. The optimized conditions used in this synthetic method were: the mixture of K_2CO_3 and pivalic acid in DMF in the presence of Pd(OAc)$_2$ as catalyst and PPh_3 as additional ligand. The desired product **137** was isolated in 35% yield (Scheme 41).[41]



136 **137**

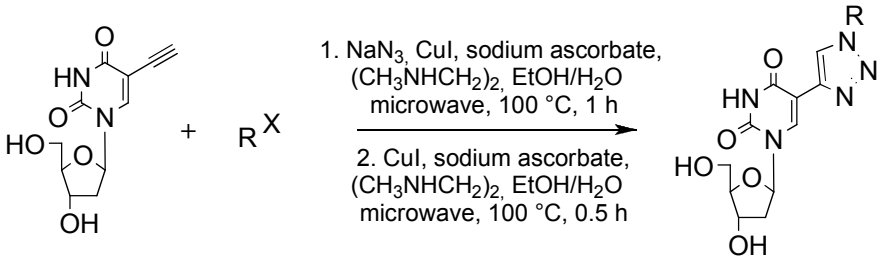
Scheme 41

2.4. Cycloaddition reaction

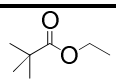
2.4.1. 1,3-Dipolar cycloaddition

1,3-Dipolar cycloaddition, also known as the Huisgen reaction,[42] is one of the most powerful reaction in the synthesis of 5-membered heterocyclic rings. The reaction proceeds between a dipolarophile (unsaturated compounds like alkenes, alkynes or nitriles) and a 1,3-dipole (*i.e.*, azides, nitrones, diazoalkanes, etc.). The proper selection of these two reagents gave a possibility of synthesis of aromatic, unsaturated and saturated heterocycles *e.g.*, triazoles, isoxazolidines, oxadiazolines and more. Although there are general terms for orientation of cycloadducts, the selectivity in these cycloaddition reactions varies. For example, in azide-alkyne coupling reactions without Cu(I) catalyst, the expected 4,5-disubstituted-1,2,3-triazole derivatives are formed in an equimolar ratio.[43] The copper-catalyzed alkyne-azide cycloaddition (CuAAC) reaction is at present the most popular variant of 1,3-dipolar cycloaddition and it is classified as the click chemistry reaction.

An interesting variant of the one-pot synthesis was described.[44] It involves formation of a dipolarophile, an azide derivative, and cycloaddition reaction runs in a single procedure using organic halides and 5-ethynyl-2'deoxyuridine (**138**) as starting material. The reaction mixture was irradiated by microwave in the presence of copper iodide, sodium ascorbate and *N,N'*-dimethylethylenediamine. The products were obtained in very good yields (Scheme 42). The pivaloyloxymethyl group in product **139** was cleaved by ammonia.[44]

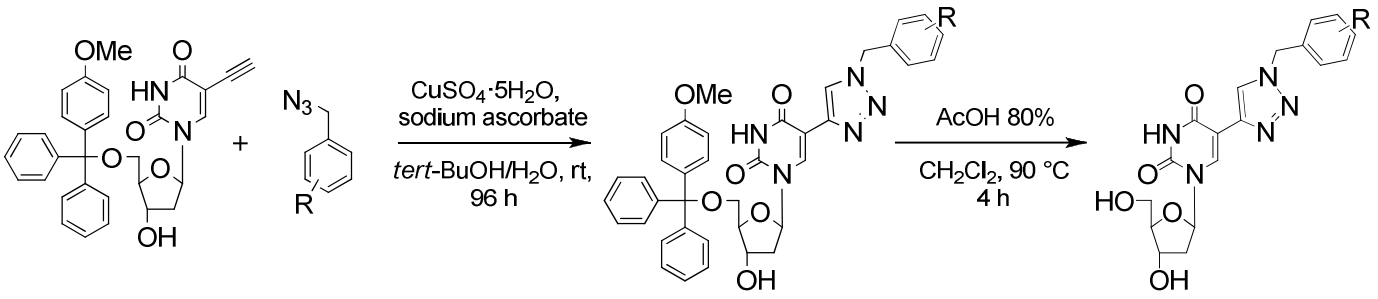


138 **139-141**

X	No	R	Yield
Cl	139		76
Br	140		68
Br	141		87

Scheme 42

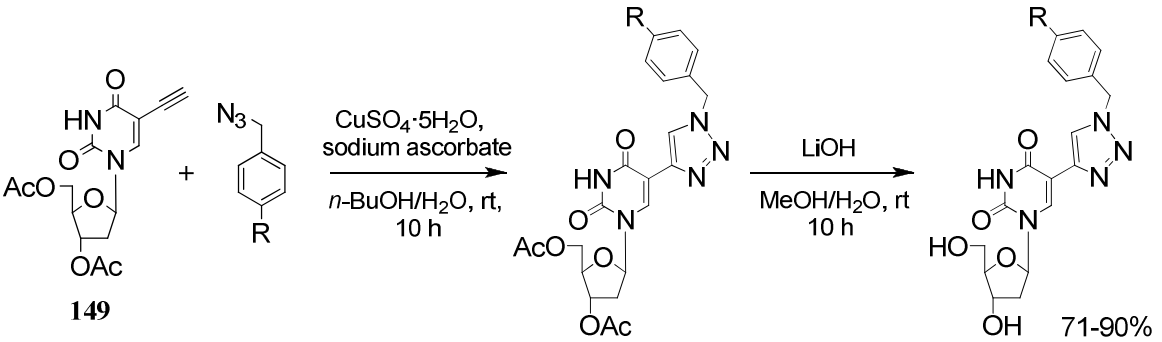
Kim *et al.* obtained several 5-(1,2,3-triazol-4-yl) derivatives of uridines employing standard click chemistry protocol using *t*-butanol/water mixture as a solvent system and $CuSO_4 \cdot 5H_2O$-sodium ascorbate as a catalyst. The protecting groups present in uridine molecule were removed by 80% aqueous acetic acid (for 4-methoxytrityl group)[45] or LiOH in a mixture of methanol/water (for acyl group) (Schemes 43 and 44).[46]



142 **143-148**

No	R	Yield	No	R	Yield
143	H	83	146	4-Me	56
144	2-Me	56	147	2-Et	87
145	3-Me	56	148	4-Bu	81

Scheme 43



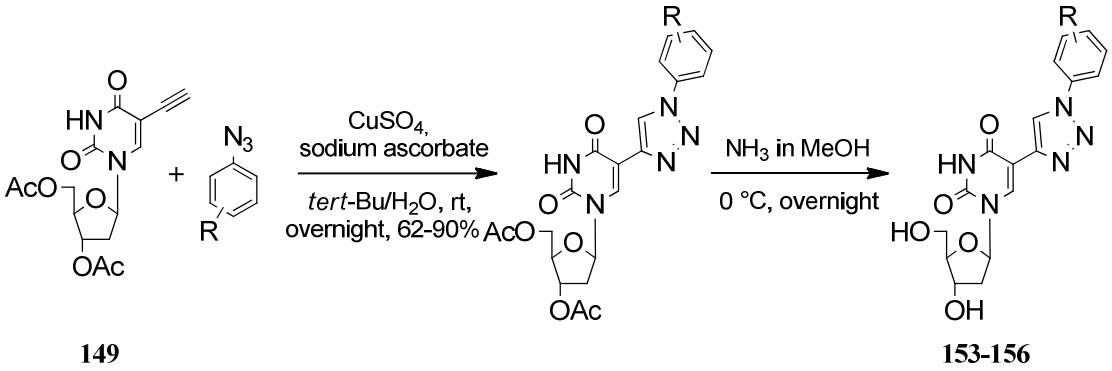
149 **143, 150-152**

No	R
143	H
150	Et
151	*i*-Pr
152	*tert*-Bu

Scheme 44

Agrofoglio and his research group reported a possibility of formation of 1,4- or 1,5-regioisomers of triazoles depending on the applied catalyst. The use of Cu catalyst like $CuSO_4 \cdot 5H_2O$-sodium ascorbate in typical synthesis led to 1,4-regioisomers of triazole ring (Scheme 45), whereas Cp*RuCl$(PPh_3)_2$ was employed instead of standard Cu catalyst: 1,5-regioisomers were obtained (Scheme 46). Deacylation in all of

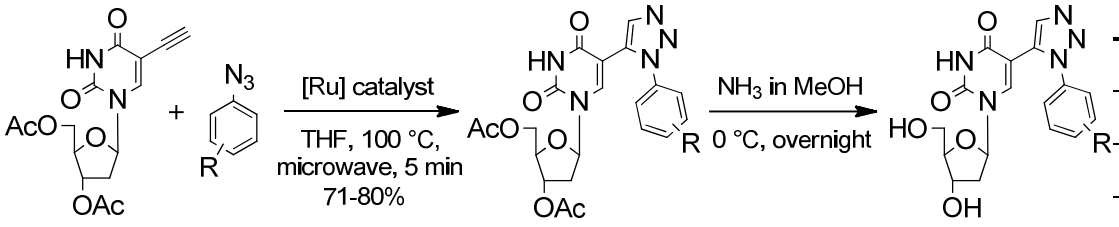
the products was performed using ammonia in methanol. 1,4-Regioisomers, in contrast to 1,5-regioisomers, showed biological activity against VZV.[47]



149 153-156

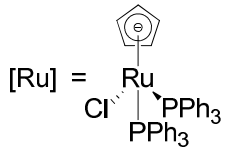
No	R	Yield
153	2,6-diF	92
154	4-*t*-Bu	97
155	4-Br	90
156	4-*O*-Ph	94

Scheme 45



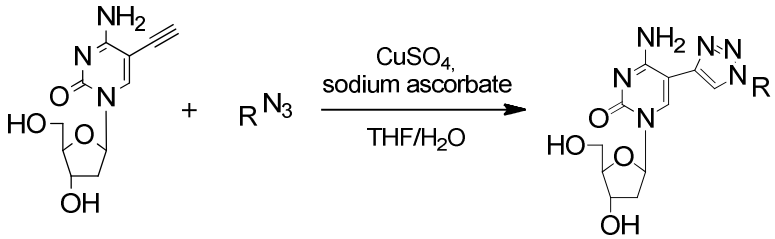
149 157-160

No	R	Yield
157	2,6-diF	94
158	4-*i*-Pr	93
159	4-Br	91
160	4-O-Ph	90

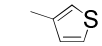
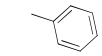
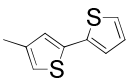


Scheme 46

Also 5-alkynylcytidine (**161**) could be coupled with some azides. These reactions were carried out in the presence of $CuSO_4$ and sodium ascorbate in THF/H_2O solution (Scheme 47). The crystal X-ray studies of the compound **107** revealed that the three aromatic rings in the solid state are coplanar. The distance between one of the protons in the amino group and ^{3}N nitrogen atom in the triazole ring was found 2.1 Å, that could stabilize the coplanar arrangement by an intramolecular hydrogen bond.[48,49]



161 162-164

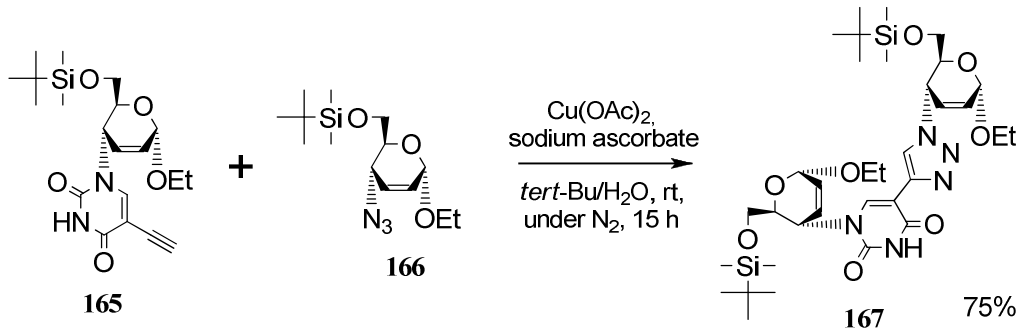
No	R	Yield
162		43
163		78
164		15

Scheme 47

By using a nucleoside derivative with a terminal alkynyl group **165** present on C-5 of uracil ring and a sugar derivative possessing azide functional group (**166**), it was possible to synthesise some new glycoconjungates. The disaccharide **167** was obtained during Cu-catalyzed cycloaddition using $Cu(OAc)_2$-sodium ascorbate as the catalyst and *tert*-BuOH/H_2O mixture as a solvent (Scheme 48).[50]

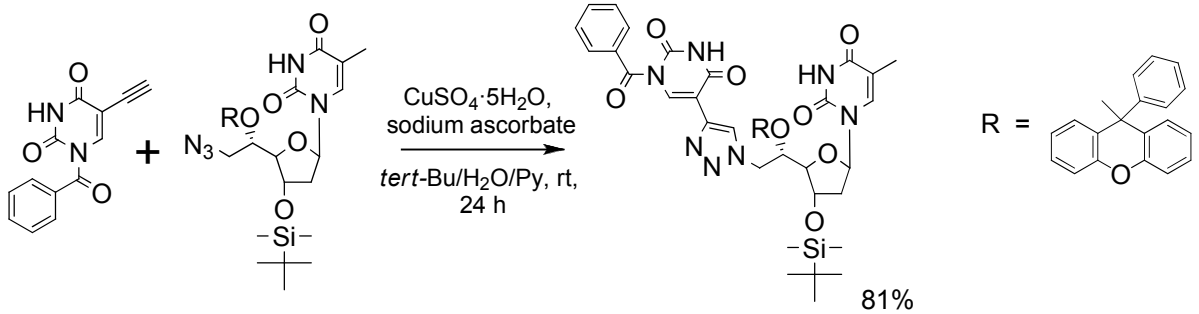
Another kind of derivatives obtained in 1,3-dipolar cycloaddition reaction are so-called "double-headed nucleosides". Uracil and thymidine ring were joined by triazolyl linker, prepared in the reaction of

appropriate 5-alkynyluracil and thymidine derivative having azido group in the presence of standard $Cu(OAc)_2$-sodium ascorbate catalyst (Scheme 49). The obtained cycloadduct **169**, incorporated into DNA strand, interacted with the complementary DNA strand by hydrogen bonds formation and π-stacking evoked by the presence of triazole and/or uracil ring. These influences caused changes of stability in the studied DNA structures.[51]



165 **166** **167**

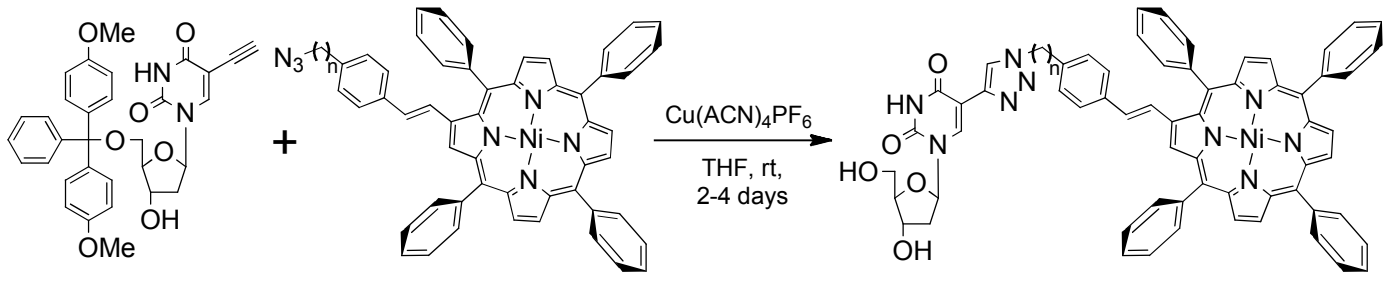
Scheme 48



168 **169**

Scheme 49

The introduction of porporphyrin molecule **171** into nucleoside derivative by triazolyl linker was carried out using ($Cu(ACN)_4PF_6$), a soluble in organic solvents Cu-catalyst (Scheme 50). The final cycloadducts possess intercalating properties affecting stabilization/destabilization of DNA strand.[52]

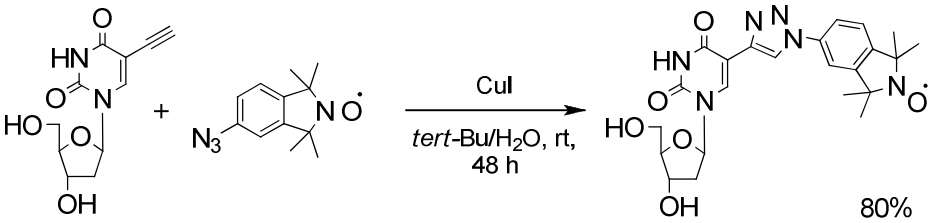


170 **171**

172 n = 0 36%
173 n = 1 28%

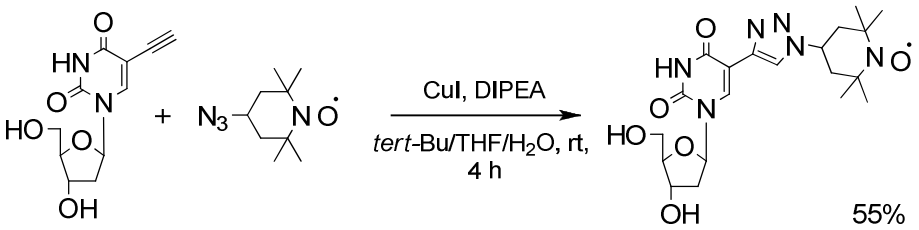
Scheme 50

In the syntheses of spin-labelling nucleosides (bearing nitroxyl group) typical catalyst system Cu(II)-sodium ascorbate must be avoided because of reductive properties of the latter. The catalyst is responsible for reduction of desired nitroxyls to hydroxylamine derivatives. Instead of this catalytic system, the cuprous iodide Cu(I) can be used directly as the click catalyst. The nitroxyls were stable under other conditions like temperature or solvents: *tert*-butanol:H_2O (Scheme 51) or *tert*-butanol:THF:H_2O (Scheme 52).[53,54]



138 174

Scheme 51

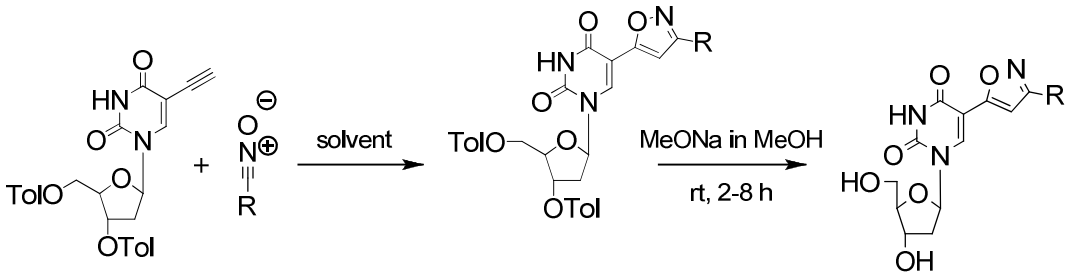


138 175

Scheme 52

Other 5-hetaryluracils were obtained in the coupling reaction of appropriate nitrile oxides with alkynyl derivatives (isoxasoles) or nitriles (1,2,4-oxadiazoles). The nitrile oxides are far less stable than azides and they must be generated *in situ* and used immediately without any purification in the cycloaddition reaction, due to possible dimerization into the furoxans.

There are few methods of the nitrile oxides generation. The most favourable, especially for aryl nitrile oxides, is chlorination of oximes by *N*-chlorosuccinimide (NCS) and further elimination of hydrochloride using a base *i.e.*, triethylamine (TEA).[3,55] According to this procedure the products **177** and **178** were obtained. When dibromoformaldoxime was treated with sodium bicarbonate as a base, bromonitrile oxide was obtained. This nitrile oxide was applied for the preparation of compound **179**.[3] The aliphatic nitrile oxides were also generated from nitroethane and nitropropane. Treatment of these nitro compounds with phenyl isocyanate in the presence of catalytic amounts of TEA led to the formation of the desired nitrile oxides and diphenylurea as a side product.[3] The above mentioned cycloaddition reactions were carried out in DMF (compounds **177**, **178**), ethyl acetate (**179**) or toluene (**180**, **181**). The toluolyl protecting groups in the all cycloadducts were removed using sodium methanolate in methanol giving unprotected nucleosides (Scheme 53).[3]

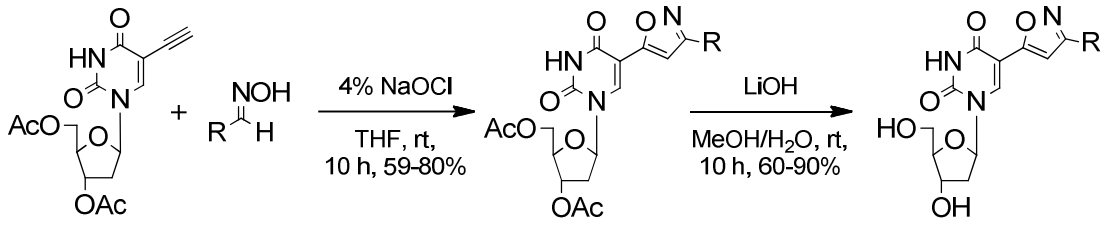


176 177-181

No	R	Yield
177	Ph	59
178	4-Cl-C_6H_4	--
179	Br	92
180	Me	69
181	Et	64

Scheme 53

In another frequently used method, nitrile oxides are generated from the appropriate oximes by treatment with a commercial bleaching agent containing NaOCl. The acyl protecting groups in the obtained products were removed using LiOH in aqueous methanol (Scheme 54).[1,46]

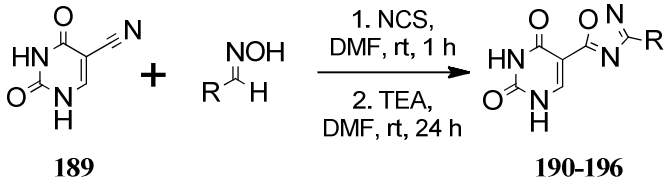


149 **177, 180, 182-188**

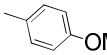
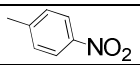
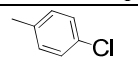
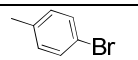
No	R	No	R	No	R
180	Me	184	Oct	186	4-*i*-Pr-C_6H_4
182	*n*-Pr	177	Ph	187	4-*n*-Bu-C_6H_4
183	*n*-Pent	185	4-Et-C_6H_4	188	4-*t*-Bu-C_6H_4

Scheme 54

As an alternative for ethynyl derivatives of nucleobases or nucleosides applied in the cycloaddition reactions, also nitriles, like 5-cyanouracil, can play a role of the dipolarophile. The chlorination of aryl aldoximes followed by base (TEA) treatment was used for generation of nitrile oxides and subsequent cyclization with unprotected 5-cyanouracil. The cycloaddition reaction was conducted at the room temperature for 24 hours (Scheme 55). The expected products (**190–196**) were obtained in moderate yields.[56]

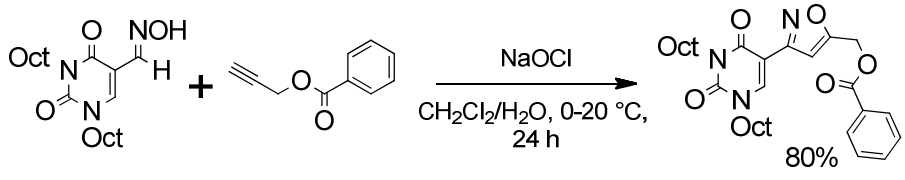


189 **190-196**

No	R	Yield	No	R	Yield
190		40	194		51
191		51	195		19
192		40	196		28
193		44			

Scheme 55

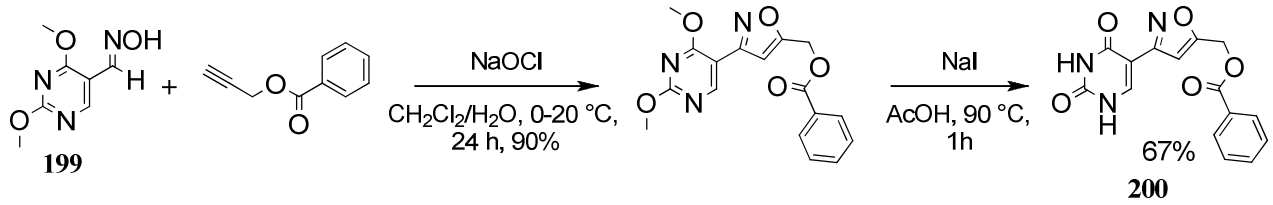
In all of the previously mentioned cycloaddition reactions, the uracil derivatives were used as the dipolarophiles. However, they could also play a role of 1,3-dipole. The oxime of 5-formyluracil is a 1,3-dipole precursor. The presence of *n*-octyl protecting groups caused better solubility in nonpolar solvent used in this synthesis (CH_2Cl_2). The reaction was conducted in a biphasic methylene chloride/aqueous solution of NaOCl system and the expected cycloadduct was obtained in good yield (Scheme 56).[57]



197 **198**

Scheme 56

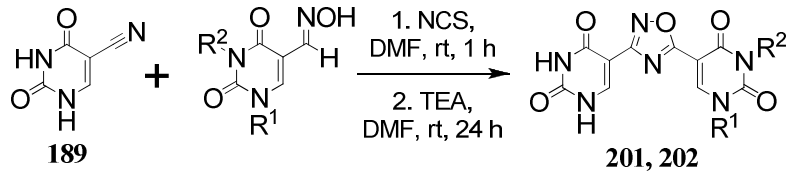
Another dipole was generated from the corresponding oxime **199** in the same biphasic system and its similar reactivity was observed. The dimethoxy cycloadduct was transformed into the unprotected uracil derivative **200** by heating in acetic acid in the presence of sodium iodide (Scheme 57).[57]



199 200

Scheme 57

In another experiment, the oxime of 5-formyluracil was coupled with 5-cyanouracil forming cycloadduct possessing two uracil rings connected by aromatic 1,2,4-oxadiazolyl link (Scheme 58).[56]



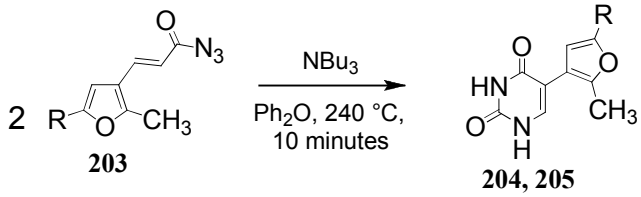
189 201, 202

No	R^1	R^2	Yield
201	Me	Me	60
202	CH_2CH_2COOMe	H	51

Scheme 58

2.4.2. Diels-Alder cycloaddition

Diels-Alder cycloaddition belongs also to pericyclic reactions. Two components, a conjugated diene and a dienophile take part in the reaction forming a 6-membered carbon or heterocyclic ring. After further transformation of the obtained ring, it is possible to obtain the aromatic analogue. During the synthesis of furo[2,3-*c*]pyridinones, unexpected 5-hetaryl derivatives of uracil were obtained. The acyl azides were transformed *in situ* to arylisocyanates which dimerized under applied conditions. Further elimination of arylvinyl group furnished products **204** and **205** (Scheme 59).[58]

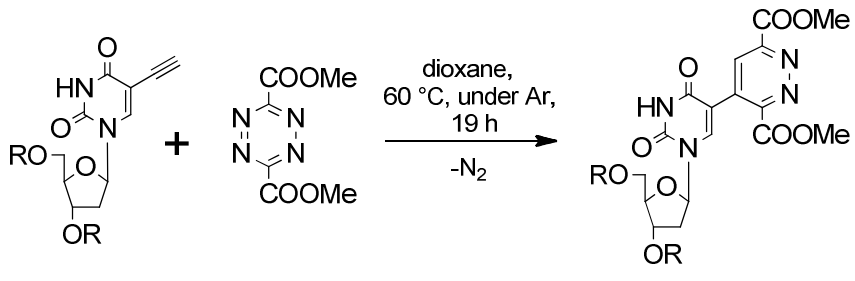


203 204, 205

No	R	Yield
204	H	traces
205	CH_3	29

Scheme 59

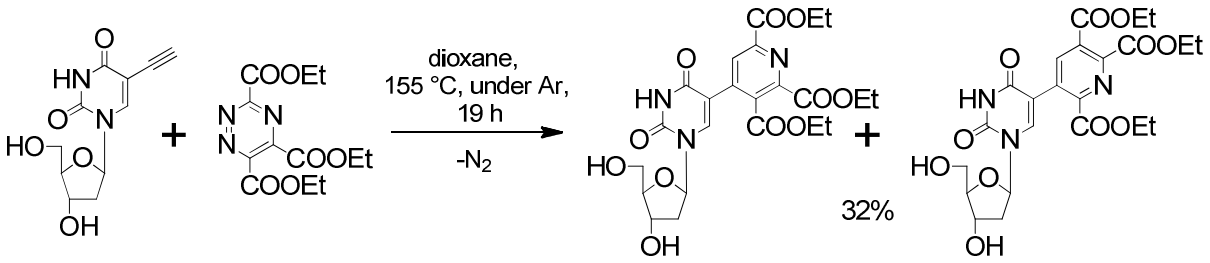
Another way for the synthesis of the heteroaromatic rings like pyridazine or pyridine was reported by Maggiora and co-workers.[57] The first step was Diels-Alder cycloaddition between 5-ethynyl-2'deoxyuridine or its acyl-protected analogue (dienophile) and tri- or tetrazine (diene). In the second step, nitrogen elimination occurred and the new 5-hetaryluracils were formed. In the case of pyridine derivatives, an equal mixture of two regioisomers was obtained in 32% yield (Schemes 60 and 61).[59]



138, 149 206, 207

No	R	Yield
206	H	71
207	Ac	70

Scheme 60

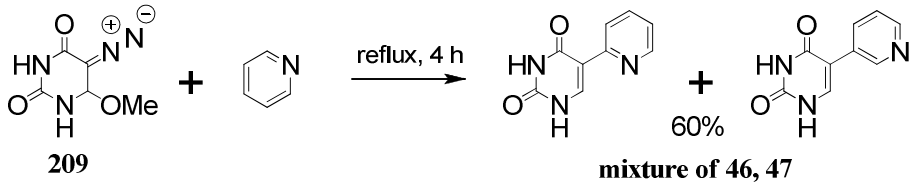


138 **208**

Scheme 61

2.5. Miscellaneous

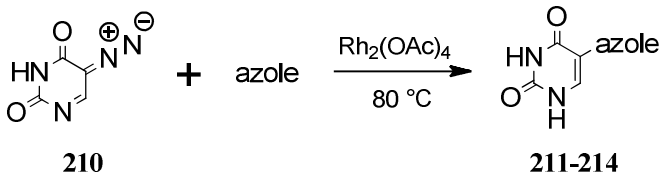
5-Diazouracils are interesting substrates for the synthesis of hetaryl ring on C-5 in uracil moiety. The substitution reaction of diazo group by pyridine resulted in the formation of a mixture of two regioisomers (**46** and **47**, in a ratio 1:2) in 60% yield (Scheme 62).[60]



209 **mixture of 46, 47**

Scheme 62

In another approach, a substitution of diazo group by azoles like imidazole, 1,3,4-triazole or pyrrole was reported. The presence of rhodium acetate as catalyst was required. The yield of products varied in the range of moderate to very good (Scheme 63).[61]

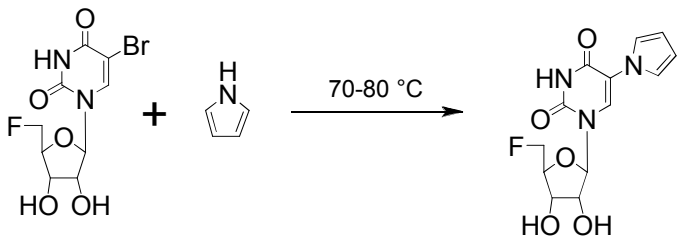


210 **211-214**

No	R	Yield
211		96
212		34
213		86
214		86

Scheme 63

A 5-(pyrrol-1-yl)substituted uridine was obtained in a direct reaction of 5-bromouridine derivative with pyrrole under heating (Scheme 64).[62]

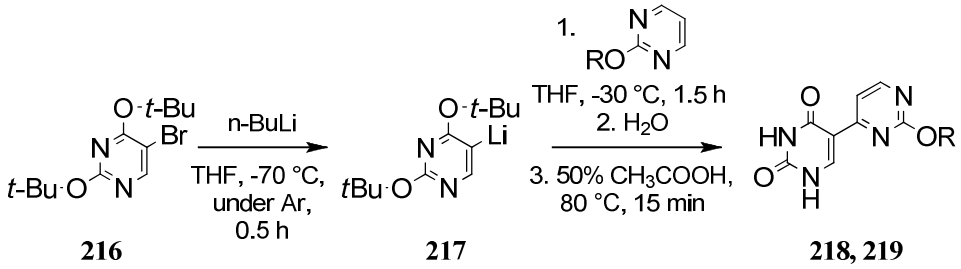


215 **216**

Scheme 64

The multi-step synthesis of 5-(pyrimidin-4-yl)-substituted uracil derivatives was reported by Strękowski. The first step was the preparation of 5-lithium pyrimidine in the reaction of 5-bromouracil

derivative with *n*-buthyllithium (*n*-BuLi) followed by treatment with 2-alkoxypyrimidine. The reaction mixture was quenched by water and hydrolyzed by 50% aq. acetic acid. The 5-(2-alkoxypyrimidin-4-yl) uracils were obtained in very low yields (Scheme 65).[63]



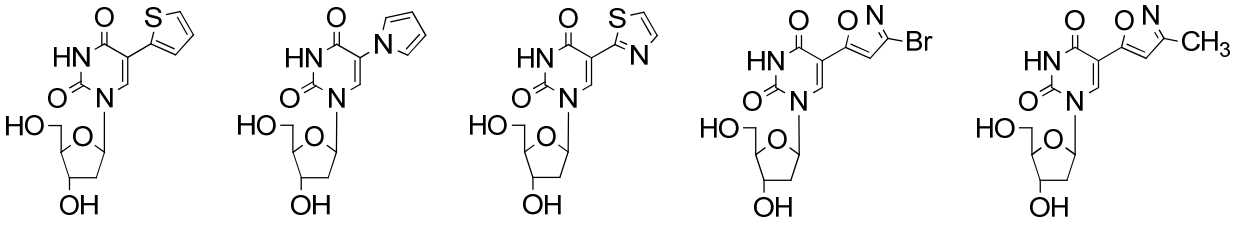
216 **217** **218, 219**

No	R	Yield
218	Me	6
219	Et	14

Scheme 65

3. Applications

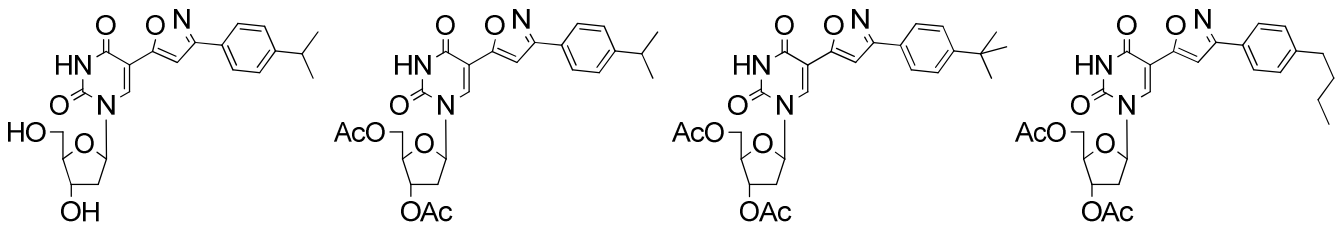
A significant number of compounds described in the previous chapters were suspected of having biological activity and potential application in medicine. The biological targets were mostly viruses (*i.e.*, HSV-1, HSV-2, VZV, HIV) and cancer cells. The most promising compounds were described by Wigerink's research group. The nucleosides possessing on carbon C-5 of uracil ring isoxazolyl, thioazolyl, pyrrolyl or thienyl substituent (Figure 4) showed activity against HSV-1 and TK^+ enzyme of VZV. Unfortunately, all the examined compounds in comparison with BVdUrd exhibited higher IC_{50}, and this eliminated them from further studies.[3,5,13]



8 **14** **26** **179** **180**

Figure 4

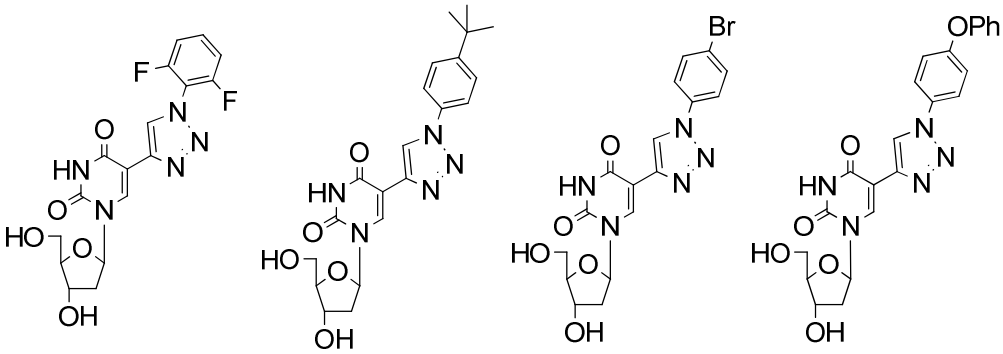
Kim and his co-workers synthesized compounds with a considerable activity against HSV-1 and HSV-2 (Figure 5). For comparison, their activity were much better than referenced drugs (*Acyclovir*-ACV and *Cytarabine*-AraC). All of the mentioned compounds showed also anti-RNA viruses (EMCV, Cox B3, VSV) activity. Three of them (**220–222**) were also tested against cancer cells (NUGC-3-stomach and PC-3-prostate). As a result of these experiments, it was concluded that the derivatives having the more bulky substituent displayed the greater anti-cancer activity. On the other hand, all of the presented compounds exhibited high cytotoxicity, higher than the permitted for medicine drugs.[1,46]



186 **220** **221** **222**

Figure 5

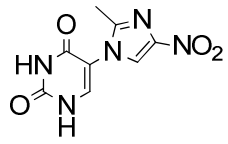
Compounds **153–156** (Figure 6) were evaluated against a variety of viruses and the best results were achieved for VZV. In contrast to their excellent IC_{50} indexes, they were also quite cytostatic and this excluded them from further bioassays.[47]



153 **154** **155** **156**

Figure 6

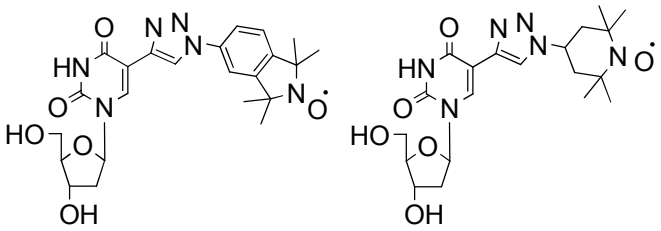
The anti-tumour activity of 5-hetaryluracil derivatives is not limited to nucleoside analogues. The modified nucleobase **42** (Figure 7) showed better inhibition of leukaemia cells (L1210) growth than 5-fluorouracil used at the same concentration.[64]



42

Figure 7

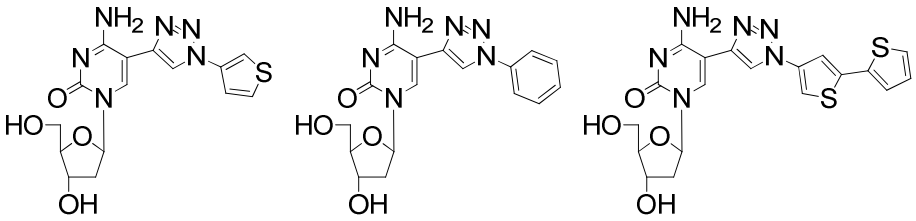
5-Hetaryluracils are used in medicinal chemistry not only as the pharmacophores but also as a tool for identification of damages in DNA/RNA strands. The synthesized compounds **174** and **175** (Figure 8), after incorporation into oligonucleosides, are applied as a site-directed spin-labels, due the presence of nitroxyl group possessing an unpaired electron. EPR spectroscopy enables detection of structural deformations in DNA strands, in particular the abasic sites.[53,54]



174 **175**

Figure 8

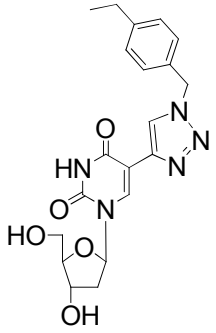
Besides, incorporation of a nucleotide bearing fluorescent substituent could be useful in study of DNA structure. Presented below cycloadducts **162–164** (Figure 9) are fluorescent in the blue region (375–385 nm). Their values of quantum yields are similar to the recently explored other fluorophore, methylpyrrolo-cytosine, dedicated for DNA investigations.[48]



162 **163** **164**

Figure 9

The compound **150** (Figure 10) was proposed to be employed as a drug delivery vehicle. Because of its low molecular weight, this molecule is bioavailable. This uridine derivative gelated water at low concentration (<0.2%). It forms a hydrogel of a fibrous structure and exhibits self-assembling properties as a result of hydrogen bonding presence.[45,65] Formation of gels in pure water is an important properties necessary for biomedical applications.



150

Figure 10

4. Summary

The different approach toward the synthesis of 5-hetaryluracil and cytosine derivatives has been presented. The classical methods of condensation reaction were under parallel developing of synthetic and theoretical chemistry exchanged into modern metal-assisted cross-coupling reactions. Application of [2+3] dipolar cycloaddition lead to another 5-substituted uracils. Described methods gave an opportunity to get a wide range of modified nucleobases or nucleosides and reflect the growing interest in the synthesis of modified nucleosides. Their biological activity against different biological targets and usefulness in medicinal applications are promising feature leading to finding more efficient and versatile routes of synthesis as the search for new analogues is an imperative in present drug design.

Acknowledgments

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INTRAMOLECULAR TRANSFORMATIONS OF 4-(2-SUBSTITUTED ARYL)-1,2,3-THIA- AND -SELENADIAZOLES. SYNTHESIS OF BENZO[*b*]FURANS, INDOLES, BENZO[*b*]THIOPHENES, BENZO[*b*]SELENOPHENES AND OTHER HETEROCYCLES

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Abstract. *An unusual transformation of 4-(2-substituted aryl)-1,2,3-thia- and selenadiazoles allows a convenient approach towards a wide variety of heterocyclic compounds: benzo[b]furans, indoles, benzo[b]thiophenes and benzo[b]selenophenes. These compounds may be the useful building blocks for constructing more complex molecules and possess potential biological activity. The scope and synthetic applications of the reaction will be discussed.*

Contents

1. Introduction

Indoles are ubiquitous among natural products and their synthesis has attracted organic chemists.[1–7] The primary reason for the sustained interest to the indoles is the wide range of biological activity found among its derivatives. The benzo[*b*]furans also appear in natural and synthetic physiologically active compounds, but not so much abundantly as indoles.[8–15]

Benzo[*b*]thiophene and its related derivatives represent an important class of fused thiophene compounds in the field of bioactive materials, as well as optoelectronic materials. In particular, multithiophene fused aromatic compounds are attracting current interest as promising electronic materials for organic conductors, organic light-emitting diodes, photovoltaic cells and field-effect transistors.[16–26]

The synthesis and characterization of benzo[*b*]selenophenes are of current interest owing to their potential applications as organic semiconductors for various optoelectronic devices.[27,28] Benzo[*b*] selenophenes have received little attention as potential drugs, although their potent biological activity and synthetic utility have been discussed in the literature.[29–31]

The presence of highly substituted benzo[*b*]furans, indoles, benzo[*b*]thiophenes and benzo[*b*] selenophenes in a number of architecturally and biologically interesting natural and non-natural products continues to inspire chemists to develop new and improved routes to their synthesis.

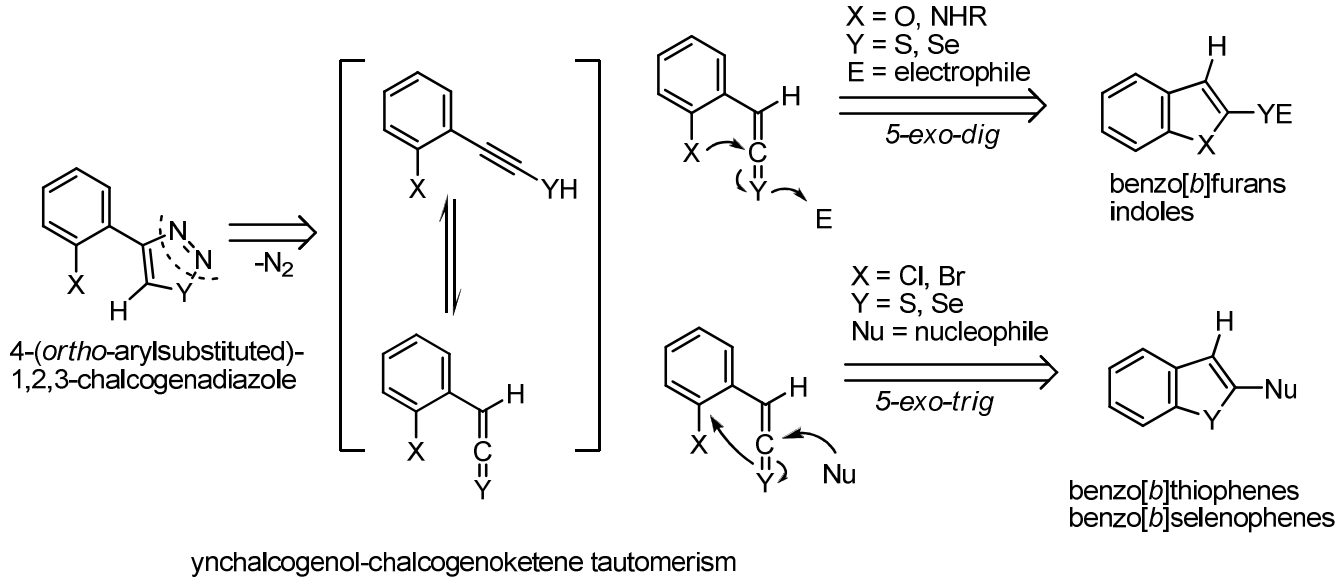
Our contribution to this area has been the synthesis of benzo[*b*]furans and indoles having sulfur and selenium substituents attached to the C2-atom, as well the development of a convenient approach towards multifunctional benzo[*b*]thiophenes and benzo[*b*]selenophenes bearing amino, hydroxy or other functional groups attached to the heterocyclic ring.

Some 2-selanylbenzofurans are known to be highly efficient antioxidants.[32] Several natural products having specific biological activity contain the 2-thioindole fragment. For example, cruciferous sulfur-containing phytoalexins: brassilexin, sinalexin, cyclobrassinin occurring in plants, have a broad antimicrobial activity playing crucial roles in their resistance to pathogen invasion.[33] For example, some 2-thioindoles have been demonstrated as useful intermediates in the synthesis of 2,2'-dithiobisindole tyrosine kinase inhibitors.[34–37]

Though derivatives of 2-dimethylamino-6-hydroxybenzo[*b*]thiophene are important intermediates in the synthesis of the selective estrogen receptor modulators - raloxifene and its analogs,[38–41] and 2-amino-benzo[*b*]thiophenes, in general, belong to an elusive group of benzo[*b*]thiophenes.

One of the most versatile and efficient routes to indoles, benzo[*b*]furans, benzo[*b*]thiophenes and benzo[*b*]selenophenes is provided by metal-catalyzed cyclization reactions of *ortho*-ethynylanilines,[42–45] *ortho*-ethynylphenols,[46–49] *ortho*-ethynylthiophenols[50–53] and *ortho*-ethynylselenophenols.[28,54] These precursors can commonly be obtained by Sonogashira coupling of corresponding *ortho*-haloanilines and *ortho*-halophenols with acetylenic compounds[55] or by nucleophilic displacement of halogen atom in *ortho* position to ethynyl group by the corresponding chalcogenide.[28] A scope of the substituents, which can be

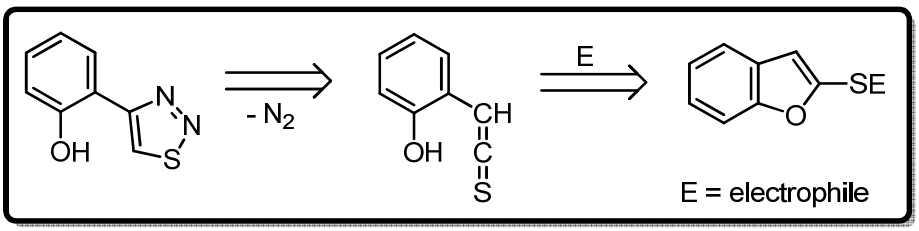
attached to the newly formed heterocyclic ring using this protocol is restricted by the nature of acetylene and commonly limited to aliphatic and aromatic moieties. Use of *ortho*-substituted arylthio- and -selenoketenes could outweigh this disadvantage and significantly expand the scope of the reaction allowing attachment of a great variety of hydroxy, amino, sulfur and selenium substituents to the heterocyclic ring. However, chalcogenoketenes, as a rule, are extremely unstable, that makes it reasonable to generate them *in situ*. 5-Unsubstituted 1,2,3-thia- and selenadiazoles are readily available and quite stable masked precursors of chalcogenoketenes.[56] The reaction of the *in situ* generated chalcogenoketene with internal nucleophiles X=O$^-$, NHR, S$^-$, Se$^-$ *via 5-exo-dig* cyclization affords corresponding benzo[*b*]furans, indoles, benzo[*b*]thiophenes and benzo[*b*]selenophenes having chalcogenoketene-derived heteroatom Y=S, Se outside of the newly formed heterocyclic ring (exocyclic Y-atom); while the similar reaction with external nucleophiles Nu=RO$^-$, R_2NH, RS$^-$, RSe$^-$ *via* an 5-*exo-trig* process results in benzo[*b*]thiophenes and benzo[*b*]selenophenes having an endocyclic heteroatom Y originating from the chalcogenoketene moiety (Scheme 1).



Scheme 1

2. Benzo[*b*]furans

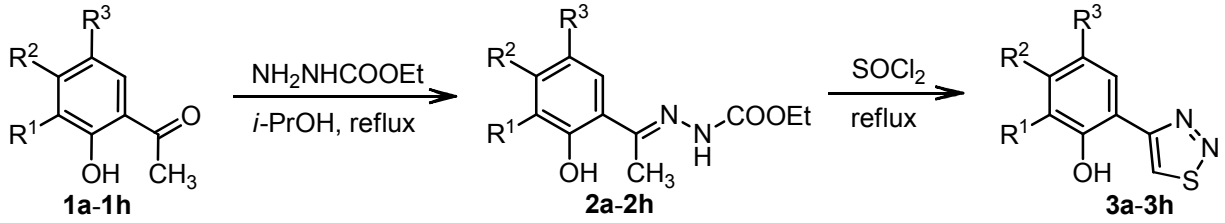
2.1. Benzo[*b*]furans-2-sulfides



2.1.1. 4-(2-Hydroxyaryl)-1,2,3-thiadiazoles

Two different approaches to the synthesis of 4-(2-hydroxyaryl)-1,2,3-thiadiazoles are documented in literature. The first approach employs the Hurd-Mori procedure starting from hydrazones of 2-hydroxyacetophenones, whereas the second approach utilizes modification of the phenyl core of already synthesized 4-(2-hydroxyaryl)-1,2,3-thiadiazoles.

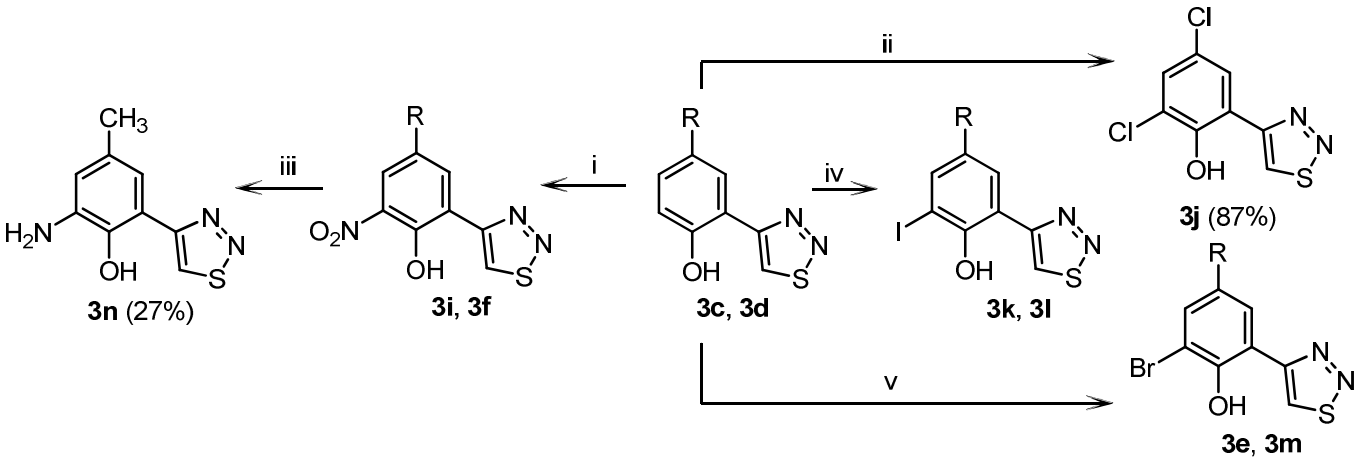
A reaction of 2-hydroxyacetophenones **1a–1h** with ethyl carbazate gave carbazones **2a–2h** (61–96% yield), which were further treated with $SOCl_2$ affording thiadiazoles **3a–3h** (64–88% yield, Scheme 2).[57]



3a, $R^1 = R^2 = R^3 = H$ (64%); **3b**, $R^1 = R^3 = H$, $R^2 = CH_3$ (87%); **3c**, $R^1 = R^2 = H$, $R^3 = CH_3$ (88%)
3d, $R^1 = R^2 = H$, $R^3 = Cl$ (85%); **3e**: $R^1 = Br$, $R^2 = H$, $R^3 = CH_3$ (61%); **3f**, $R^1 = NO_2$, $R^2 = H$, $R^3 = CH_3$ (71%)
3g, $R^1 = R^3 = H$, $R^2 = OH$ (61%), **3h**, $R^1 = R^2 = H$, $R^3 = OH$ (69%)

Scheme 2

An alternative approach involves modification of the benzene ring of already synthesized 4-(2-hydroxyaryl)-1,2,3-thiadiazoles (Scheme 3).[58]

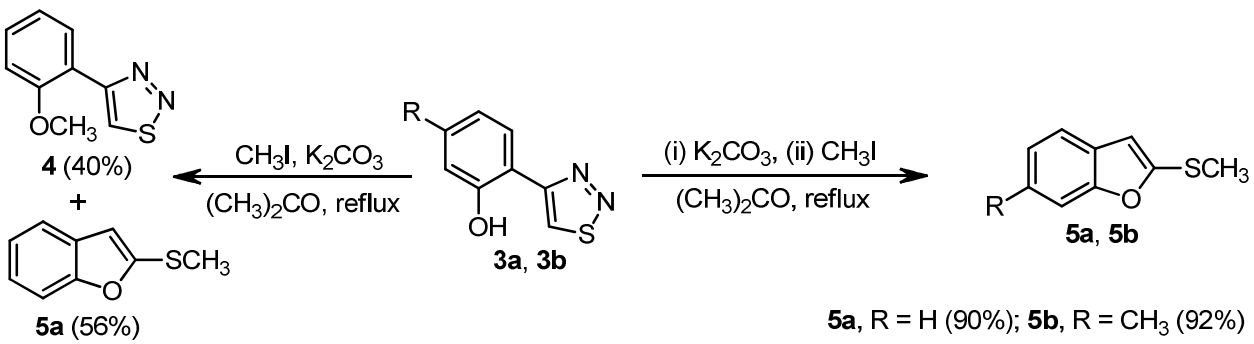


3e, R = CH_3 (85%); **3f**, R = CH_3 (57%); **3i**, R = Cl (78%); **3k**, R = CH_3 (83%); **3l**, R = Cl (77%); **3m**, R = Cl (73%)
conditions: (i) HNO_3, Ac_2O, AcOH; (ii) Cl_2, AcOH; (iii) Fe, AcOH; (iv) I_2, NaOH, MeOH; (v) Br_2, AcOH

Scheme 3

2.1.2. Benzo[*b*]furan-2-thiolates. Reactions with alkyl halides

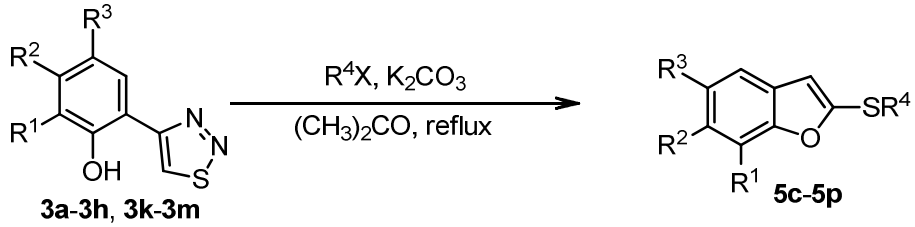
The reaction of 4-(2-hydroxyphenyl)-1,2,3-thiadiazole **3a** with K_2CO_3 and CH_3I under aprotic conditions (acetone) afforded *O*-alkylated thiadiazole **4** (40%) along with 2-(methylthio)benzofuran **5a** (56%). In order to obtain methylthiobenzofurans **5a**, **5b** selectively, it was necessary to add CH_3I when the decomposition of **3a**, **3b** was over (Scheme 4).[58,59]



5a, R = H (90%); **5b**, R = CH_3 (92%)

Scheme 4

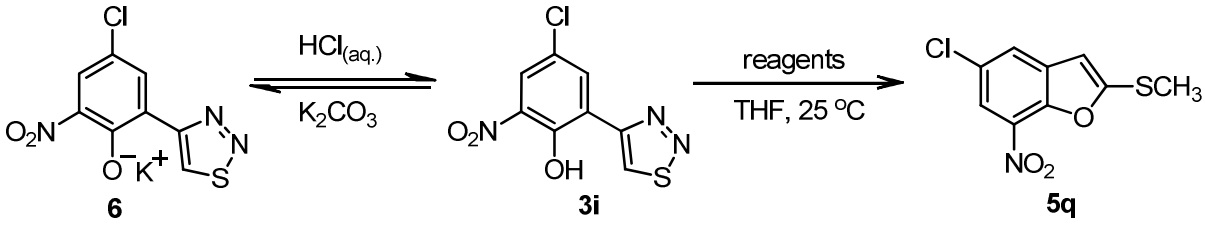
The less active alkylating agents could be introduced at the beginning of the reaction giving 2-(alkylthio)benzofurans **5c–5p** as single products of the reaction (Scheme 5).[58–61]



5c, $R^1 = R^2 = R^3 = H$, $R^4X = n\text{-}C_{16}H_{33}Br$ (92%); **5d**, $R^1 = R^2 = H$, $R^3 = OH$, $R^4X = n\text{-}C_{16}H_{33}Br$ (97%)
5e, $R^1 = R^3 = H$, $R^2 = OH$, $R^4X = n\text{-}C_{16}H_{33}Br$ (46%); **5f**, $R^1 = R^2 = R^3 = H$, $R^4X = BnCl$ (90%)
5g, $R^1 = R^3 = H$, $R^2 = CH_3$, $R^4X = BnCl$ (72%); **5h**, $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4X = ClCH_2C(O)NH_2$ (67%)
5i, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4X = ClCH_2C(O)NHPh$ (82%); **5j**, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4X = ClCH_2C(O)NH(4\text{-}PhOCH_3)$ (87%)
5k, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4X = ClCH_2C(O)NH[2,6\text{-}Ph(CH_3)_2]$ (63%)
5l, $R^1 = Br$, $R^2 = H$, $R^3 = CH_3$, $R^4X = ClCH_2C(O)NHPh$ (65%); **5m**, $R^1 = Br$, $R^2 = H$, $R^3 = Cl$, $R^4X = ClCH_2C(O)NHPh$ (74%)
5n, $R^1 = NH_2$, $R^2 = H$, $R^3 = CH_3$, $R^4X = ClCH_2C(O)NH[2,6\text{-}Ph(CH_3)_2)]$ (61%)
5o, $R^1 = I$, $R^2 = H$, $R^3 = CH_3$, $R^4X = ClCH_2C(O)NH(4\text{-}PhOCH_3)$ (71%)
5p, $R^1 = I$, $R^2 = H$, $R^3 = Cl$, $R^4X = ClCH_2C(O)NH(4\text{-}PhOCH_3)$ (77%)

Scheme 5

An attempt to decompose 4-(2-hydroxy-3-nitro-5-chlorophenyl)-1,2,3-thiadiazole **3i** under similar conditions (K_2CO_3, $(CH_3)_2CO$) led to phenolate **6**. The starting material **3i** could be regenerated upon addition of aqueous HCl. However, the ring-opening could be promoted using a stronger base (*tert*-BuOK, THF). The successful recyclization to 5-chloro-2-(methylthio)-7-nitrobenzofuran **5q** required a proton donor. Thus, addition of aqueous CH_3OH followed by addition of CH_3I afforded **5q** in 48% yield, whereas the addition of aqueous HCl followed by the addition of KOH and CH_3I yielded 65 % of **5q** (Scheme 6).[58]



reagents: procedure A: 1) *tert*-BuOK, 0.5 h; 2) $CH_3OH_{(aq.)}$ 1.5 h; 3) CH_3I, 2 h (48%)
procedure B: 1) *tert*-BuOK, 0.5 h; 2) $HCl_{(aq.)}$ 5 min; 3) $KOH_{(aq.)}$ 5 min; 4) CH_3I, 2 h (65%)

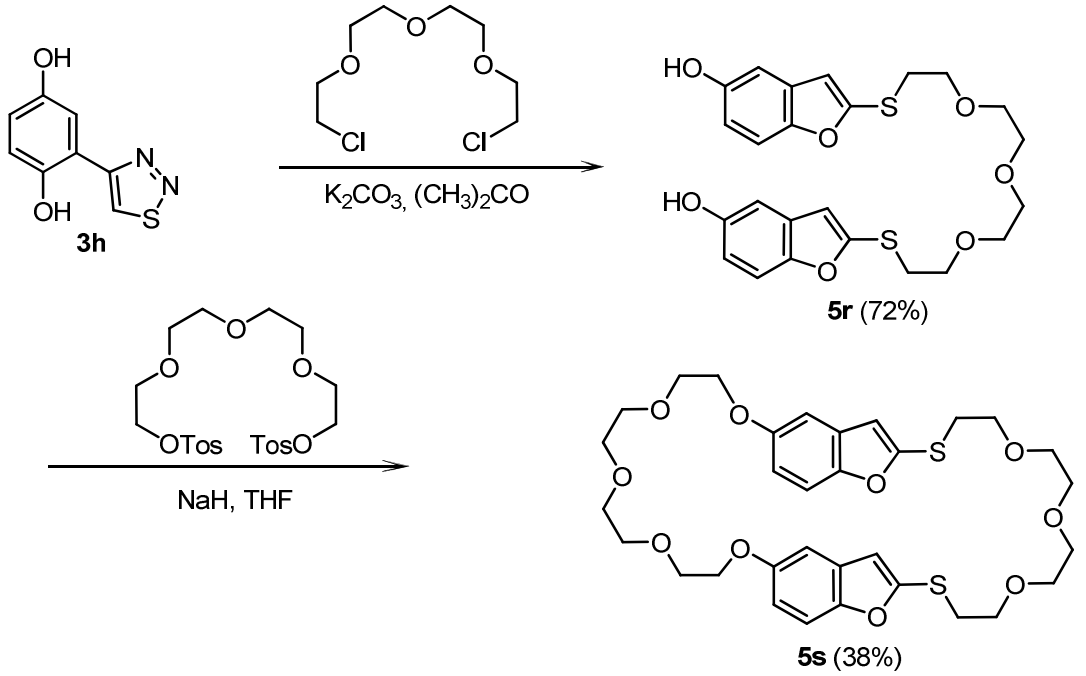
Scheme 6

The reaction was applied to the synthesis of crown ether **5s** by a stepwise selective alkylation of 5-hydroxybenzofuran-2-thiolate which was generated *in situ* from thiadiazole **3h** (Scheme 7).[59]

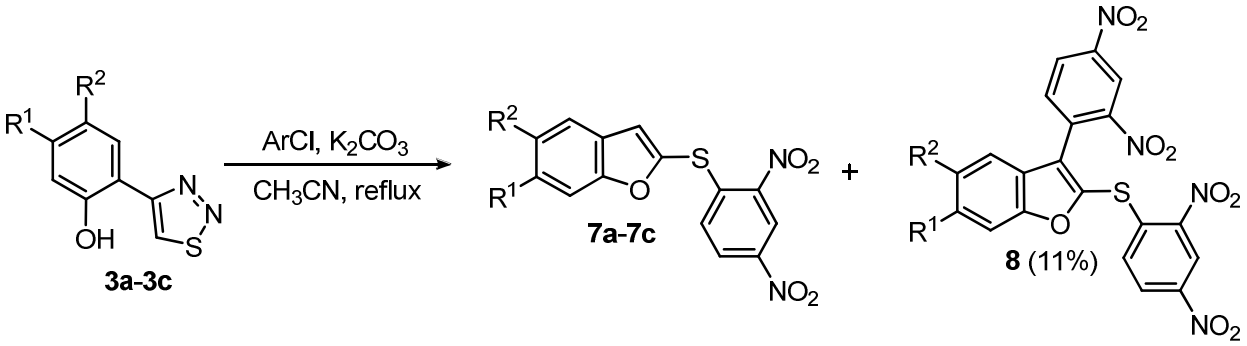
2.1.3. Benzo[*b*]furan-2-thiolates. Reactions with aryl halides

Similarly to the alkylation, benzofuran-2-thiolates **3a–3c** could be arylated *in situ* with 2,4-dinitrochlorobenzene: the products of the reaction in these cases were 2-(2,4-dinitrophenylthio)benzofurans **7a–7c** along with 3-(2,4-dinitrophenyl)-2-(2,4-dinitrophenylthio)benzofuran **8** (Scheme 8). The formation of **8** accompanied by a deep-red color of the reaction mixture may evidence the anion-radical nature of the reaction. Similar reactivity of benzofuran-2-thiol with two molecules of styrene is reported in literature

supporting this assumption.[62] When the reaction was carried out under an atmosphere of argon, formation of **8** was not observed.[61]



Scheme 7



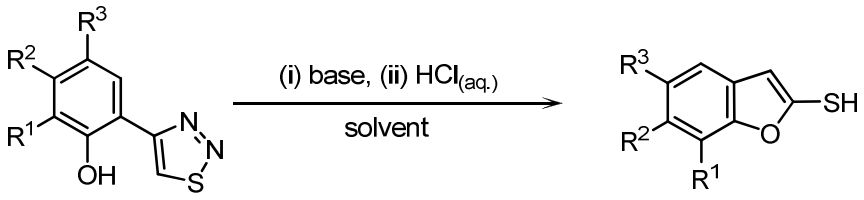
7a, $R^1 = R^2 = H$ (93%); **7b**, $R^1 = CH_3$, $R^2 = H$ (59%); **7c**, $R^1 = H$, $R^2 = CH_3$ (46%); **8**, $R^1 = H$, $R^2 = CH_3$
ArCl = 2,4-dinitrochlorobenzene

Scheme 8

2.1.4. Benzo[*b*]furan-2-thiolates. Formation of benzo[*b*]furan-2-thiols

Benzofuran-2-thiols **9a–9e** were synthesized by K_2CO_3 that promoted decomposition of thiadiazoles **3a–3d**, **3l** in DMF. Thiadiazole ring opening in compound **3i** required the use of a stronger base such as *tert*-BuOK in THF at 25 °C (Scheme 9).

^{1}H NMR spectra of thiols **9a–9f** acquired in $CDCl_3$ (25 °C) evidenced that these compounds existed as a tautomeric mixture and electron-withdrawing substituents stabilized the thiol form (Scheme 10, Table 1). Thus, in ^{13}C NMR spectra of benzo[*b*]furan-2-thiols **9a** and **9c**, the ^{13}C signals of carbon atoms corresponding to enethiol and thione tautomers were well resolved. The methylene group signals of the thione tautomers $\delta_C(CH_2)$ appeared in the region of 48.6–48.1 ppm, while the signals of the thiocarbonyl groups δ_C(C=S) appeared at 215.8–216.7 ppm. The characteristic ^{13}C signals of the enethiol form resided in the region 110.7–111.3 ppm for δ_C(C3) and 150.5–155.8 ppm for δ_C(C2).[63,64]



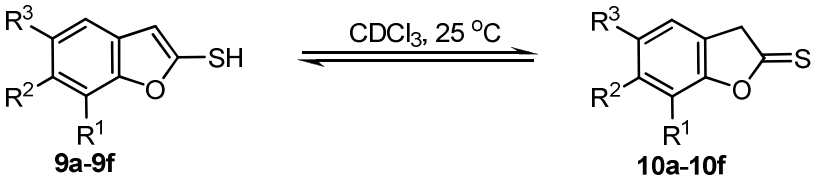
3a-3d, **3i**, **3l** **9a-9f**

9a, $R^1 = R^2 = R^3 = H$ (68%); **9b**, $R^1 = R^3 = H$, $R^2 = CH_3$ (32%); **9c**, $R^1 = R^2 = H$, $R^3 = CH_3$ (55%)
9d, $R^1 = R^2 = H$, $R^3 = Cl$ (86%); **9e**, $R^1 = I$, $R^2 = H$, $R^3 = Cl$ (90%); **9f**, $R^1 = NO_2$, $R^2 = H$, $R^3 = Cl$ (80%)
conditions: **9a-e**, base K_2CO_3, solvent DMF; **9f**, base *tert*-BuOK, solvent THF

Scheme 9

Table 1. Ratio of thiol-thione tautomers in $CDCl_3$ at 25 °C.

compound #	δ_H, ppm ($CDCl_3$), 25 °C			thiol-thione
	SH	CH_2 (thione)	H3 (thiole)	tautomer ratio
9a	3.70	4.23	6.79	1.04:1
9b	3.66	4.18	6.74	0.68:1
9c	3.68	4.16	6.69	0.61:1
9d	3.76	4.19	6.70	2.13:1
9e	3.85	4.32	6.81	6.25:1
9f	4.02	4.40	6.85	16.7:1



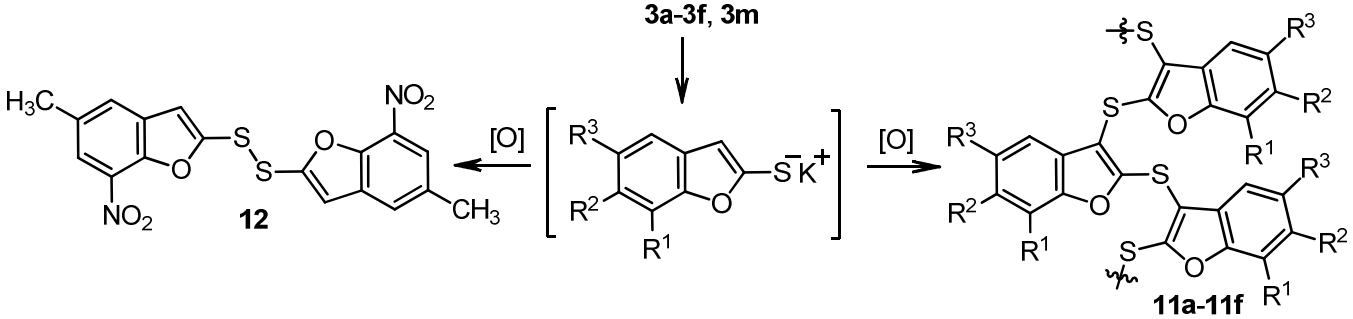
9a-9f **10a-10f**

$R^1 = R^2 = R^3 = H$ (**9a/10a** = 1.04); $R^1 = R^3 = H$, $R^2 = CH_3$ (**9b/10b** = 0.68)
$R^1 = R^2 = H$, $R^3 = CH_3$ (**9c/10c** = 0.61); $R^1 = R^2 = H$, $R^3 = Cl$ (**9d/10d** = 2.13)
$R^1 = I$, $R^2 = H$, $R^3 = Cl$ (**9e/10e** = 6.25); $R^1 = NO_2$, $R^2 = H$, $R^3 = Cl$ (**9f/10f** = 16.7)

Scheme 10

2.1.5. Benzo[*b*]furan-2-thiolates. Reactions with oxidizing agents

Oxidation reactions (air, I_2, H_2O_2) of thiolates derived from thiadiazoles **3a–3f**, **3m** produced poorly soluble orange oligomers **11a–11f** instead of expected disulfides. In the case of thiadiazole **3f**, it was possible to isolate disulfide **12** in 68% yield (Scheme 11).[58]

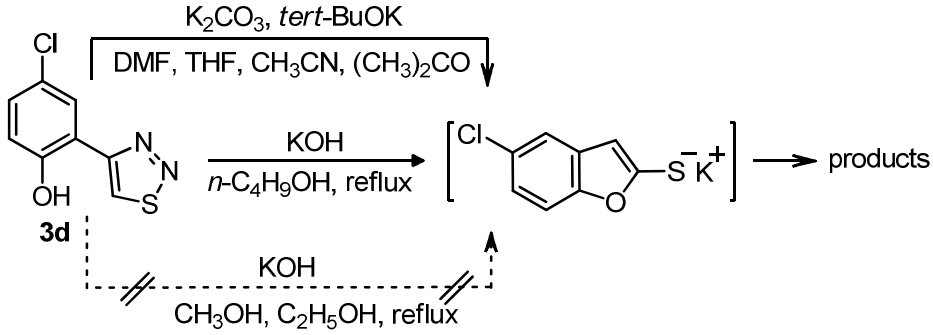


11a, $R^1 = R^2 = R^3 = H$; **11b**, $R^1 = R^3 = H$, $R^2 = CH_3$; **11c**, $R^1 = R^2 = H$, $R^3 = CH_3$; **11d**, $R^1 = R^2 = H$, $R^3 = Cl$
11e, $R^1 = Br$, $R^2 = H$, $R^3 = CH_3$; **11f**, $R^1 = Br$, $R^2 = H$, $R^3 = Cl$

Scheme 11

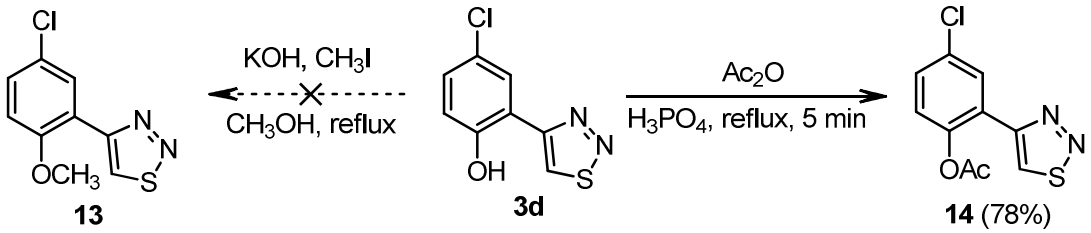
2.1.6. 4-(2-Hydroxyaryl)-1,2,3-thiadiazoles. Aspects of reactivity

It was found that the nature of solvent and base strongly affected the course of the reaction: aprotic solvents like $(CH_3)_2CO$, MeCN, DMF and THF were favorable, whereas protic solvents like CH_3OH and C_2H_5OH inhibited the reaction (Scheme 12).



Scheme 12

An attempt to methylate the *O*-atom of **3d** failed, whereas an acid-catalized acetylation of **3d** succeeded (Scheme 13).[58]

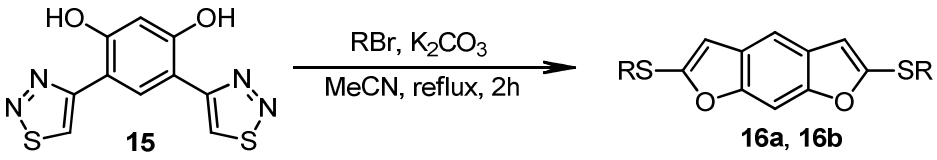


Scheme 13

2.1.7. Benzo[*b*]furan-2-thiolates. Synthesis of polycyclic compounds

The reaction was used for the synthesis of heterocycles having more than one furan ring. Compounds containing benzo[1,2-*b*:5,4-*b'*]difuran heterocyclic substructure were found in some algae (cyperaquinone). As a rule, this class of heterocycles is synthesized from resorcinol and has been first mentioned in literature in 1932.

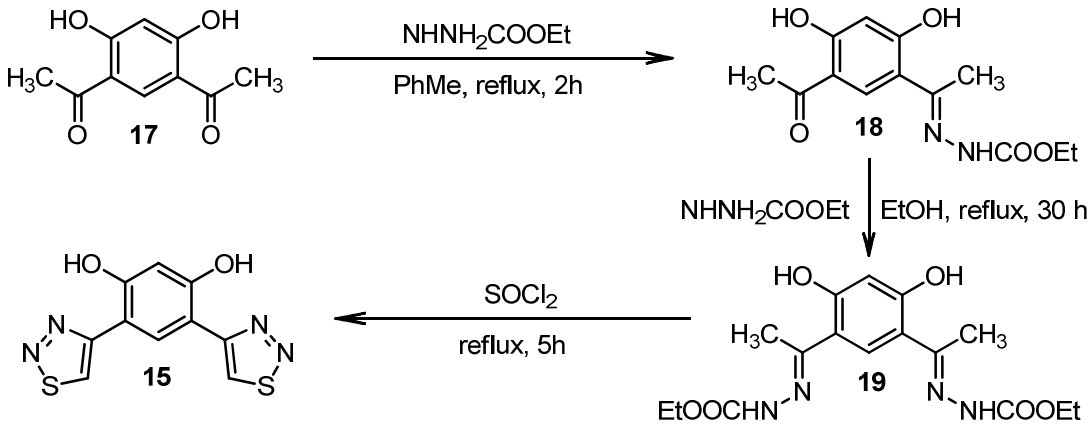
The decomposition of 4,6-di(1,2,3-thiadiazol-4-yl)benzene-1,3-diol **15** followed by alkylation with *n*-butyl- or benzyl bromide afforded corresponding benzo[1,2-*b*:5,4-*b'*]difuran-2,6-disulfides **16a**, **16b** (Scheme 14).[65]



16a, R = *n*-Bu (42%); **16b**, R = Bn (39%)

Scheme 14

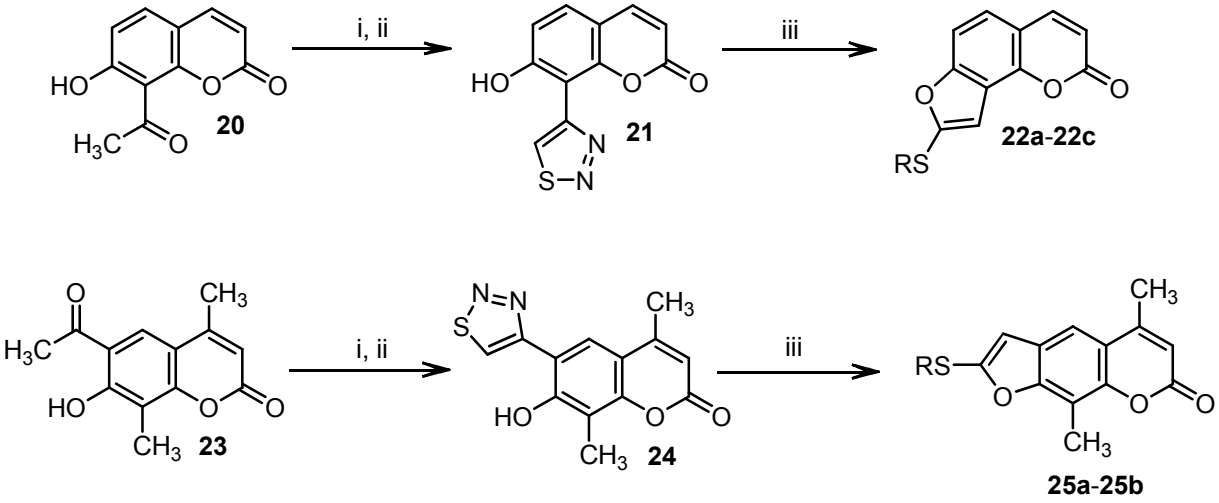
The diol **15** was synthesized by stepwise reaction of diketone **17** with two equivalents of ethyl carbazate, followed by cyclization of dihydrazone **19** upon treatment with $SOCl_2$ (Scheme 15).[65]



Scheme 15

Furocoumarins, such as the angular angelicin and the linear psoralen, are natural products derived from umbelliferone (7-hydroxycoumarin), which are present in members of the *Apiaceae*, *Leguminosae*, *Rutaceae* and *Umbelliferae* families. Psoralen derivatives react with DNA upon excitation with long wavelength UV light and have been widely used in treatment of skin diseases. Undesired side effects, such as skin phototoxicity and skin cancer may occur, mainly due to the formation of crosslinks between the DNA or RNA. Other applications are found in the treatment of cutaneous T-cell lymphoma, AIDS and in molecular biology as reagents for the investigation of nucleic acid structure and function. The less toxic angelicin derivatives have similar photoactivity. They are described to give mainly mono-adducts to DNA and RNA.[66]

The method was used for the synthesis of the novel thiolate derivatives of furocoumarins **22a–22c** and **25a**, **25b**. The alkylated sulfide derivatives may possess interesting pharmacological, photophysical and photochemical properties. Moreover, the reactive thiolate function may allow, in combination with a suitable electrophile, the smooth conjugation with another group of interest, affording novel and specific drugs for photodynamic therapy (Scheme 16).[66]

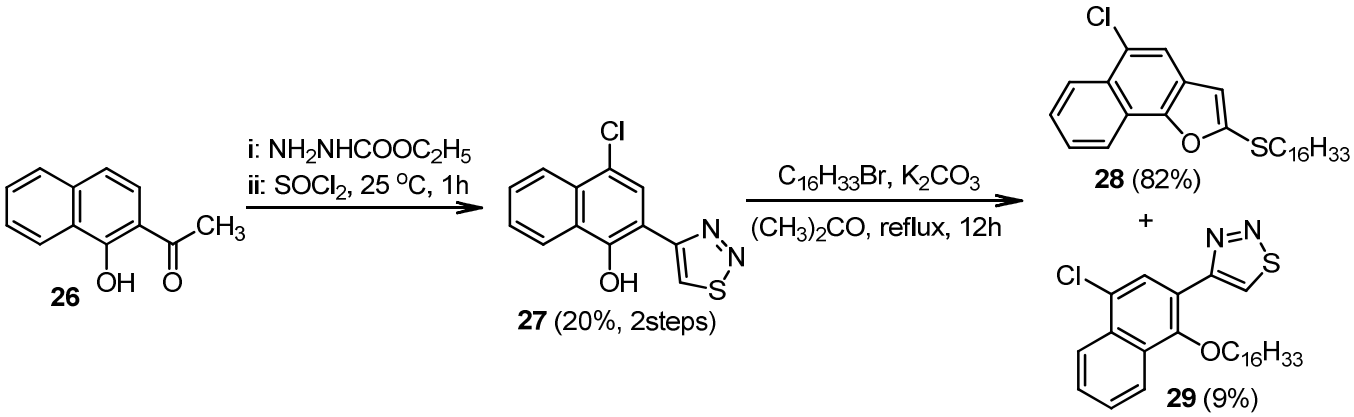


22a, R = CH_3; **22b**, R = *n*-$C_{16}H_{33}$; **22c**, R = $CH_2(4\text{-}FC_6H_4)$; **25a**, R = CH_3; **25b**, R = *n*-$C_{16}H_{33}$
conditions: (i) $NH_2NHCOOC_2H_5$; (ii) $SOCl_2$, 25 °C, 2h; (iii) base, RX, MeCN, reflux, 2h

Scheme 16

When 2-acetyl-naphthol **26** was consequently treated with ethyl carbazate and thionyl chloride, 4-(4-chloro-1-hydroxy-2-naphthyl)-1,2,3-thiadiazole **27** formed unexpectedly. Apparently, the electron-rich

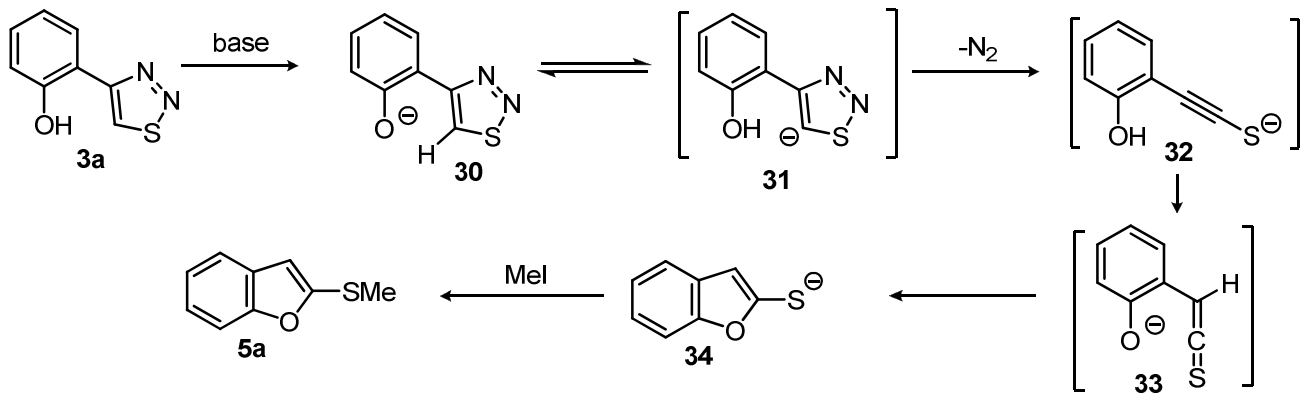
naphthalene ring is chlorinated under the conditions of Hurd-Mori reaction. The treatment of the thiadiazole **27** with potassium carbonate in the presence of 1-bromohexadecane led to 2-*n*-hexadecylsulfanyl-5-chloronaphtho[2,3-*a*]furan **28** in good yield. A small amount of 4-(4-chloro-1-(hexadecyloxy)-2-naphthyl)-1,2,3-thiadiazole **29** was isolated at the same time. Probably, the alkylation reaction of the electron-rich naphtholate anion is faster than that of the corresponding phenolate and will compete with the decomposition reaction (Scheme 17).[59]



Scheme 17

2.1.8. Mechanistic considerations

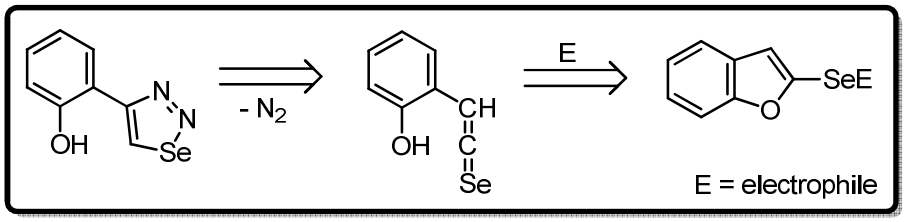
The mechanism of this unusual reaction was elucidated by following the decomposition of **3a** by ^{1}H NMR (400 MHz) spectroscopy.[60] Thus, a solution of compound **3a** in CD_3CN was treated with aqueous tetrabutylammonium hydroxide at room temperature. Initially, the phenolate **30** was present as indicated by the disappearance of the phenolic OH at δ_H 9.69 ppm (as compared to the spectrum without base) and the downfield shift of the thiadiazole 5H from δ_H 9.20 to 9.76 ppm. In addition, the phenyl protons at the 3, 4 and 5 positions moved upfield by 0.42, 0.34 and 0.64 ppm, respectively, whereas the 6H was little affected ($\Delta\delta$ +0.17 ppm). Slow nitrogen evolution was observed and, after a period of 21 hours, the ^{1}H NMR spectrum corresponded to a 1:1 mixture of compounds **30** and **34**. The 5H of the 1,2,3-thiadiazole ring of **30** was partially deuterated under these conditions, proving the intermediacy of the 1,2,3-thiadiazol-5-yl anion **31**. After 93 hours the reaction was completed and the NMR spectrum showed a clean absorption pattern of benzofuran-2-thiolate **34** with δ_H 5.98 (3H), 6.81, 6.90 (5H and 6H) and 7.06 ppm (4H and 7H), with no detectable impurities present.



Scheme 18

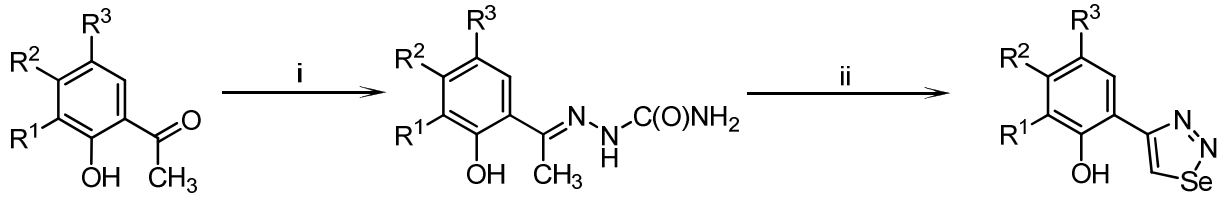
When the same reaction was followed by NMR spectroscopy in DMSO-d_6, the alkynethiolate **32** (48%) was observed after 15 minutes, together with the phenolate **30** (35%) and benzofuran **34** (17%). Compound **32** showed peaks in the ^{13}C NMR spectrum at δ_C 71.8 ppm (d) and 101.2 ppm (s) for the alkyne carbons (respectively β and α to sulfur). After 3 hours, the phenolate **30** had disappeared and the spectrum showed a 1:1 mixture of **32** and **34**. The ^{13}C NMR spectrum of thiolate **34** had peaks at 173.9 ppm (d, $^2J_{CH}$ 9 Hz) and 99.1 ppm (d, $^1J_{CH}$ 173 Hz) for the C2 and C3 carbons of the benzofuran, respectively. After one week, the transformation to benzofuranthiolate **34** was complete and the reaction mixture could be treated with methyl iodide to give an immediate and quantitative reaction, affording the sulfide **5a** (Scheme 18).

2.2. Benzo[*b*]furans-2-selenides



2.2.1. 4-(2-Hydroxyaryl)-1,2,3-selenadiazoles

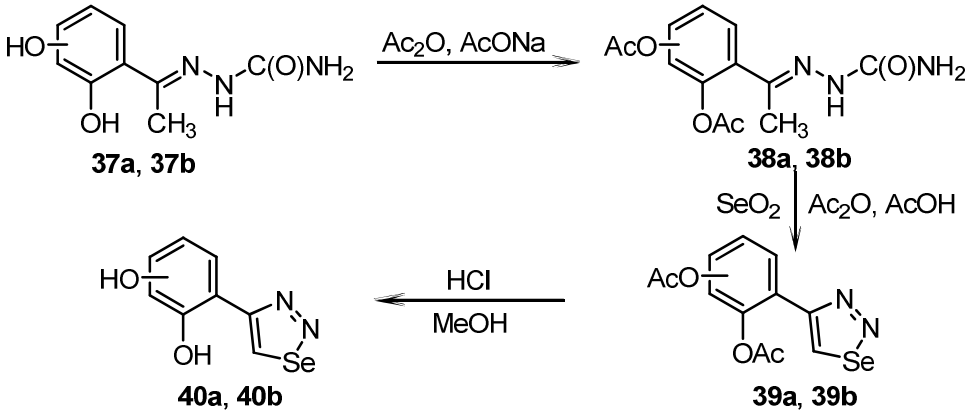
4-(2-Hydroxyaryl)-1,2,3-selenadiazoles **36a–36g** were synthesized in two steps from the corresponding 2-hydroxyacetophenones **1a–1d**, **1f**, **1i**, **1j** *via* semicarbazones **35a–35g** using the reported procedure (Scheme 19).[67–69]



1a-1d, **1f**, **1i**, **1j** **35a-35g** **36a-36g**

36a, $R^1 = R^2 = R^3 = H$ (64%); **36b**, $R^1 = R^3 = H$, $R^2 = CH_3$ (70%); **36c**, $R^1 = R^2 = H$, $R^3 = CH_3$ (70%)
36d, $R^1 = R^2 = H$, $R^3 = Cl$ (61%); **36e**, $R^1 = NO_2$, $R^2 = H$, $R^3 = CH_3$ (60%); **36f**, $R^1 = R^2 = H$, $R^3 = OCH_3$ (71%)
36g, $R^1 = R^2 = H$, $R^3 = OBn$ (62%)
conditions: (i) $NH_2NHC(O)NH_2 \cdot HCl$, AcONa, *i*-PrOH; (ii) SeO_2, AcOH.

Scheme 19



37a, **37b** **38a**, **38b** **40a**, **40b** **39a**, **39b**

38a, 2,4-$(OAc)_2$ (68%); **38b**, 2,5-$(OAc)_2$ (59%); **39a**, 2,4-$(OAc)_2$ (87%)
39b, 2,5-$(OAc)_2$ (81%); **40a**, 2,4-$(OH)_2$ (90%); **40b**, 2,5-$(OH)_2$ (92%)

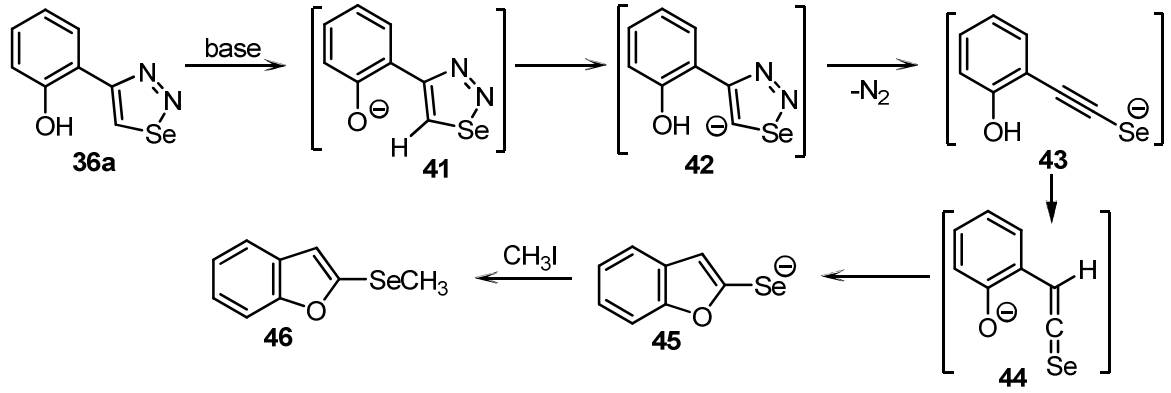
Scheme 20

Selenadiazoles **40a**, **40b** having two hydroxyl groups on the benzene ring could not be synthesized by the action of SeO_2 on the corresponding semicarbazones **37a**, **37b** due to the ease of oxidation that is typical for aromatic diols. However, the problem was solved by the protection of the phenolic hydroxyls (Scheme 20).[70]

2.2.2. Transformation of 4-(2-hydroxyaryl)-1,2,3-selenadiazoles into benzo[*b*]furan-2-selenolates. Mechanistic considerations

The progress of the base-promoted ring-opening of selenadiazole **36a** was followed by ^{1}H NMR spectroscopy in DMSO-d_6 in the presence of one equivalent of tetrabutylammonium hydroxide.

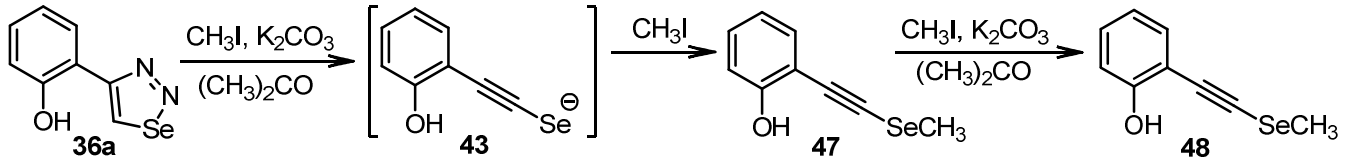
The formation of **45** was observed clearly, without an accumulation of intermediates **41–44**. It is interesting to note that for the alkynethiolate **32**, the corresponding intermediates could be detected by ^{1}H NMR spectroscopy. Apparently, the alkyneselenolate **43** is too unstable to be observed under these conditions (Scheme 21).[67]



Scheme 21

2.2.3. Benzo[*b*]furan-2-selenolates. Reactions with alkyl halides

Despite of a high rate of the intramolecular cyclization the intermediate **43** was trapped by addition of CH_3I in the course of the reaction (Scheme 22). Methylation of **43** was apparently faster than the ring closure to benzofuran **45**, which was not the case for other, less active alkylating agents.[67]

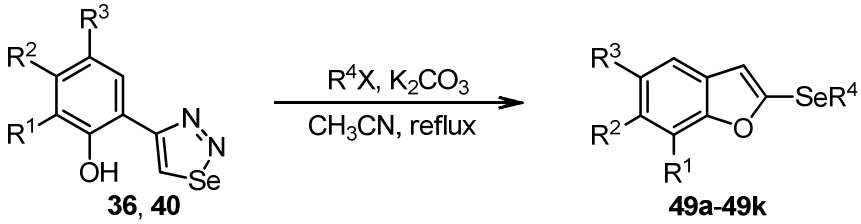


Scheme 22

The less active alkylating agents (long-chain alkyl halides, chloroacetamides, benzyl halides) can be introduced to the mixture in the very beginning of the reaction, along with a base (Scheme 23).[57,67,69]

2.2.4. Benzo[*b*]furan-2-selenolates. Reactions with aryl halides

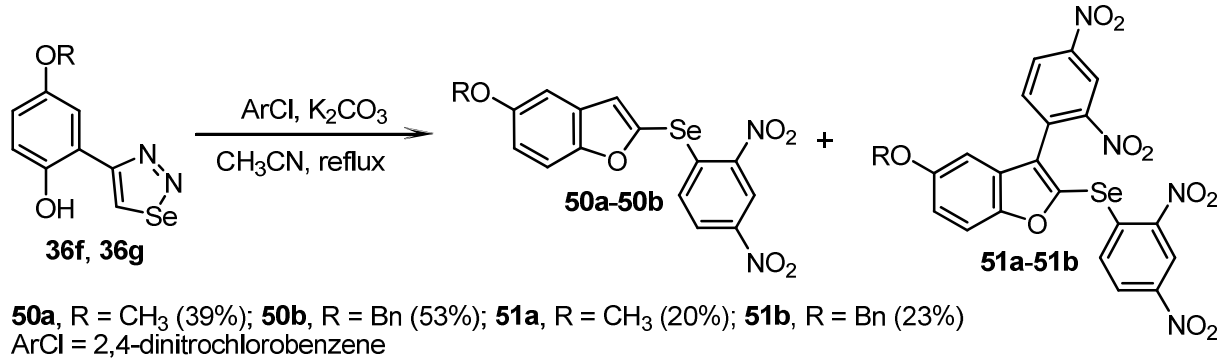
Arylation of benzofuran-2-selenolates, similar to the arylation of the isomeric thiolates, resulted in a formation of by-products **51a**, **51b** evidencing co-existence of anion-radical pathway of the reaction (Scheme 24). The formation of **51a**, **51b** could be suppressed by carrying out the reaction under an atmosphere of argon.[69]



36, **40** **49a-49k**

49a, $R^1 = R^3 = H$, $R^2 = OH$, $R^4X = n\text{-}C_4H_9Br$ (30%); **49b**, $R^1 = R^2 = H$, $R^3 = OH$, $R^4X = n\text{-}C_4H_9Br$ (38%)
49c, $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4X = BnCl$ (66%); **49d**, $R^1 = R^2 = H$, $R^3 = OH$, $R^4X = BnCl$ (59%)
49e, $R^1 = R^2 = H$, $R^3 = OH$, $R^4X = 4\text{-}(t\text{-}BuPh)CH_2Cl$ (69%); **49f**, $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4X = ClCH_2C(O)NH_2$ (53%)
49g, $R^1 = R^2 = H$, $R^3 = Cl$, $R^4X = ClCH_2C(O)NH[2,6\text{-}Ph(Me)_2]$ (73%)
49h, $R^1 = R^2 = H$, $R^3 = OCH_3$, $R^4X = ClCH_2C(O)NH_2$ (56%)
49i, $R^1 = NH_2$, $R^2 = H$, $R^3 = CH_3$, $R^4X = ClCH_2C(O)NH[2,6\text{-}Ph(Me)_2]$ (59%)
49j, $R^1 = R^2 = H$, $R^3 = OH$, $R^4X = ClCH_2C(O)NH_2$ (89%)
49k: $R^1 = R^3 = H$, $R^2 = OH$, $R^4X = ClCH_2C(O)NH[2,6\text{-}Ph(Me)_2]$ (64%)

Scheme 23



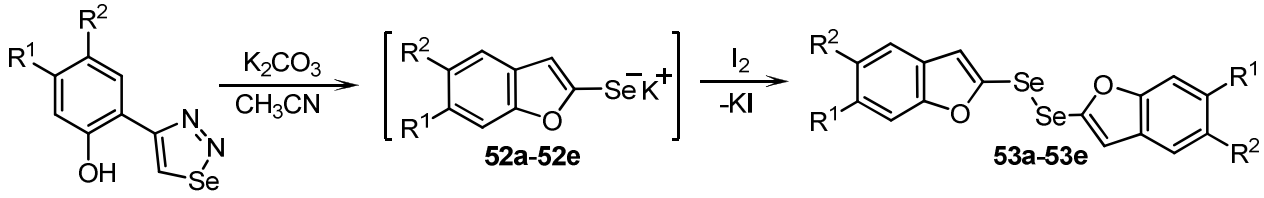
36f, **36g** **50a-50b** **51a-51b**

50a, R = CH_3 (39%); **50b**, R = Bn (53%); **51a**, R = CH_3 (20%); **51b**, R = Bn (23%)
ArCl = 2,4-dinitrochlorobenzene

Scheme 24

2.2.5. Benzo[*b*]furan-2-selenolates. Reactions with oxidizing agents

Oxidation of potassium salts of benzofuran-2-selenolates **52a–52e** with I_2 led to *bis*(2-benzofuranyl) diselenides **53a–53e** (Scheme 25).[68,71]

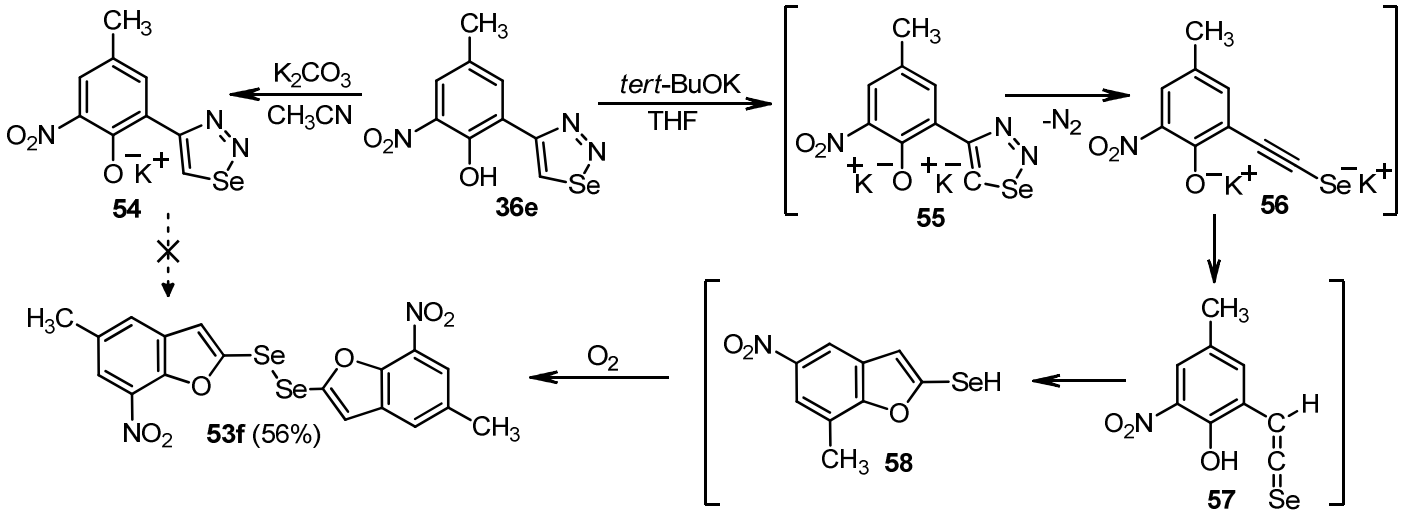


36a-36c, **36f**, **36g** **52a-52e** **53a-53e**

53a, $R^1 = R^2 = H$ (85%); **53b**, $R^1 = CH_3$, $R^2 = H$ (76%); **53c**, $R^1 = H$, $R^2 = CH_3$ (81%)
53d, $R^1 = H$, $R^2 = OCH_3$ (81%); **53e**, $R^1 = H$, $R^2 = OBn$ (54%)

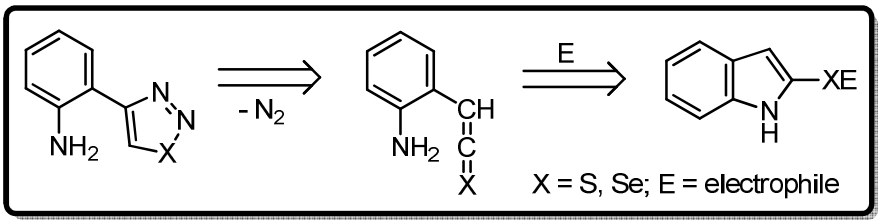
Scheme 25

The proton of the hydroxyl group of selenadiazole **36e** is more acidic comparing to the hydroxyl group of **36c** due to significant electron-withdrawing effect of the nitro group in *ortho* position. This effect reduces the basicity of the conjugated phenolate **54** (produced by the action of K_2CO_3), thus preventing further abstraction of the heterocyclic proton, which makes impossible subsequent ring-opening. An addition of a stronger base like *tert*-BuOK allows generating the di-anion **55** which further transforms into acyclic alkyneselenolate **56**. The latter intermediate was prompted to cyclize upon addition of aqueous HCl forming selenol **58** which was oxidized to diselenide **53f** by air oxygen (Scheme 26).[58]



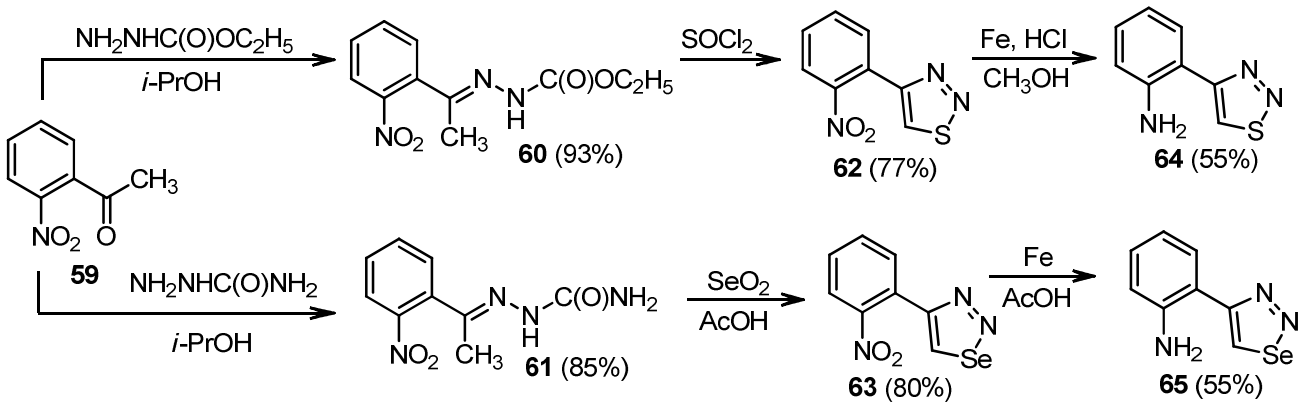
Scheme 26

3. Indoles



3.1. 4-(2-Aminoaryl)-1,2,3-thia- and selenadiazoles

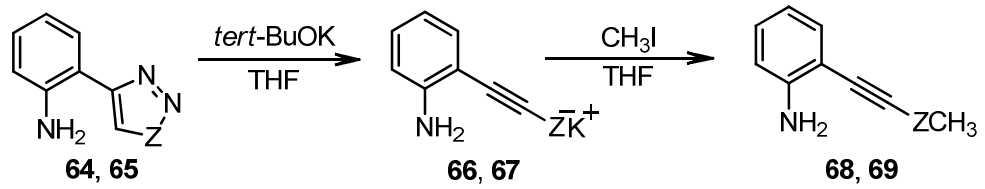
The method for the synthesis of benzofurans from 4-(2-hydroxyaryl)-1,2,3-thia- and -selenadiazoles was shown to be applicable for the synthesis of indoles from the corresponding 4-(2-aminoaryl)-1,2,3-thia- and -selenadiazoles **64** and **65**. These anilines were, in turn, obtained by the reduction of nitro precursors **62** and **63** (Scheme 27).[22,35]



Scheme 27

3.2. Indolyl-2-chalcogenolates. Synthesis and reactions

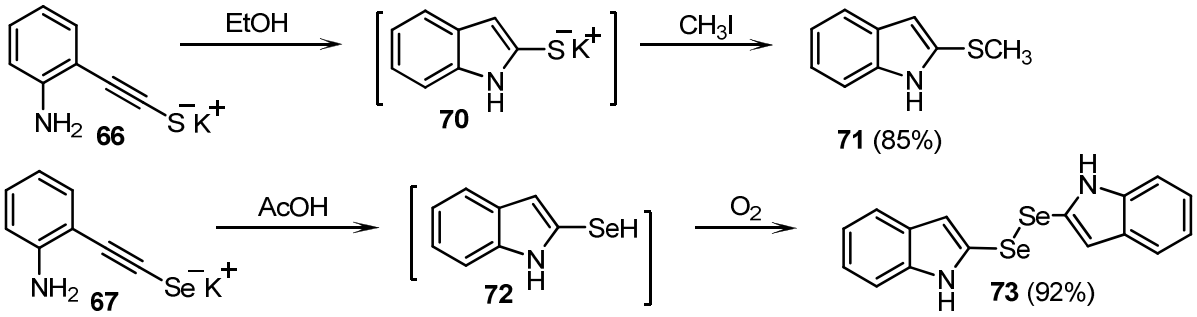
A weak acidity of the amino group protons of compounds **64** and **65** in respect to that of the hydroxyl groups of chalcogenadiazoles **3** and **36** prevents the intramolecular cascade proton transfer (Schemes 18 and 21). A stronger base (*tert*-BuOK in place of K_2CO_3) was then required for direct proton abstraction from the heterocyclic ring. The intermediates **66** and **67** were trapped upon addition of CH_3I (Scheme 28).[59,72]



66, Z = S; **67**, Z = Se; **68**, Z = S (85%); **69**, Z = Se (55%)

Scheme 28

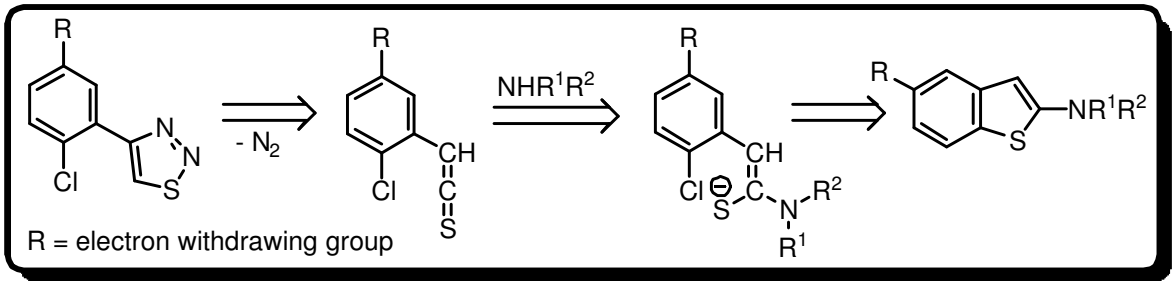
Intramolecular cyclization of 2-(2-aminophenyl)ethynethiolate **66** was driven by the addition of a proton-donating solvent like EtOH and the newly formed indole-2-thiolate **66** was then trapped as a methyl ether **71**. The ring-closure of 2-(2-aminophenyl)ethyneselenolate **67** to selenol **72** followed by a rapid oxidation to diselenide **73** was observed upon addition of acetic acid as a proton donor (Scheme 29).[72]



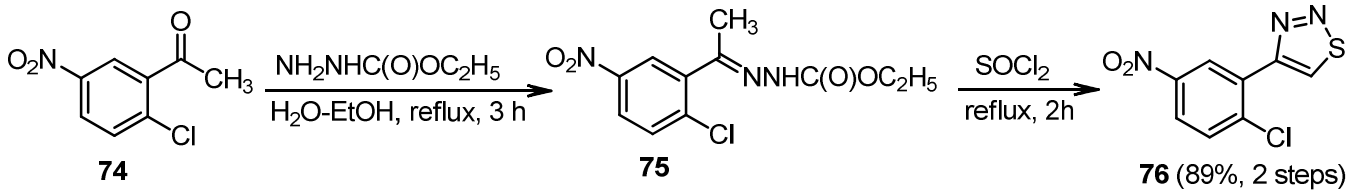
Scheme 29

4. Benzo[*b*]thiophenes

4.1. Benzo[*b*]thiophene-2-amines



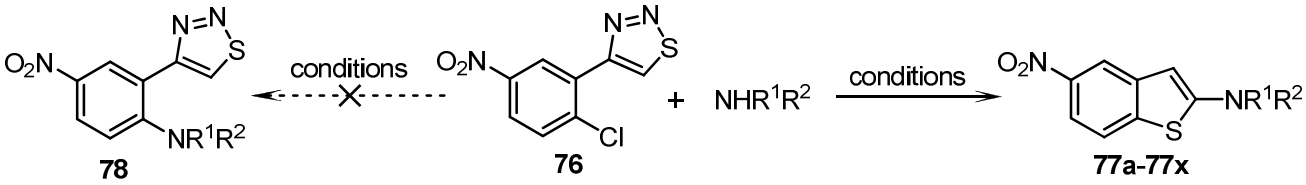
For the synthesis of benzo[*b*]thiophene, 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **76** has been selected and synthesized as a starting material from 1-(2-chloro-5-nitrophenyl)-ethanone **74** *via* its ethyl carbazone **75** in 89% overall yield (Scheme 30).[73]



Scheme 30

Base-catalyzed (K_2CO_3) alkylamination of **76** with a variety of primary and secondary amines was performed in DMF at moderate temperature (50–90 °C). The products of the reaction were unexpected

2-aminobenzo[*b*]thiophenes **77a–77x** in place of substitution products **78** (Scheme 31). It was found that the reaction is tolerant to the nature of a reaction medium and CH_3CN, $(CH_3)_2CO$, CH_3OH, C_2H_5OH can be used as the solvents. The use of DMF allows the reaction even at room temperature (20–25 °C).



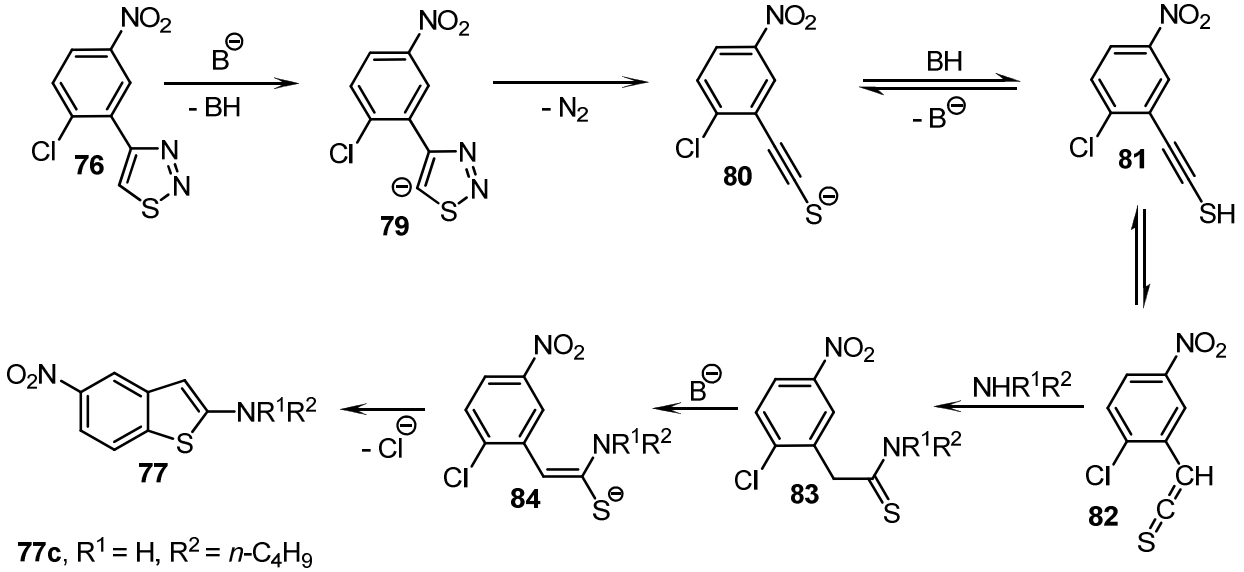
77a, R^1 = H, R^2 = CH_3 (6%); **77b**, R^1 = H, R^2 = allyl (42%); **77c**, R^1 = H, R^2 = *n*-C_4H_9 (44%); **77d**, R^1 = H, R^2 = Bn (33%)
77e, R^1 = H, R^2 = *i*-C_3H_7 (29%); **77f**, R^1 = H, R^2 = cyclopentyl (33%); **77g**, R^1 = H, R^2 = cyclohexyl (38%)
77h, R^1 = R^2 = CH_3 (75%); **77i**, R^1 = R^2 = $(CH_2)_4$ (7%); **77j**, R^1 = R^2 = $(CH_2)_5$ (17%); **77k**, R^1 = R^2 = $(CH_2)_2O(CH_2)_2$ (49%)
77l, R^1 = H, R^2 = 1-adamantyl (26%); **77m**, R^1 = H, R^2 = 2-morpholinoethyl (61%); **77n**, R^1 = R^2 = C_2H_5 (55%)
77o, R^1 = R^2 = *n*-C_4H_9 (33%); **77p**, R^1 = R^2 = *i*-C_3H_7 (25%); **77q**, R^1 = *n*-C_3H_7, R^2 = methylcyclopropyl (38%)
77r, R^1 = CH_3, R^2 = Bn (41%); **77s**, R^1 = H, R^2 = *tert*-C_4H_9 (39%); **77t**, R^1 = H, R^2 = $CH_2CO(O)C_2H_5$ (9%)
77u, R^1 = H, R^2 = 2-(3-indolyl)ethyl (23%); **77v**, R^1 = R^2 = $CH_2CH(CH_3)(CH_2)_3CH(CH_3)CH_2$ (63%)
77w, R^1 = R^2 = $CH_2CH((CH_2)_2OH)(CH_2)_4$ (20%); **77x**, R^1 = R^2 = *N*-methylpiperazine (74%)

conditions: K_2CO_3, DMF, 50 - 90 °C, 3 -12 h

Scheme 31

The reaction conditions (molar ratio of reagents, solvent, temperature) were not optimized in each particular case. It was observed that the yield of the desirable 2-aminobenzo[*b*]thiophene can be increased at lower reaction temperature (92%, 22 hours, 25 °C *vs* 44%, 3 hours, 50 °C) for product **77c**. The reaction of **76** with aniline and *N*-phenylhydrazine under the same conditions failed to form the expected 2-amino-benzo[*b*]thiophene.[73]

The mechanism of this reaction was studied by ^{1}H NMR monitoring the reaction mixture containing **76**, amine and K_2CO_3 in DMF at 25 °C (Scheme 32). Initially, the thiadiazole ring opening was indicated by the disappearance of the thiadiazole H5 at δ_H 9.19 ppm. Decomposition of the electron-withdrawing thiadiazole ring was accompanied by nitrogen evolution and formation of thioamide **83**.

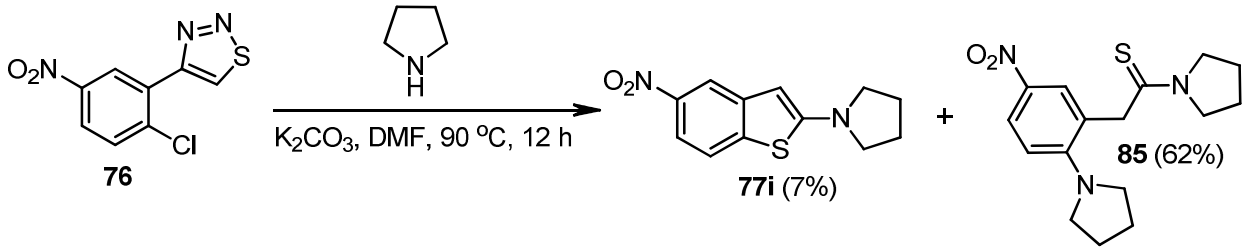


77c, R^1 = H, R^2 = *n*-C_4H_9

Scheme 32

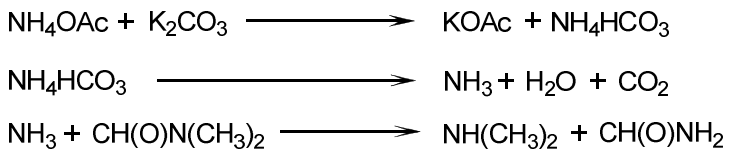
The appearance of NH at δ_H 7.44 ppm and an upfield shift of phenyl protons at the 3, 4 and 6 positions, shifted by 0.30, 0.16 and 0.89 ppm, respectively, were observed. The reaction progress was also followed by GC-MS. This supports formation of intermediate **83** (m/z 286). After 22 hours, the transformation was complete and the ^{1}H NMR spectrum showed a clean absorption pattern of *N*-butyl-5-nitrobenzo[*b*]thiophen-2-amine **77c** with δ_H 0.97 ppm ($C\underline{H}_3CH_2CH_2CH_2$-NH), 1.46 ppm ($CH_3C\underline{H}_2CH_2CH_2$-NH), 1.67 ppm ($CH_3CH_2C\underline{H}_2CH_2$-NH), 3.24 ppm ($CH_3CH_2CH_2C\underline{H}_2$-NH), 4.28 ppm ($CH_3CH_2CH_2CH_2$-N$\underline{H}$), 6.12 ppm (H3), 7.59 ppm (H7), 7.87 ppm (H6), 8.21 ppm (H4). There were no detectable impurities present. The hypothetical intermediates **79–82** and **84** were not detected by ^{1}H NMR but their formation was not in conflict with the authors observations and the data documented in literature.[74,75]

Compound **77i** was obtained in a low yield (7%) due to the relatively high nucleophilicity of pyrrolidine, which displaces the chlorine atom on the benzene ring faster than cyclization to **77i** occurs, affording thioamide **85** (62%) as main product (Scheme 33).



Scheme 33

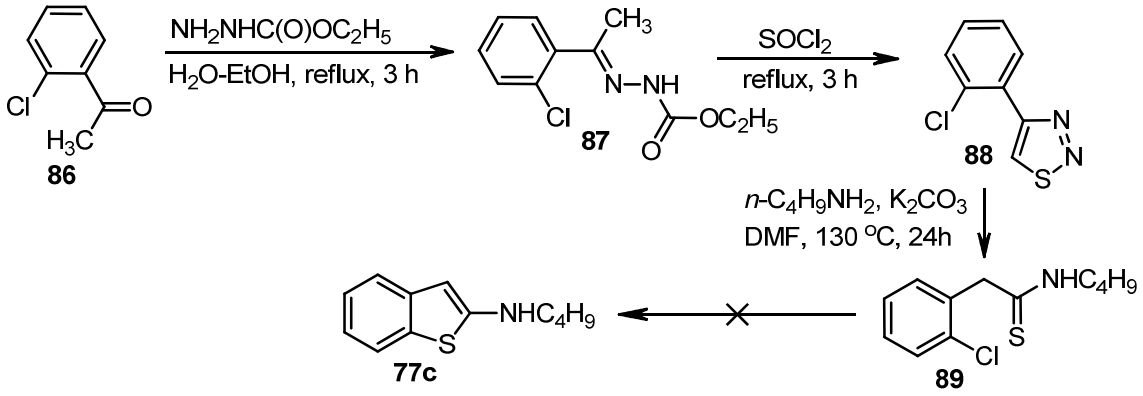
The best result in the synthesis of compound **77h** was achieved using the combination NH_4OAc/K_2CO_3/DMF that made it possible to generate dimethylamine *in situ* (Scheme 34).



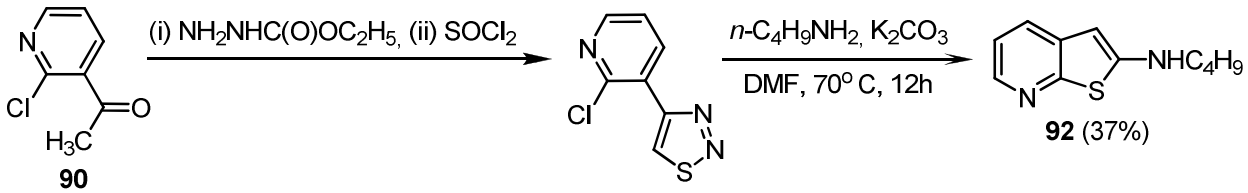
Scheme 34

In order to understand how the electron-withdrawing nitro group affects the reaction, 4-(2-chlorophenyl)-1,2,3-thiadiazole **88** was prepared from 1-(2-chlorophenyl)-ethanone **86** in 37% overall yield. Compound **88** was heated in the presence of *n*-$C_4H_9NH_2$ and K_2CO_3 at 70 °C for 24 hours, but only starting material **88** and thioamide **89** were detected in the reaction mixture. Complete conversion of **88** to **89** was achieved at higher temperature (130 °C), but no traces of cyclic product **77c** were found. Thus, the presence of the electron-withdrawing nitro group on the phenyl ring makes thiadiazole ring susceptible to proton abstraction assisting anionic ring-opening. Additionally, cyclization of **89** to **77c** did not occur, since the chlorine atom is unreactive to intramolecular nucleophilic attack by sulfur under the reaction conditions (Scheme 35).

2-Chloro-3-(1,2,3-thiadiazol-4-yl)-pyridine **91** was synthesized in 79% yield (2 steps) from 1-(chloropyridin-3-yl)-ethanone **90**. Following reaction of **91** with *n*-$BuNH_2$ in the presence of K_2CO_3 (DMF, 70 °C, 12 hours) resulted in *N*-butylthieno[2,3-*b*]pyridine-2-amine **92** (yield 37%, Scheme 36).

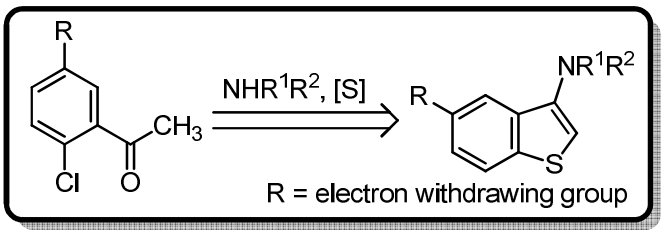


Scheme 35



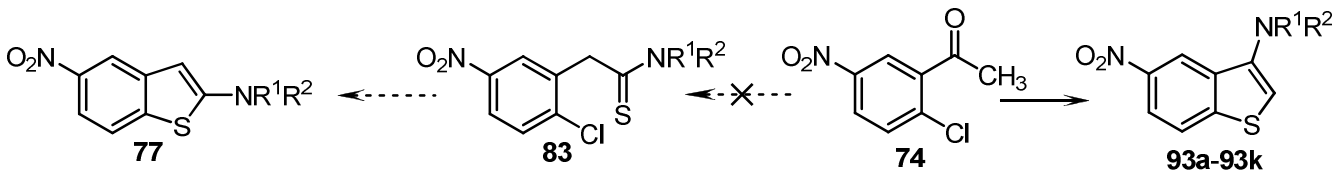
Scheme 36

4.2. Benzo[*b*]thiophene-3-amines



An alternative approach to 2-aminobenzo[*b*]thiophenes was attempted using Willgerodt-Kindler reaction of 1-(2-chloro-5-nitrophenyl)ethanone **74** with a variety of primary and secondary amines.[73]

According to the general procedure, the substrate **74** was heated in DMF at 35−100 °C in the presence of amine (1.2−3.7 equiv.), sulfur (1.5−5 equiv.) and NaOAc (0−3 equiv.) for 6−20 minutes. The solvent was removed under reduced pressure and the desired product was isolated by column chromatography. Surprisingly, the reaction afforded 3-aminobenzo[*b*]thiophenes **93a−93k** instead of the expected 2-substituted derivatives **77** (Scheme 37).

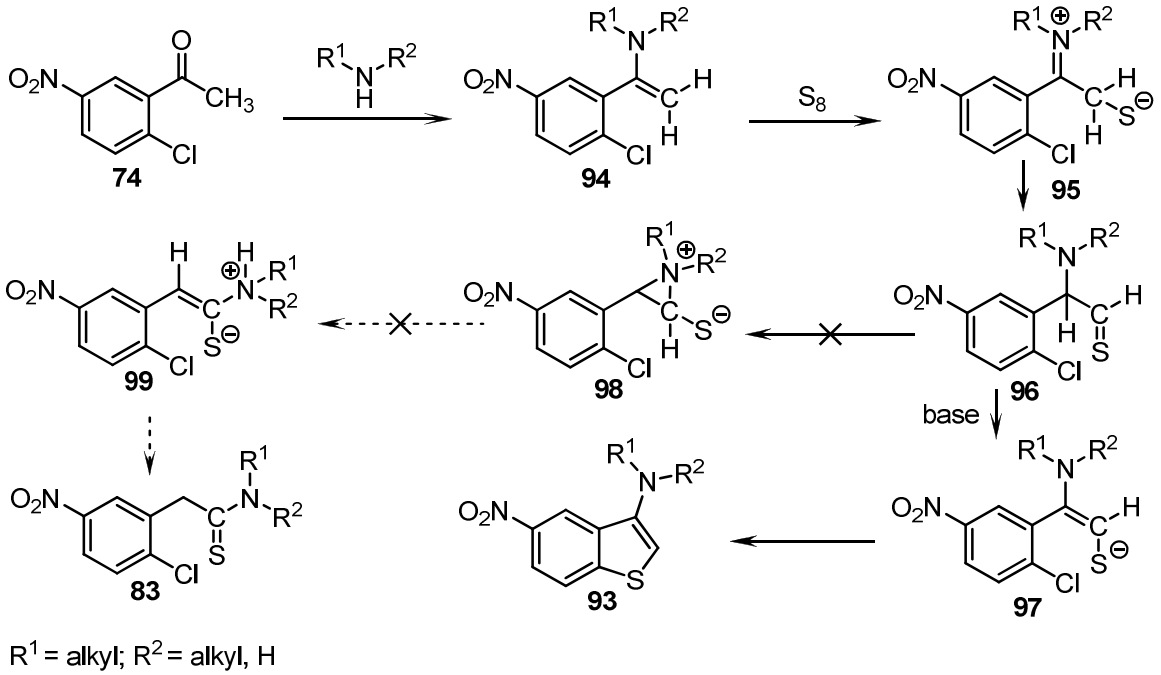


93a, R^1 = H, R^2 = CH_3 (46%); **93b**, R^1 = H, R^2 = allyl (47%); **93c**, R^1 = H, R^2 = *n*-C_4H_9 (36%); **93d**, R^1 = H, R^2 = Bn (30%)
93e, R^1 = H, R^2 = *i*-C_3H_7 (14%); **93f**, R^1 = H, R^2 = cyclopentyl (40%); **93g**, R^1 = H, R^2 = cyclohexyl (19%)
93h, R^1 = R^2 = CH_3 (4%); **93i**, R^1 = R^2 = $(CH_2)_4$ (31%); **93j**, R^1 = R^2= $(CH_2)_5$ (10%); **93k**, R^1 = R^2 = $(CH_2)_2O(CH_2)_2$ (12%)

conditions: S_8, HNR^1R^2, NaOAc, DMF, 36 - 100 °C, 6 - 180 min

Scheme 37

A plausible mechanism of the reaction is shown below (Scheme 38). The first stage of the reaction is the formation of enamine **94** that reacts with sulfur to give the sulfide **95**. Subsequent formation of enthiolate **97**, followed by cyclization, leads to the final product **93**. Most probably, in this case, the isomerization/deprotonation/cyclization sequence (**95** to **93**) is faster than Willgerodt-Kindler reaction, that proceeds *via* aziridine intermediate **98** that, after rearrangement to **99** (the amine group moving along the central C–C bond), proton exchange and tautomerization affords thioacetamide **83**.[73]



Scheme 38

It was found that the presence of nitro group *para* to chlorine atom is crucial for the success of the reaction: for example, 1-(2-chlorophenyl)ethanone yielded a complex mixture of products instead of corresponding benzo[*b*]thiophene.

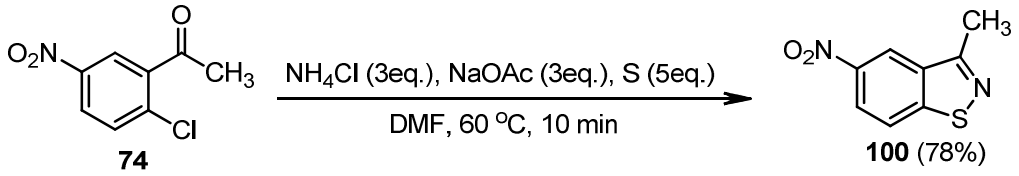
The nature of base is not important: in fact, K_3PO_4, NaOAc or excess of amine can serve as a base. Primary amines gave better yields of 3-aminobenzo[*b*]thiophenes than secondary amines.

The reaction outcome is strictly dependent on the amine concentration. A 1.5 to 3 fold excess was preferable using secondary amines, while a 1.5 to 2 fold excess was better for primary amines. The nature of by-products depends on the type of amine utilized in the reaction: using primary amines, the major by-product was 3-methyl-5-nitrobenzo[*d*]isothiazole, becoming major product raising molar ratio of nitrogen compound up to 8–10. In contrast, in the case of secondary amines, the main by-product was that formed through direct nucleophilic aromatic substitution on the benzene ring.

It was found that the optimal molar ratio acetophenone:sulfur is 1:5. The better yields of primary amines were observed at lower temperature (35–60 °C), while higher temperature (60–100 °C) are required for secondary amines. DMF was found to be the most favourable solvent. Meanwhile, secondary amines are usually more reactive than primary amines in the classical Willgerodt-Kindler reaction.[76]

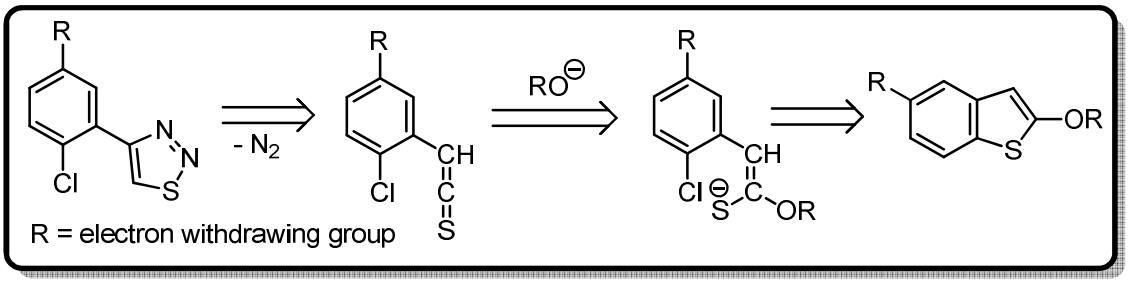
Steric effects play an important role. The yield of 2-cyclopentylaminobenzo[*b*]thiophene **93f** (40%) was higher than the yield of 2-cyclohexylaminobenzo[*b*]thiophene **93g** (19%). Sterically hindered (di-*n*-butylamine, diallylamine, di-*iso*-propylamine), aromatic (aniline) and heterocyclic (benzotriazole)

amines failed to give the desired products. *N*-Unsubstituted benzo[*b*]thiophene are formed using NH_4Cl in the presence of NaOAc: for example, starting from **74**, 3-methyl-5-nitro-benzo[*d*]isothiazole **100** was obtained in 78% yield (Scheme 39). The synthesis of **100** under harsh conditions is also reported in literature.[77]

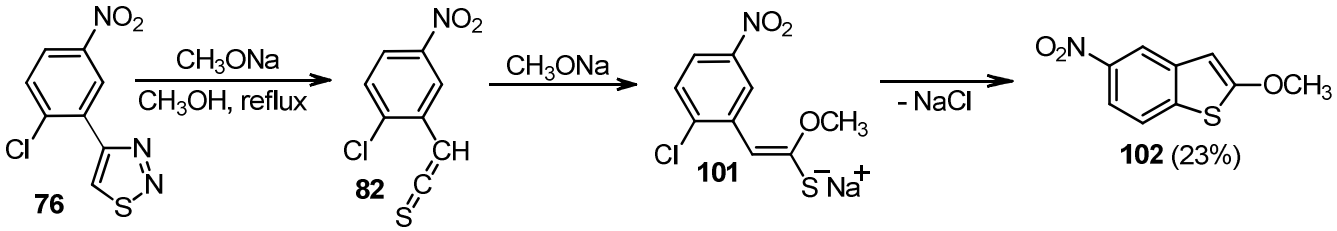


Scheme 39

4.3. Benzo[*b*]thiophene-2-oxides



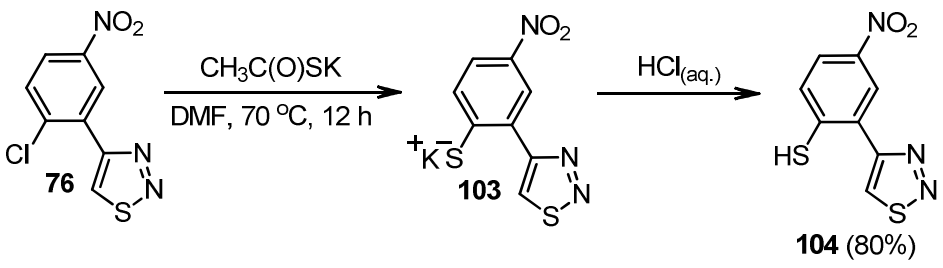
Treatment of **76** with CH_3ONa in CH_3OH under an inert atmosphere led to 2-methoxy-5-nitrobenzo[*b*]thiophene **102** (yield 23%). By analogy with the process shown in Scheme 32, the addition of CH_3ONa to thioketene **82** results in enethiolate **101** cyclizing to benzo[*b*]thiophene **102** (Scheme 40).[73]



Scheme 40

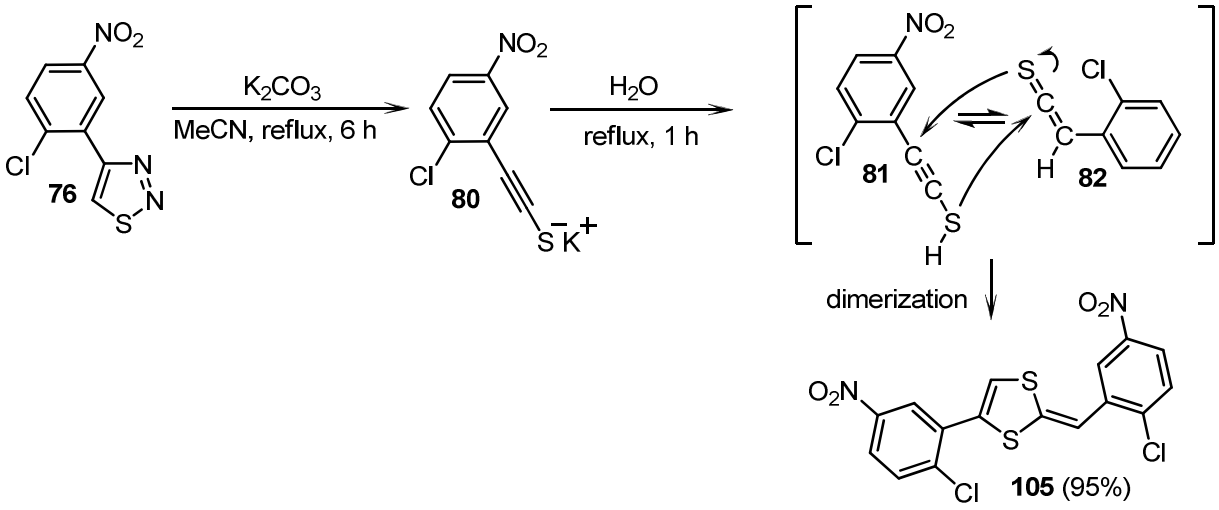
4.4. Miscellaneous reactions

An attempt to introduce the sulfur-containing nucleophile by reaction of **76** with potassium thioacetate resulted in the product of nucleophilic substitution on the benzene ring. This gave thiophenolate **103** without decomposition of the heterocyclic ring. Anion **103** can be trapped as thiol **104** (yield 80%) by addition of diluted aqueous HCl (Scheme 41).[73]



Scheme 41

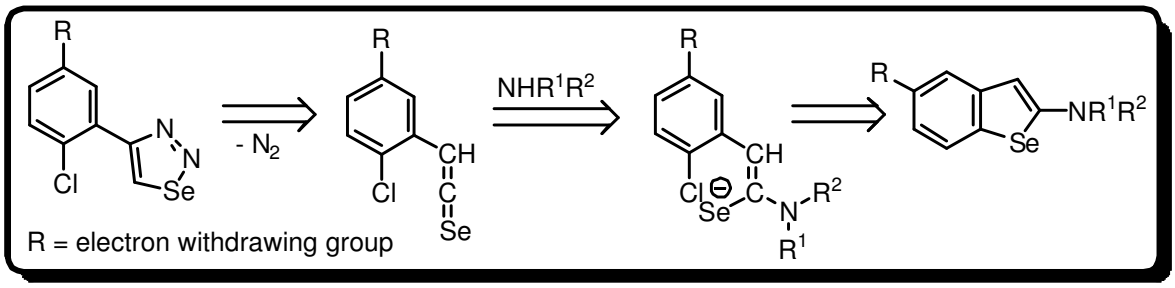
Base-promoted decomposition of **76** (K_2CO_3, CH_3CN, 80 °C, 6 hours) in the absence of nucleophiles formed alkynethiolate **80**, which reacted with water giving alkyne thiol **81**. Tautomerization of **81** to **82** and subsequent dimerization afforded 2-[(*E*)-2-chloro-5-nitrobenzylidene]-4-[2-chloro-5-nitrophenyl]-1,3-dithiole **105** in 95 % yield (Scheme 42).[73]



Scheme 42

5. Benzo[*b*]selenophenes

5.1. Benzo[*b*]selenophene-2-amines

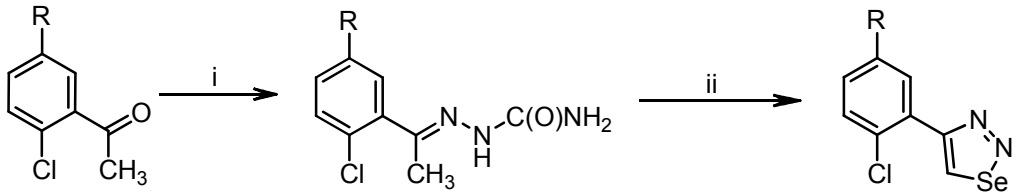


Up to now, the only reported method for the synthesis of 2-aminobenzo[*b*]selenophene was the reduction of 2-nitrobenzo[*b*]selenophene. 2-Aminobenzo[*b*]selenophene was used for the preparation of selenium-containing polymethine dyes.[78] Beckmann rearrangement of 2-acetyl-3-phenylbenzo[*b*]selenophene oxime promoted by polyphosphoric acid gave 2-acetylamino-3-phenylbenzo[*b*]selenophene.[79] Another 2-aminobenzo[*b*]selenophene derivative, 2-benzoyl-amino-3-phenylbenzo[*b*]selenophene, was synthesized by reaction of diphenyldiazomethane with benzoyl isoselenocyanate.[80]

A new procedure for the synthesis of 2-aminobenzo[*b*]selenophenes from readily accessible 4-(2-chloroaryl)-1,2,3-selenadiazoles was proposed.[81] The reaction of 2-chloroacetophenones **74** and **86** with semicarbazide hydrochloride gave the corresponding semicarbazones **106a** and **106b** which were converted into 4-(2-chloro-aryl)-1,2,3-selenadiazoles **107a** and **107b** by the action of selenium dioxide (Scheme 43).

Treatment of 4-(2-chlorophenyl)-1,2,3-selenadiazole **107a** with potassium hydroxide in an excess of diethylamine resulted in a decomposition of the five-membered ring accompanied by elimination of the nitrogen molecule and formation of potassium 2-(2-chlorophenyl)ethyneselenolate **108a** that reacted with diethylamine to produce potassium 2-(2-chlorophenyl)-1-diethylaminoetheneselenolate **109a**. Compound

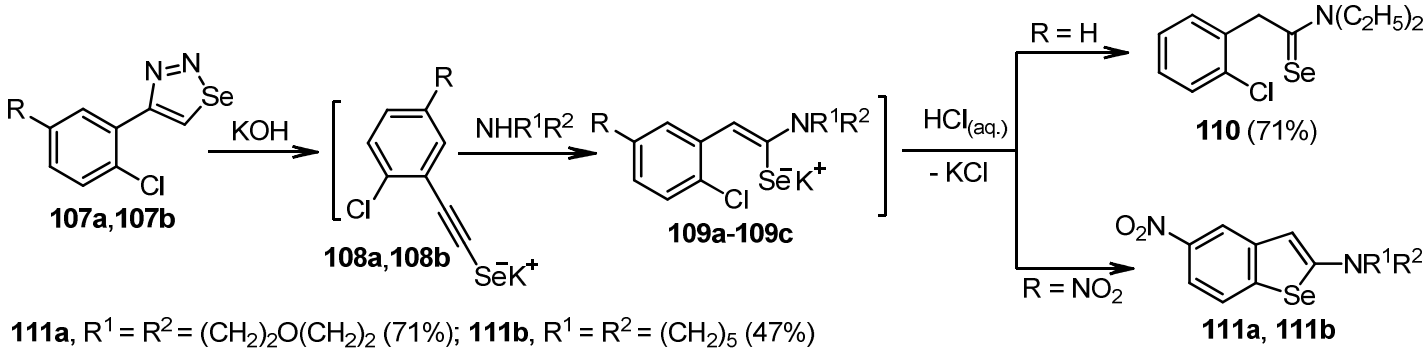
109a did not undergo further cyclization *via* intramolecular nucleophilic replacement of the chlorine atom, and acidification of the reaction mixture afforded 2-(2-chlorophenyl)-*N*,*N*-diethylselenoacetamide **110**.



106a, R = H; **106b**, R = NO_2 (88%); **107a**, R = H (65%); **107b**, R = NO_2 (63%)
conditions: (i) $NH_2NHC(O)NH_2 \cdot HCl$, AcONa, *i*-PrOH-H_2O, reflux, 2h; (ii) SeO_2, AcOH, 66 °C, 4h

Scheme 43

4-(2-Chloro-5-nitrophenyl)-1,2,3-selenadiazole **107b** reacted with KOH in excess of secondary amine (morpholine or piperidine) to generate potassium 2-(2-chloro-5-nitrophenyl)ethyneselenolate **108b**, which took up secondary amine molecule with formation of potassium 2-(2-chloro-5-nitrophenyl)-1-dialkyl amino-etheneselenolate **109b** or **109c**. Intramolecular cyclization of the latter produced 2-aminobenzo[*b*]-selenophenes **111a**, **111b** (Scheme 44).[81]

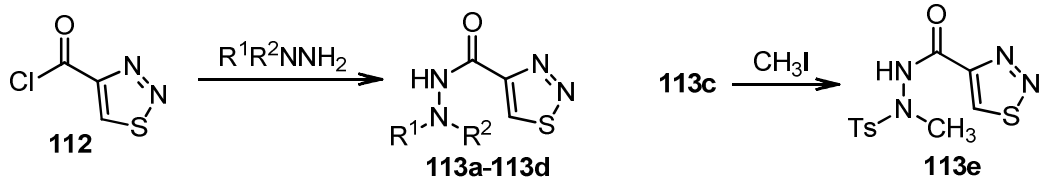


111a, $R^1 = R^2 = (CH_2)_2O(CH_2)_2$ (71%); **111b**, $R^1 = R^2 = (CH_2)_5$ (47%)

Scheme 44

6. Other heterocycles

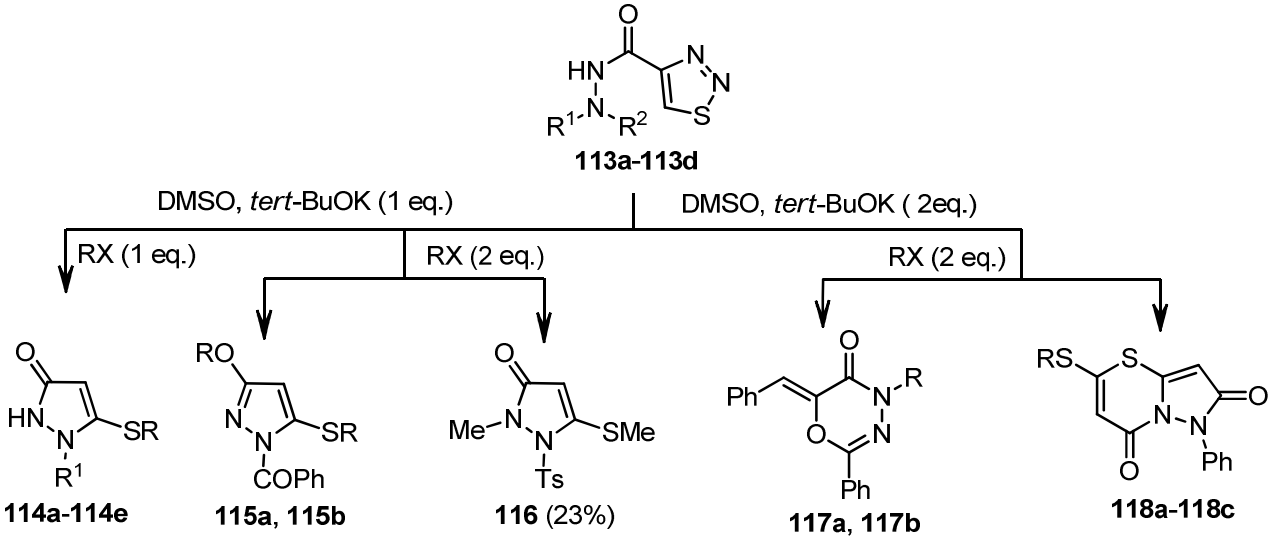
The scope of the methodology was expanded to the synthesis of other classes of nitrogen heterocycles.[82] In order to have an entry to 1,2,3-thiadiazoles, and hence alkynethiolates, having a nucleophilic nitrogen atom, the reaction of 1,2,3-thiadiazole-4-carbonyl chloride **112** with several hydrazines was used and 1,2,3-thiadiazole-4-carbohydrazides **113a–113c** were obtained in 60–75% overall yield. Phenyl hydrazine, on treatment with an excess of the acid chloride **112**, gave the diacylated hydrazide **113d** (Scheme 45).



113a, R^1 = Ph, R^2 = H (75%); **113b**, R^1 = PhCO, R^2 = H (74%); **113c**, R^1 = Ts, R^2 = H (60%)
113d, R^1 = Ph, R^2 = 1,2,3-thiadiazole-4-carbonyl (70%); **113e**, R^1 = Ts, R^2 = CH_3 (35%)

Scheme 45

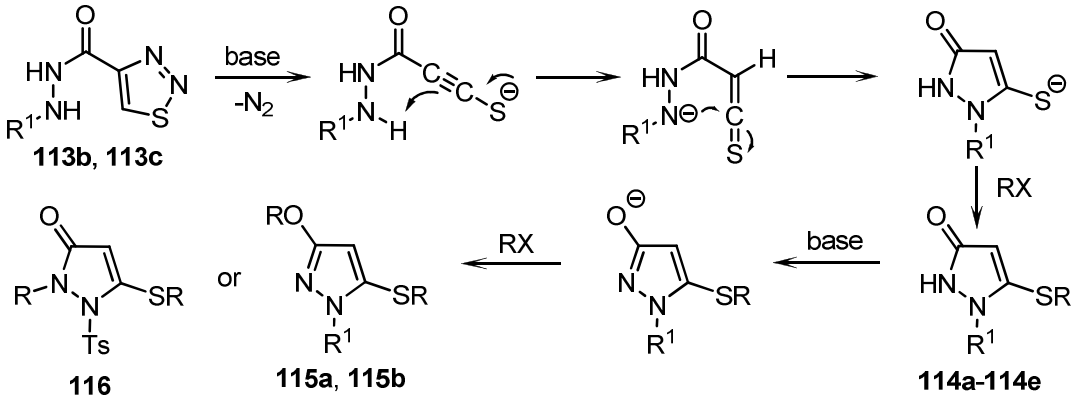
The base-catalyzed ring cleavage of compounds **113a** and **113b** with 1 equiv. of *tert*-BuOK followed by alkylation afforded either the expected 5-alkylthiopyrazolone derivatives **114a–114e** (with 1 equiv. of alkylating agent) or the pyrazoles **115a**, **115b** and **116** (with 2 equiv. of alkylating agent). The same reaction conditions applied to hydrazide **113a** gave no product (Scheme 46).[82]



114a, R = CH_3, R^1 = COPh (20%); **114b**, R = *n*-$C_{16}H_{33}$, R^1 = COPh (25%); **114c**, R = CH_3, R^1 = Ts (30%)
114d, R = *n*-$C_{16}H_{33}$, R^1 = Ts, (35%); **114e**, R = Bn, R^1 = Ts (34%); **115a**, R = CH_3 (20%); **115b**, R = *n*-$C_{16}H_{33}$ (35%)
117a, R = CH_3 (40%); **117b**, R = Bn (51%); **118a**, R = CH_3, R^1 = 1,2,3-thiadiazole-4-carbonyl (30%)
118b, R = *n*-$C_{16}H_{33}$, R^1 = 1,2,3-thiadiazole-4-carbonyl (20%); **118c**: R = Bn, R^1 = 1,2,3-thiadiazole-4-carbonyl (25%)

Scheme 46

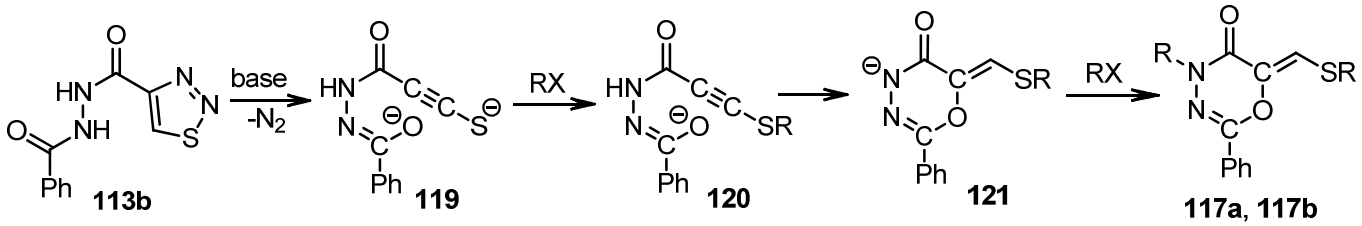
The pyrazoles **114–116** apparently resulted from a multistep process involving the cleavage of the thiadiazole ring with formation of the alkynethiolate (Scheme 47). Fast intramolecular proton shift gave the reactive thioketene, which underwent intramolecular nucleophilic cyclization to a pyrazolone-5-thiolate anion that could be easily alkylated, forming either 1-substituted-5-(alkylthio)-1*H*-pyrazol-3(2*H*)-ones **114a–114e** or 1-substituted-3-alkyloxy-5-(alkylthio)-1*H*-pyrazoles **115a**, **115b** and 1-substituted-alkyl-5-(alkylthio)-1*H*-pyrazol-3(2*H*)-ones depending on reaction condition (Scheme 47).



Scheme 47

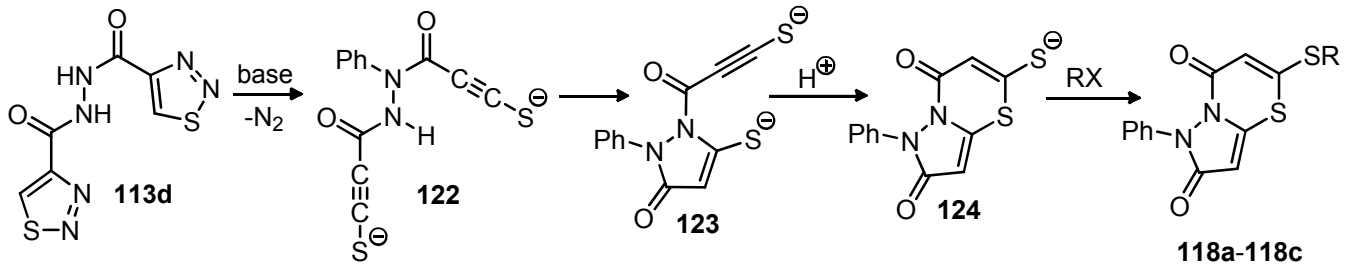
When the ring cleavage of hydrazides **113b–113d** was carried out in the presence of 2 or more equiv. of *tert*-BuOK, the cyclization took another course. Thus, the decomposition of benzoyl hydrazide **113b**, followed by alkylation, resulted in 1,3,4-oxadiazin-5-one derivatives **117a**, **117b**. On the other hand, the

tosylhydrazide **113c** under the same conditions, yielded benzyltolylsulfinate as the only identifiable decomposition product. The formation of six-membered heterocycles **117a**, **117b** can be rationalized as follow: the alkynethiolate dianion **119**, instead to cyclize to pyrazole ring, was faster alkylated to the alkynesulfide **120**, that underwent an *exo-dig* cyclization to the six-membered ring by the attack of the imidate anion on the alkynesulfide, faster than the alternative *endo-dig* process. The resulting anion **121** was finally nitrogen alkylated (Scheme 48).



Scheme 48

1,2,3-Thiadiazole-4-carbohydrazide **113d**, after cleavage of two 1,2,3-thiadiazole rings, recyclization and alkylation gave the novel fused 7*H*-pyrazolo[5,1-*b*][1,3]thiazine-2,7-diones **118a–118c**. It is assumed that the bis(alkynethiolate) **122** is formed first, which then cyclized, similar to Scheme 47, to the pyrazole-5-thiolate **123**. This could undergo a second cyclization with the formation of a thiazine-6-thiolate **124**, which finally is alkylated to give the products **118a–118c** (Scheme 49).



Scheme 49

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RECENT TRENDS IN HETEROCYCLIC QUINONES

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Abstract. *Hetrocyclic quinones are plant secondary metabolites that have found numerous applications. Resulting from exhaustive studies of the past decades, their biological activity in relation to a variety of diseases was reported and countless attempts for development of synthetic routes to their analogues with improved pharmacological properties were published. Unnoticed for many, they have been around as drugs and drug precursors since long. This review provides an overview on the latest trends of the chemistry of hetrocyclic quinones with focus on the most impactful results of the past two decades; however, in certain cases it goes back to the '80s to provide the necessary context. The structural groups mitomycins, streptonigrin, isoquinolones, kinamycins*, *mimosamycins*, *azaanthraquinones, secobatzellines*, *pyrano- and furanonaphthoquinone*s, *dimeric heterocyclic quinones*, *kalafungins and nanaomycines are discussed with respect to their biosynthesis, synthesis and biological activities.*

Contents

1. Introduction

Natural products remain an important source of novel pharmacons.[1,2] Resulting from their frequently reported bioactivity, the past decades herbal heterocyclic quinones received increasing attention. Quinones fused to quinoline, indole, benzimidazole, pyrrole or triazole rings were often reported from herb extracts and bacterial fermentation broths. The antimalarial, antibacterial and antitumour activities of quinones attached to imidazole,[3] pyrrole,[4] triazole[5] or quinolone[6] moieties were proposed to be related to the ability of the quinone to accept one or two electrons to form the corresponding radical anion or dianion species.[7,8] In general, more information is available on *p*-quinones than on *o*-quinones. Following the first overview of the synthesis of heterocyclic quinones in 1971 by Baxter and Davis,[9] the field has been reviewed with various focuses, latest by Tišler in 1989.[10] In spite of intense efforts of several research groups, synthetic routes to some heterocylic quinones are yet missing. A systematic summary of the vast information, collected over the past decades, on the chemistry and biology of heterocyclic quinones is still lacking despite significant advances on their synthesis and on the understanding of the basis of their pharmaceutical potency. Motivated by this fact and by recent developments of the field, a systematic review of the recent advances of the biosynthesis, synthesis, biological activities of this compound class is disclosed here.

Heterocyclic quinones are discussed with respect to their heteroatoms: N, O and S containing ones. The natural sources and biosynthetic routes along with the biological activity and recent synthetic approaches are here reviewed for the three compound classes. Originating from the vast amount of available literature, only representative examples are given without attempting to cover all available data.

2. Nitrogen containing heterocylic quinones

The high antitumour activity of nitrogen containing heterocyclic quinones received special attention of the pharmaceutical industries.[9,11] Several mechanisms were proposed to explain their cytotoxicity, including their ability to (a) alkylate biopolymers, (b) intercalate DNA, inhibit (c) topoisomerase and (d) phosphatase, (e) trigger apoptosis or (f) produce reactive oxygen radicals by redox cycling. The claimed tumour selective toxicity of nitrogen containing quinones was proposed to originate from the different oxygen tension and the difference in enzyme activities of healthy and malignant tissues.[11]

2.1. Mitomycins

Common sources of natural nitrogenous quinones are fungi belonging to the genus *Streptomyces* such as *S. caespitosus*, *S. verticillatus* and *S. ardus*.[12,13] Since the isolation of mitomycines A (**1**), B (**2**) and C (**3**) from the culture broth of *S. caesipitosus*,[14,15] mitomycins (Figure 1) remain intensely studied. Mitomycins have a pyrrolo[1,2-*a*]indole core comprising an aziridine fused to a pyrrolo[1,2]indole and an amino-benzoquinone. The scaffold was confirmed *via* total synthesis by Kishi[16] with the stereochemistry revised by the X-ray studies of Hirayama.[17] Natural mitomycines are often classified into three main structural groups based on their substituent at the C-9 position, thus (i) 9α-carbamoylmethyl, (ii) 9β-carbamoylmethyl and (iii) 9-methylene.[18] These classes may be further differentiated based on the substitution pattern of the backbone at C-7, C-9a and N-1a, with the numbering being given in Figure 1.

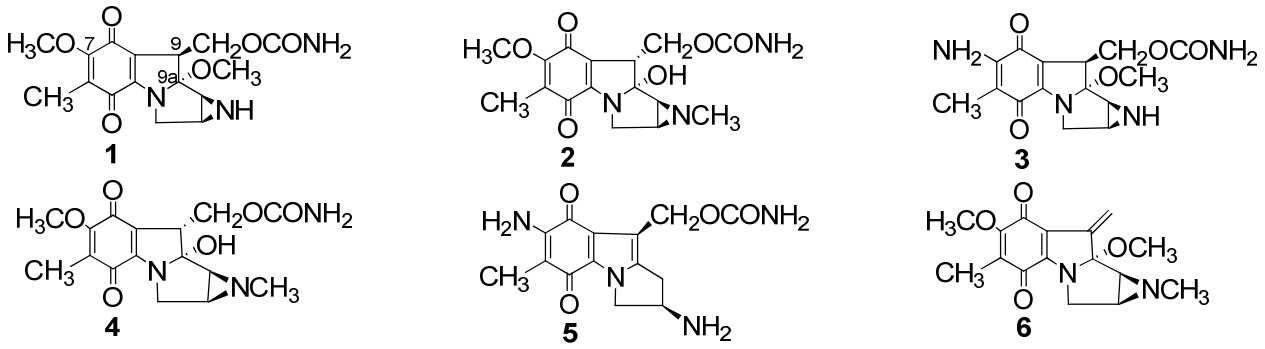


Figure 1. The structure of typical mitomycin antibiotics: mitomycins A (**1**), B (**2**), C (**3**), D (**4**), 2,7-diaminomitosene (**5**) and mitomycin K (**6**).

2.1.1. Bioactivity

Of the seventeen known mitomycins, sixteen exhibit antibiotic and/or antitumour activity. Mitomycin C (**3**) was marketed by Bristol-Myers Squibb under the name Mutamycin® for the treatment of stomach and pancreatic cancer. The potential use of mitomycins as antitumour[19] and antibiotic[20] agents is related to their ability to alkylate and crosslink DNA.[21] Their aziridine ring was suggested to play a crucial role in an irreversible bis-alkylation.[22–24] Cytotoxic selectivity for oxygen-deficient cells, which is a characteristic of solid tumours, was reported for mitomycin C (**3**).[25] A very recent report by Paz *et al.* proposed that the antiproliferative activity of **3** originates from thioredoxin reductase inhibition.[26]

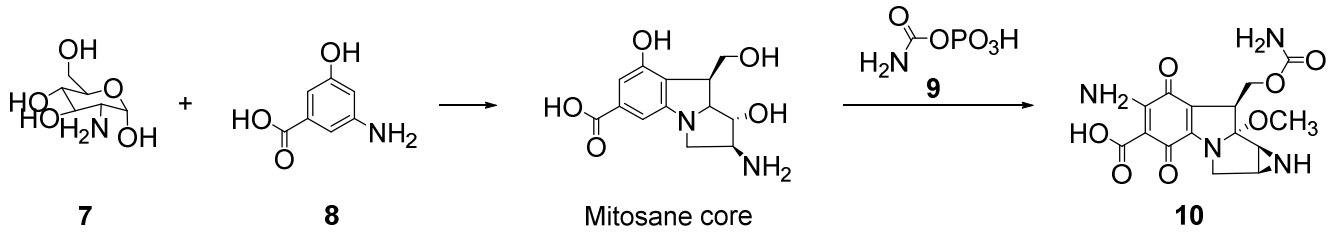
2.1.2. Biosynthesis

Precursor incorporation experiments demonstrated that the mitosane skeleton is derived from the coupling of *D*-glucosamine (**7**), 3-amino-5-hydroxybenzoic acid (**8**) and carbamoyl phosphate (**9**, Scheme

1).[27–29] 3-Amino-5-hydroxybenzoic acid is a common precursor to other anticancer drugs as well, such as rifamycin and ansamycin. Feeding experiments indicated that the C-10 carbamoyl group originates from *L*-arginine or *L*-citrulline,[30] whereas the *N*-and *O*-methyl moieties originate from *L*-methionine.[31] Despite decades of efforts, the specific order of assembly leading to the backbone of mitomycins remains a topic for further research. For more details of the biosynthesis of isoprenoid quinones the reader is advised to the recent review of Nowicka and Kruk.[32]

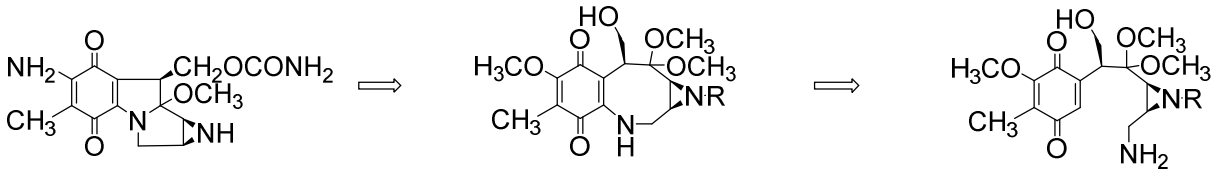
2.1.3. Total synthesis

The presence of a carbamoyl moiety and a bridged carbinolamine within a constrained architecture makes mitomycins sensitive to bases, acids, nucleophiles and reducing agents. They easily undergo interconversion, *i.e.* mitomycin A (**1**) may be converted to mitomycin C (**3**) by treatment with methanolic ammonia, whereas hydrolysis of **3** followed by methylation produces **1**.[33] Mitomycin D, (**4**) may be synthesized by methylation of the aziridine of **1**. Mitomycins A (**1**) and B (**2**) have opposite configuration at C-9. This chiral centre was later proven to easily epimerize. Interestingly, the C-9-epimerized analogue of **2**, 9-*epi*-mitomycin B[34] shows higher antibacterial activity than mitomycin B (**2**) itself.[33] Semisynthetic analogues of mytomicins were prepared in the course of the optimization of their anticancer properties.[35,36]



Scheme 1. The schematic biosynthetic route of mitomycins.

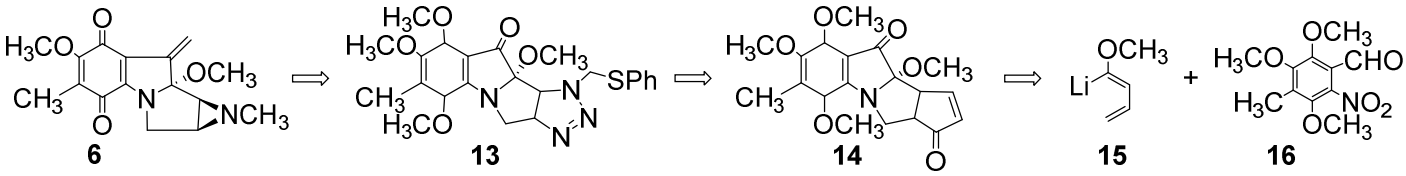
The major challenges of the synthesis of mitomycins were attributed to their complex stereochemistry, to the avoidance of aromatization of the mitosane core and to the sensitivity of their aziridine and quinone systems. Despite these and the delicate pattern of functional groups, several strategies have been proposed for their chemical synthesis.[37–44]



Scheme 2. The key retrosynthetic steps of Kishi's retrosynthesis of mitomycin C (**3**).

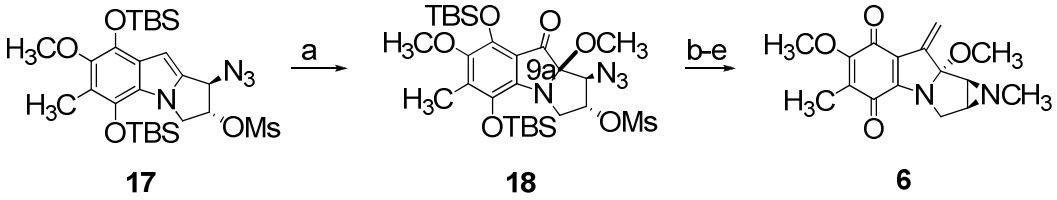
The first total synthesis of mitomycins A and C was reported by Kishi *et al.*[38,40,41] with forty-four linear steps and 0.16% overall yield. Despite the large number of steps and the low yield, the Kishi protocol was a milestone with the key features being the *trans*-annular cyclization of the methoxyketal derivative **11** and formation of the eight-membered ring by Michael addition of **12** (Scheme 2). As the aminal functionality was considered the most sensitive part of the target molecule, it was introduced at the very last step.

Mitomycin K (**6**) was synthesized by Danishefsky *et al.* in 1993 utilizing an intermolecular Diels-Alder reaction of an electron-poor aryl ring (**16**) and a lithiated diene (**15**).[42] In this protocol, the tetracyclic core was furnished in only four whereas the *N*-methyl aziridine group in three steps from the olefin by cycloaddition of methylthiophenyl azide onto the unsaturated amide **14**, as shown in Scheme 3. The developed route is a short and elegant strategy for the synthesis of **6** although originally it was designed for producing FR-900482.



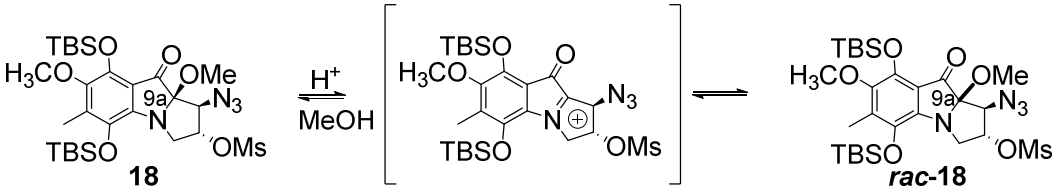
Scheme 3. Danishefsky's retrosynthetic approach towards mitomycin K (**6**).

A few years later, in 1994, Jiménez and co-workers[44,45] converted an indole derivative (**17**) into mitomycin K (**6**). Direct oxidation of **17** using (hexamethylphosphoramido)oxodiperoxomolybdenum (VI) gave a diastereomeric mixture of the quinoid intermediate **18**, which was readily transformed into **6** (Scheme 4). This method provides a 1:1 mixture of the diastereomers of **6** at C-9a, however, simultaneously presents a simplified route by starting from an indole derivative and providing an overall yield of 1.4% in thirteen steps.



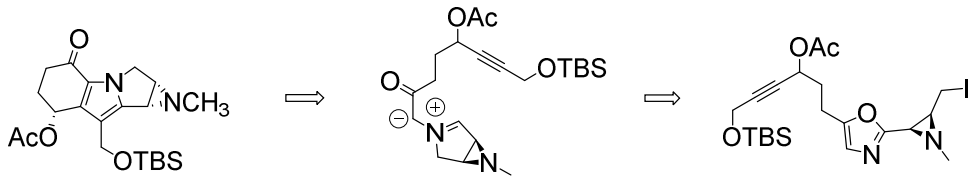
Scheme 4. Synthesis of mitomycin K (**6**), as suggested by Jimenez *et al.*:[44] (a) MoO_5, HMPA, CH_3OH; (b) PPh_3, Et_3N, THF, H_2O; (c) CH_3OTf, pyridine, DCM; (d) Me_3SiCH_2Li, THF; (e) PCC.

Danishefsky observed a higher configurational stability of C-9a of *epi*-mitomycin K,[46] possibly explainable by its inability to open to a carbinolamine intermediate in contrary to that observed for **2**. Double-TBS protection of the hydroquinone in intermediate **18** in the Jiménez protocol however, enhances the nucleophilic character of the aromatic nitrogen, promoting the formation of the reactive iminium species under acidic conditions yielding rapid epimerization of C-9a (Scheme 5).



Scheme 5. The proposed epimerization scheme of C-9a of intermediate **18** in the Jiménez protocol.

Recent update on the synthetic approaches towards mytomicins, with further discussion of the early strategies, was given by Andrez[33] and Coleman.[47] Previous reviews are available from Waldmann[48] and Remers.[49]

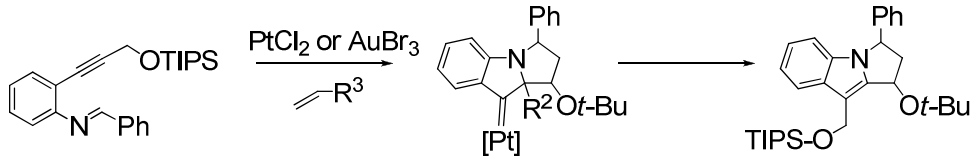


21 **20** **19**

Scheme 6. Retrosynthetic strategy towards the enantioselective synthesis of aziridinomitosenes.[50]

Besides the total syntheses of mitomycins providing racemic product,[37,42,44] Vedejs and co-workers developed an enantiocontrolled strategy for construction of aziridinomitosenes starting from allyl-protected *L*-serinal.[50] A silver(I) assisted intramolecular [3+2] cycloaddition of an azomethine ylide and an alkyne (**20**) was used to assemble the tetracyclic ring system of aziridinomitosene in twelve steps. This strategy provides a suitable route to analogues lacking the C-7 methoxy functionality.

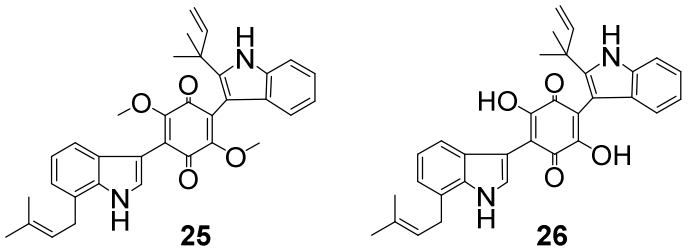
In 2006 Iwasawa *et al*. disclosed a facile synthetic strategy towards the mitosene skeleton,[51] starting from monocyclic substrates. This approach provides pyrroloindoles using the transition metal-catalyzed one-pot reaction shown in Scheme 7. A catalytic (1−3 mol%) amount of $PtCl_2$ or $AuBr_3$ was applied to activate the alkyne of **22** for nucleophilic attack by the imino nitrogen in a 5-*endo* cyclization. Subsequent [3+2] cycloaddition and 1,2-alkyl migration yielded the mitosene **24** in 73% yield. This seemingly attractive route to mitosenes remains to be validated for the synthesis of mitomycin derivatives, which in turn require its use with an electron-rich aromatic ring and an easy to remove imine alkyl substituent.



22 **23** **24**

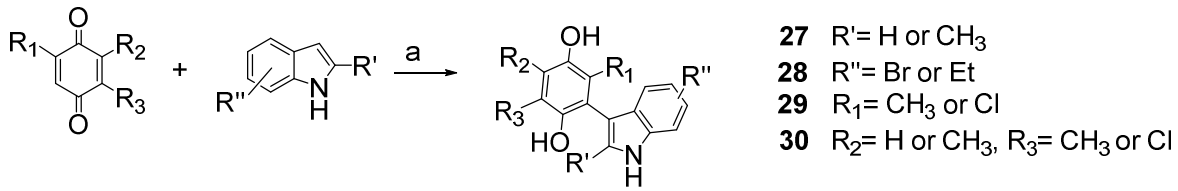
Scheme 7. The key steps of the Iwasawa synthesis of the mitosene skeleton.[51]

The 3-indolylbenzoquinone core is present in a variety of biologically active natural products, such as asterriquinones (**25**, **26**), shown in Figure 2.[52] Asterriquinone B1 (**25**) and demethylasterriquinone B1 (**26**) were isolated from a wide range of fungi including *Aspergillus terreus*, *Chaetomium* sp. and *Pseudomassaria* species.[53–55] Asterriquinone B1 (**25**) arrests the cell cycle in G1 and promotes apoptotic cell death and thereby was recognized as a promising anti-tumour lead.[56] In a related study, it was reported to possess antidiabetic activity upon oral ingestion.[57] The first total synthesis of asterriquinone B1 was presented by Liu *et al.* in 1999 and was based on the rearrangement of a pyranedione. Being a convergent approach, it allows rapid generation of large number of analogues.[58]



25 **26**

Figure 2. The structures of asterriquinone B1 (**25**) and demethylasterriquinone B1 (**26**)



Scheme 8. Syntheses of 3-indolylhydroquinone derivatives (**27–30**). (a) 450W MW-irradiation.

Syntheses of related 3-indolylhydroquinone derivatives **27–30** (Scheme 8) were conducted under solvent-free conditions by Yadav and co-workers.[59] An advantage of this methodology is that it provides products free from chlorinated side products, commonly observed under standard protic conditions using concentrated HCl in THF. Moreover, the method works with electron-deficient 2-ethoxycarbonyl indoles to give corresponding 3-indolylhydroquinones in fairly good yield; however, it is incapable to produce 3-indolylhydroquinones with electron-deficient indoles.

2.2. Streptonigrin

Streptonigrin (**31**), produced by *Streptomyces flocculus*,[60,61] *Streptomyces rufochromogenes*, *Streptomyces chinatues*, *Actinomyces albus*,[62] the Actinomycete strain IM 2670[63] and *Micromonospora*[63] was recognized for its antineoplastic properties.[64] Several attempts for the total synthesis of **31** and its derivatives, along with reviews of its chemistry, are available.[65–67]

2.2.1. Bioactivity

The aminoquinone antibiotic streptonigrin (**31**, Figure 3) was proposed to act through inhibition of DNA replication by formation of solitary cleavages and by inhibition of topoisomerase II.[68] DNA strand breakage *via* free radical mechanism was observed *in vitro* and *in vivo*[69] leading to unscheduled DNA synthesis.[70]

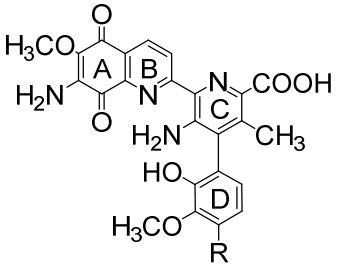
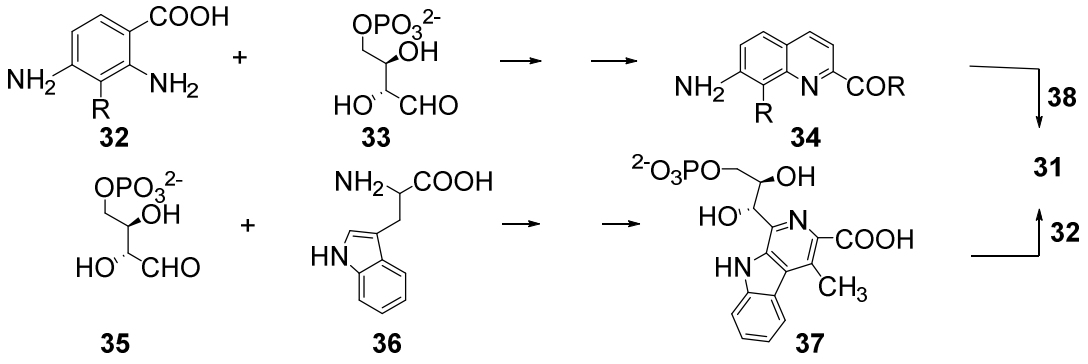


Figure 3. (±)-Streptonigrin (**31**, R=OCH_3) and (±)-10'-desmethoxystreptonigrin (**32**, R=H).



Scheme 9. The proposed biosynthetic route of streptonigrin (**31**, R=H, OH).

The inhibition of topoisomerase II[71] induces chromosomal aberrations and sister-chromatid exchanges in mammalian and other cell types.[72] The presence of redox active metals, such as Fe and Cu, were shown to be required for it to exhibit full antibiotic and antitumour activities.[73] *In vivo*, Zn(II), Cu(II) and Mn(II) were demonstrated to facilitate the initial reduction of streptonigrin (**31**) to its semiquinone.[73,74]

2.2.2. Biosynthesis

Significant details of the pathway leading from tryptophan to the C/D rings of streptonigrin (**31**) were clarified by the early investigations of Gould and co-workers.[75,76] *L*-Tryptophan was identified as the natural precursor in the biosynthetic pathway and by use of $^{15}N,^{13}C$-heteronuclear spin correlation NMR experiments, which revealed that N–C bond cleavage leads to formation of the 4-phenylpicolinic acid subunit (C/D rings). Formation of the A/B-rings was investigated in depth by Gerwick *et al.*[77] by feeding [U-$^{13}C_6$]-D-glucose to *Streptomyces flocculus* ATCC-13257 cultures. This study suggested that D-erythrose, presumably in its erythrose-4-phosphate form, is the specific precursor to all three C4 biogenetic units of the molecule, which is in agreement with the view that the A-ring is generated by a shikimate-type pathway (Scheme 9).

2.2.3. Total synthesis

The connection of the B and C rings (Figure 3) can be viewed as the lynch-pin of the molecule, which may be furnished in different ways: by connection of an amino anthranilic acid derivative (**32**) to yield a quinoline carboxylic acid; alternatively the aldehyde (**33**) may be condensed with **32**, or it may first react with tryptophan (**36**) to yield a β-carboline (**37**) that condenses with **32** (Scheme 9).[77] The striking cytotoxicity of streptonigrin (**31**) initiated intense efforts for isolation of bioactive analogues leading to streptonigrone (**39**)[78] and lavendamycin (**40**)[79] (Figure 4).

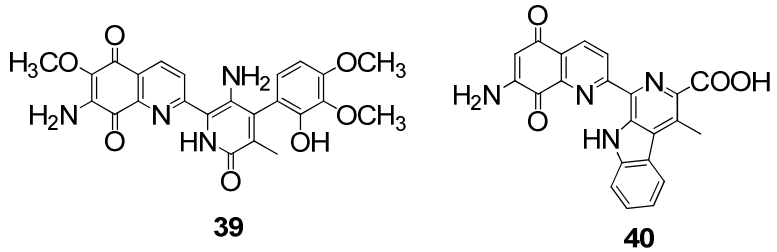
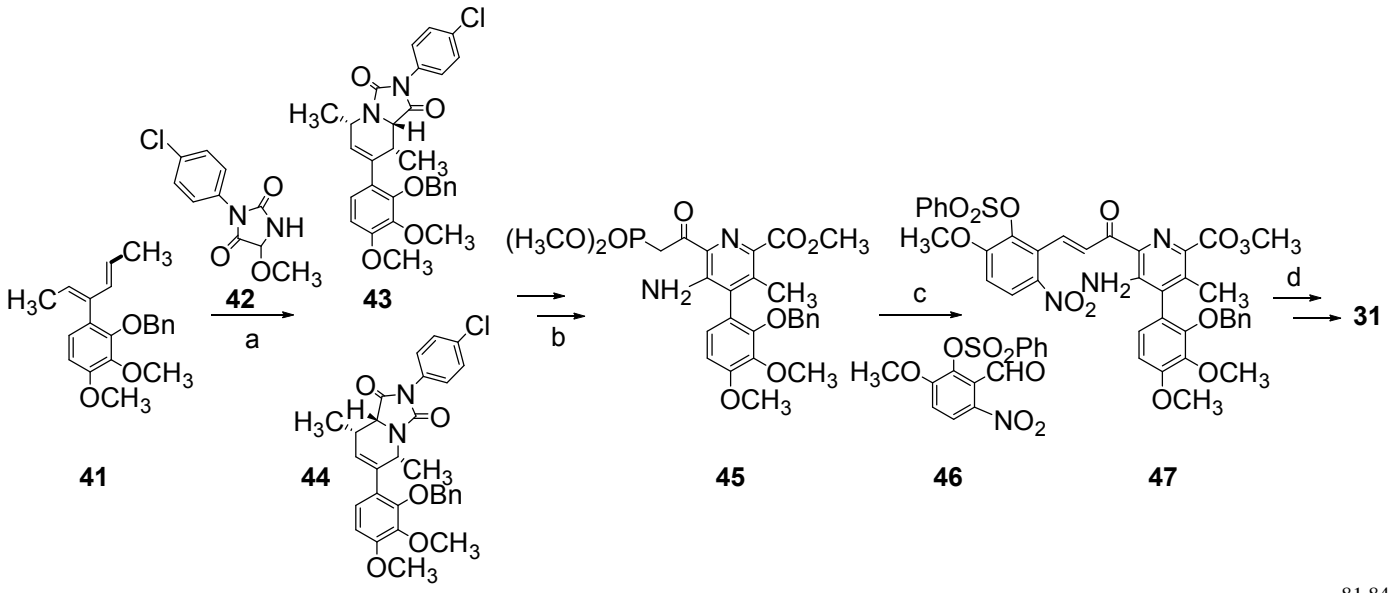


Figure 4. The structure of streptonigrin (**31**) analogues streptonigrone (**39**) and lavendamycin (**40**).

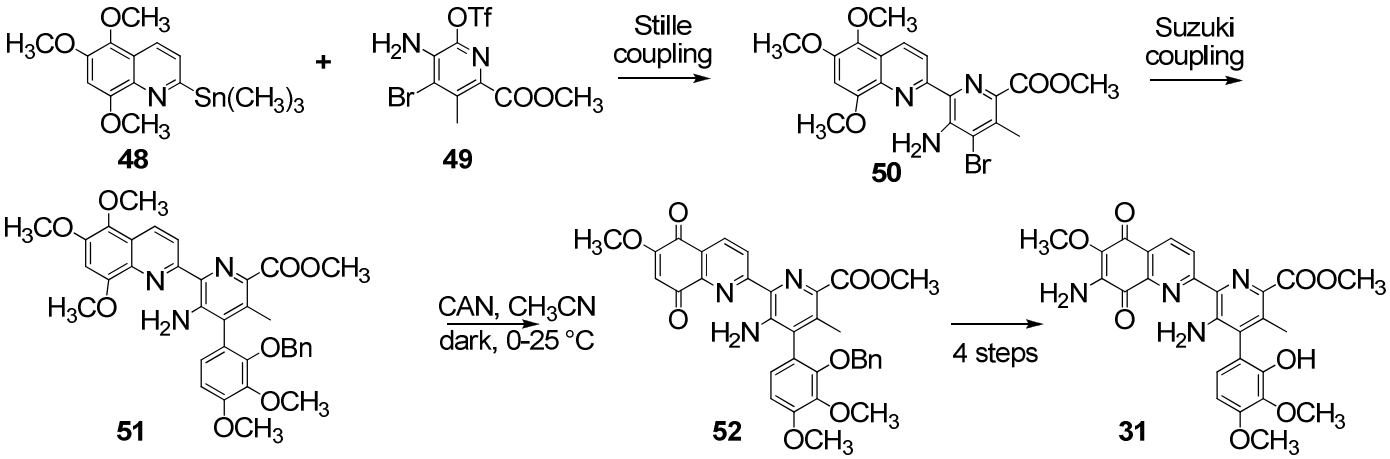
The sterically hindered biphenyl connection of streptonigrins is a challenging feature of their synthesis. The first route to streptonigrins was presented by Weinreb and co-workers in 1980[80,81] adopting a modified Friedländer reaction[82,83] to form the quinoline core (A/B-rings), followed by an imino-Diels-Alder reaction for construction of the C- and D-rings.[67,80,81] The C-ring was synthesized through a hetero Diels-Alder reaction of diene **41** and dienophile **42** providing regioisomers **43** and **44**, the last being undesired (Scheme 10), in 56% yield. Conversion of **43** to phosphonate ester **45** was achieved in several steps, followed by Horner- Wadsworth-Emmons condensation of **45** with aldehyde **46** to afford enone **47** in 80% yield.

Reduction of the nitro group triggered spontaneous cyclization to a quinoline establishing the tetracyclic core of **31**. Additional six synthetic steps yielded (±)-streptonigrin (**31**). Although a milestone in natural product synthesis, this approach is hampered by a large number of steps, lack of regioselectivity of the key Diels-Alder condensation of **41** and **42**, resulting in a low overall yield (10%).

Donohoe *et al.* achieved the total synthesis of (±)-streptonigrin (**31**) in an overall yield of 11% in fourteen linear steps (Scheme 11) utilizing transition metal-mediated cross coupling reactions for several of the critical reactions (2011).[85] Thus, Suzuki coupling was used for establishment of the biaryl system (C/D-rings), whereas Stille coupling for connection of the B and C rings. The C ring was formed *via* ring-closing metathesis by application of Hoveyda-Grubs second generation catalyst, followed by elimination and aromatization (Scheme 11). Compound **52** in this synthetic strategy is identical to a late stage intermediate of Weinreb's methodology. However, the authors provided a shorter and more efficient reaction route for the final steps (**52** to **31**) as compared to the original Weinreb approach, 50% and 17% yields, respectively. Importantly, this approach likely allows generation of a range of diverse synthetic analogues.



Scheme 10. The key steps of the total synthetic strategy of Weinreb *et al.* towards (±)-streptonigrin (**31**):[81,84] (a) xylene, reflux; (b) 17 steps; (c) KH, C_6H_6; (d) 8 steps.

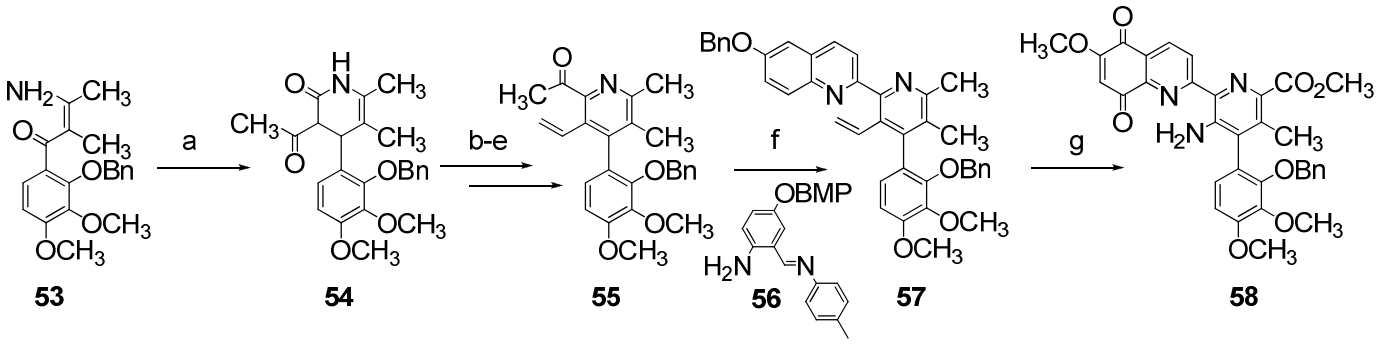


Scheme 11. The total synthetic strategy of Donohoe *et al.* applied Pd-mediated cross-couplings for connection of the B-C and C-D rings of streptonigrin (**31**). CAN=$(NH_4)_2Ce(NO_3)_6$.

In addition to the above two total syntheses, two previous formal synthesis of streptonigrin (**31**) were presented in 1981 and 1985. The formal synthesis of Kende stops five steps from the target, however, reaches this intermediate in a fewer number of steps.[86,87] In this protocol, the C/D rings were prepared by condensation of amino ketone **53** with methyl acetoacetate to afford pyridine **54**. The methyl ketone **55**

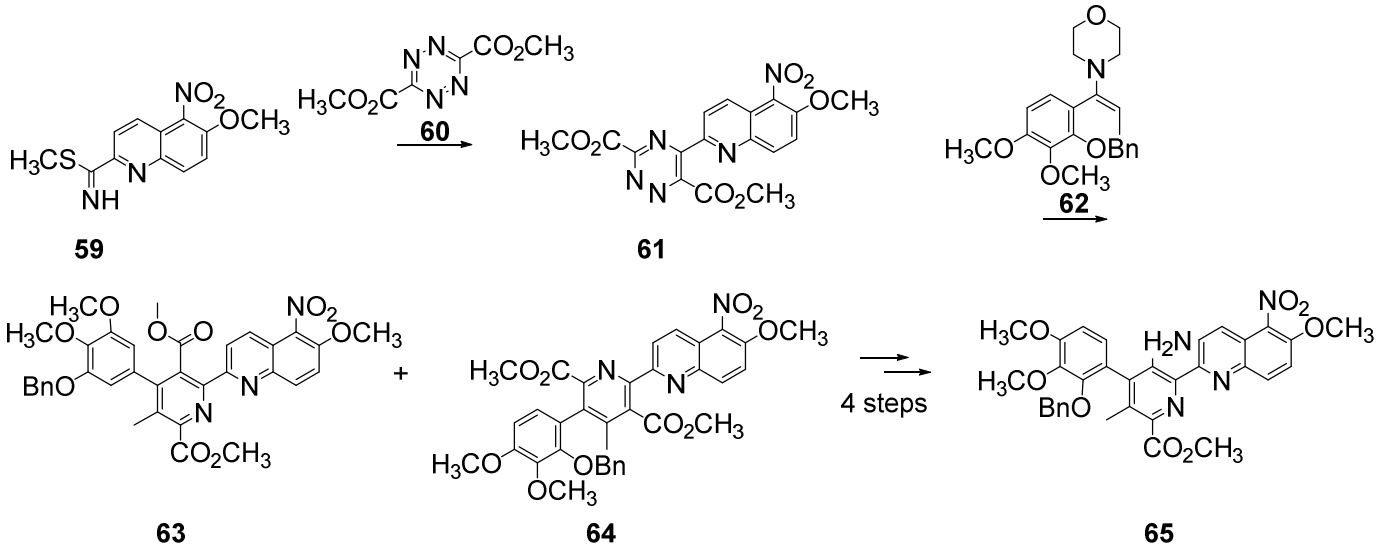
(Borsche adduct) was allowed to cyclize with amino imine **56** (A-ring precursor) to deliver quinolone **57** in high yield (96%, Scheme 12). Further eleven steps, mostly involving functionalization of the A ring, were required to convert **57** into **58**, an advanced intermediate towards streptonigrin (**31**). The synthesis is almost entirely linear and unfortunately does not allow easy generation of diverse analogues.

Boger *et al.* proposed a seven-step formal synthesis towards (±)-streptonigrin (**31**) relying on two successive imino Diels-Alder reactions for the preparation of its C ring (Scheme 13).[88–90] The key steps of this approach are two consecutive inverse electron demand Diels-Alder reactions and a subsequent *in situ* cycloreversion.



Scheme 12. The key steps of the Kende strategy towards (±)-streptonigrin (**31**): (a) $CH_3COCH_2COOCH_3$; (b) $NaBH_4$; (c) $PhPOCl_2$; (d) CuCN; (e) CH_3MgBr then H^+; (f) *t*-BuOK, *t*-BuOH, toluene; (g) 11 steps.

Thioimidate **59** was prepared from commercially available 6-methoxyquinoline and then forced to undergo Diels-Alder cycloaddition with 1,2,4,5-tetrazine-3,6-dicarboxylate (**60**) upon N_2 extrusion providing the 1,2,4-triazine **61** in 82% as a single regioisomer. Subsequent treatment of **61** with morpholino enamine **62** yielded a 1:1 mixture of the regioisomeric Diels-Alder adducts **63** and **64** in a combined 65% yield. The regioselectivity of this process is comparable to that reported by Weinreb regarding the construction of ring C. In four additional steps, compound **64** was elaborated to **65**, which has previously been converted to (±)-sterptonigrin (**31**) by Weinreb. The strength of Boger's strategy is the preparation of the A/B ring system prior to its attachment to ring C, providing a straightforward route to analogues.



Scheme 13. The key steps of the strategy of Boger *et al.* towards (±)-streptonigrin (**31**); a formal synthesis.

One limitation is the late stage conversion of the pyridine C-5 methyl ester of **64** into an amine as this requires differentiation of the two methyl esters on the same ring. Functionalized streptonigrin analogues were synthesized by Harding and co-workers[91] Despite existing syntheses, streptonigrin and its derivatives remain to draw significant synthetic interest.[67]

2.3. Isoquinolones

Isoquinolones belong to alkaloids isolated from *Streptomyces*,[92] marine sponges of the genus *Petrosia*,[93] and *Cribrochalina*[94] and bryozoans *Caulibugula intermis*[95] that have an oxidized bis(carbonyl)-isoquinoline backbone as the common structural motive.

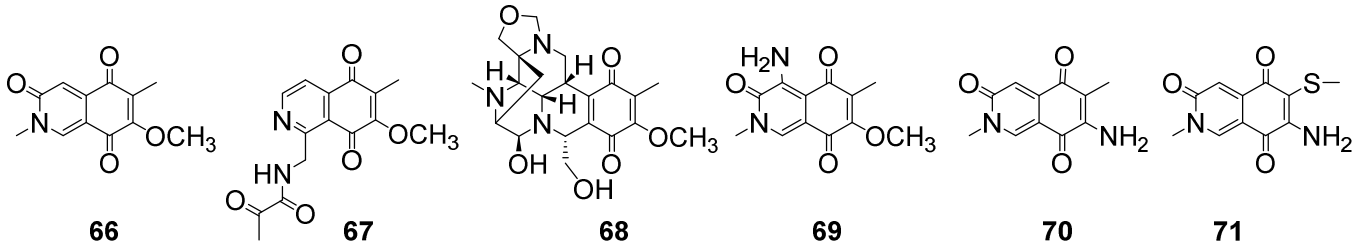


Figure 5. The structure of isoquinolones mimosamicyn (**66**), mimocine (**67**), naphthyridinomycin (**68**), 4-aminomimosamycin (**69**), 7-amino-7-demethoxymimosamycin (**70**) and perfragillin A (**71**).

2.3.1. Bioactivity

Isoquinolone quinones **66** and **67** (Figure 5) were isolated from the fermentation broth of *Streptomyces lavendulae*.[92] The antituberculotic mimosamycin (**66**) is the structurally simplest example of this group. Mimocine (**67**), a closely related antibiotic, showed high activity against *B. subtilis* and *C. alibicans*.[96] Naphthyridinomycin (**68**) is a broad spectrum antibiotic that inhibits DNA and RNA replication and is produced by *Streptomyces lusitanus*.[97] Mimosamycin (**66**) and its analogues 4-aminomimosamycin (**69**), 7-amino-7-demethoxymimosamycin (**70**) and perfragillin A (**71**) were identified in marine sponges of the genera *Reniera*,[98] *Petrosia*,[99] *Xestospongia*[100] and in the bryozoan *Membranipora perfragilis*.[100]

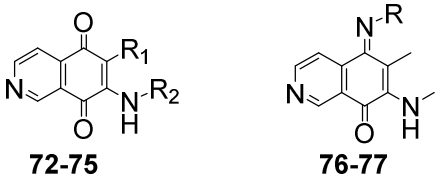
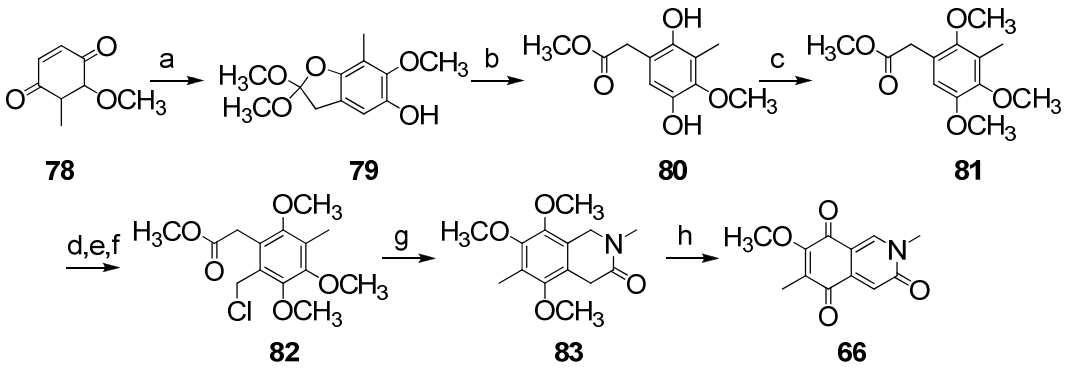


Figure 6. The structure of caulibugulones A (**72**, R_1=H, R_2=CH_3), B (**73**, R_1=Br, R_2=CH_3), C (**74**, R_1=Cl, R_2=CH_3), D (**75**, R_1=H, R_2=OC_2H_5), E (**76**, R=H) and F (**77**, R=CH_3).

Caulibugulones A–F (**72–77**, Figure 6) were isolated through bioactivity-directed fractionation of the marine bryozoan *Caulibugula intermis*.[101] The similar IC_{50}'s of **72–75** (0.22–0.34 μg/ml) indicated that halogen substitution at C-6 (**73**, **74**) is not necessary for the cytotoxicity of caulibugulones; however, ethoxy substitution (**75**) at this position causes a 5−10 fold reduced cytotoxicity.[102] Natural products of marine origin, which are often halogenated, have lately received increasing attention as they are expected to provide novel leads against multiresistant bacteria. More than 15000 marine natural products have been described so far and every year hundreds of new compounds are discovered, continuously providing challenges for structure elucidation and synthesis and novel leads for drug development.[103]

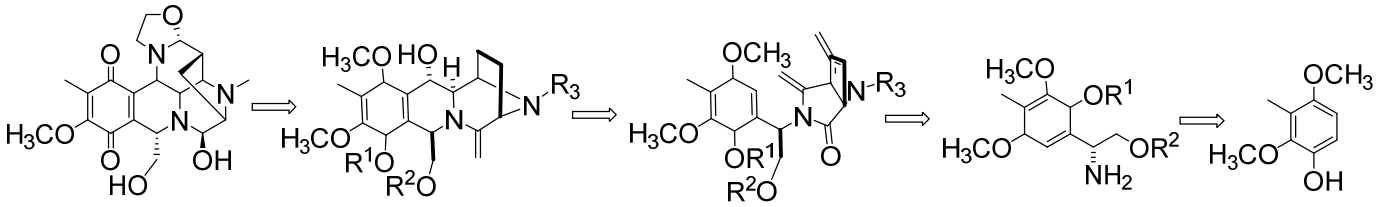
2.3.2. Total synthesis

Following the total synthesis of Fukumi *et al.* (1977) from 6-methyl-7-isoquinolinol in five steps and 80% overall yield,[104] a two-step synthesis of mimosamycin (**66**) was published by Mckillop and Brown in 1987 applying cycloaddition of 1,4-benzoquinone with 2-aza-bis(1,3-*t*-butyl-dimethylsiloxy)-1,3-butadine followed by hydrolytic work-up and *N*-alkylation.[105] An alternative eight-step synthetic route providing mimosamycin (**66**) in an overall yield of 13% was reported year 2000 by Kesteleyn and De Kimpe (Scheme 14).[106] 2-Methoxy-3-methyl-1,4-benzoquinone (**78**) was furnished by oxidation of 2-methylresorcinol-dimethyl ether with sodium dichromate. Following unsuccessful attempts for selective alkoxymethylation at its C-1 position, **78** was refluxed with keten dimethyl acetal to obtain **79** in 44% yield that could easily be separated from the rests of the starting material (52%). Hydrolysis of the *ortho*-ester led to the methoxycarbonylmethyl hydroquinone **80**, which was protected by methylation. Compound **81** was converted in three steps into the methyl [*o*-(chloromethyl)phenyl]acetate **82**, which was converted into lactam **83** using methylamine. This in turn could be converted into mimosamycin (**66**) using cerium(IV) ammonium nitrate in aqueous acetonitrile.



Scheme 14. The De Kimpe synthesis of **66**:[106] (a) $CH_2CH(OCH_3)_2$, toluene; (b) CH_3OH, reflux; (c) $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux; (d) $(CH_2O)_n$, $ZnCl_2$, CH_3COOH, HCl, rt; (e) K_2CO_3, acetone, reflux; (f) HCl, CH_3OH, rt; (g) CH_3NH_2, CH_3OH, rt; (h) cerium(IV) ammonium nitrate, CH_3CN, H_2O, 0 °C.

Its antitumour and antibiotic activity along with a comparably complex structure makes naphthyridino-mycin (**68**) to an attractive target for total synthesis. However, so far only two approaches towards a stable derivative of **68** were presented, by Evans *et al.* (1985)[107] and Fukuyama *et al.* (1986–87),[108–110] respectively. Recently, the Fukuyama group presented a new strategy,[111] with the strength that it considers the sensitivity of the hemiaminal and quinone moieties and introduces them first in a late stage of the pathway. A crucial step in the preparation of **68** is construction of its highly strained 3,8-diaza-bicyclo[3.2.1]octane framework. The tetracyclic diol **85** is a key intermediate of this route as it allows the establishment of the oxazolidine ring of **68** (Scheme 15). Intermediate **84** was constructed by stereoselective hydroboration of the *exo*-olefin of the tetracyclic intermediate following the formation of the B-ring of the target from **86**. The bicyclo[3.2.1]octane ring of enamide **86** was furnished *via* intramolecular Mizoroki-Heck reaction of arylglycinol **87**, which was prepared in six steps *via* a Mannich-type reaction of an electron-rich phenol **88** with a chiral precursor. Further work for conversion of **84** into **68** is in progress in the Fukuyama laboratory. There is a significant work carried out for the synthesis of related isoquinoline quinoid structures in the exploration of their structure-activity relationships in the context of cancer and antibiotics.[112]



Scheme 15. Retrosynthetic analysis towards (+)-naphthyridinomycin (**68**) according to Fukuyama.[111]

2.4. Kinamycins

Kinamycins A, B, C and D (**89**–**92**) were isolated from the fermentation broth of *Streptomyces murayamaensis* and were originally proposed to have a cyanobenzo[*b*]carbazolic structure.[113] Later it turned out that the two nitrogens of the compound are positioned in a diazo substituent connected to a benzo[*b*]fluorene ring system (Figure 7), and thus it is not heterocyclic;[114] however, for historic reasons, kinamycins are shortly discussed here. Originating from their antibiotic activity, kinamycins (**89**–**94**) raised significant academic and industrial interest.[113,115,116] Nevertheless, their tetracyclic skeleton encompassing four chiral centres along with a sensitive diazo group makes their chemical synthesis challenging. *Streptomyces murayamaensis* was early believed the only bacterium to produce kinamycins; however, later *Streptomyces saccharothrix*,[117] an unidentified actinomycete[118] and *Streptomyces chattanoogensi*s subsp. taitungensis[119] were observed to synthesize these metabolites as well. Interest in kinamycins is maintained mainly due to (1) their structural novelty, (2) their intriguing and yet poorly understood mode-of-action and (3) their unique biosynthetic pathways.

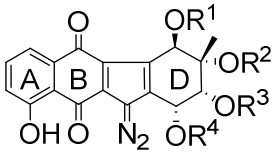


Figure 7. Kinamycins A (**89**, $R_{1–3}$=H, R_4=OAc), B (**90**, $R_{1,2,4}$=H, R_3=OAc), C (**91**, $R_{1,3,4}$=OAc, R_3=H), D (**92**, $R_{1,3}$=H, $R_{2,4}$=OAc), F (**93**, $R_{1–4}$=H) and J (**94**, $R_{1–4}$=OAc), isolated from *S. muraymaensis*.

2.4.1. Bioactivity

The antibiotic and antitumour activities of kinamycins was originally associated with their DNA crosslinking ability[120] and later on to the reactivity of their diazo functionality.[121,122] Jebaratnam proposed the formation of a radical intermediate triggered by endogenous oxidants resulting in oxidative DNA damage.[123] Nevertheless, close analogues were reported to show cytotoxicity even under reductive conditions.[124] As an alternative route, inhibition of DNA topoisomerase IIα was proposed. The fact that kinamycins do not seem to undergo crosslinking or intercalation with DNA suggests a different mechanism as compared to most other anticancer drugs. Dimitrienko proposed that the amino functionalities of guanine and adenine may act as nucleophiles towards the diazo group providing unstable triazenes that, upon decomposition, yield radicals, which in turn may cause DNA damage by depurination of the phosphodiesterase backbone.[125] Feldman and Estman suggested formation of a highly reactive sp^2 radical upon N_2 loss of kinamycin providing a species that is capable of attacking both electron-poor and -rich arenes and abstract hydrogen from DNA.[116] In a further study, Dimitrienko and Hasinoff[126,127] investigated the interaction of kanamycin F, proposed to be the bioactive form of all kinamycins, with glutathione yet

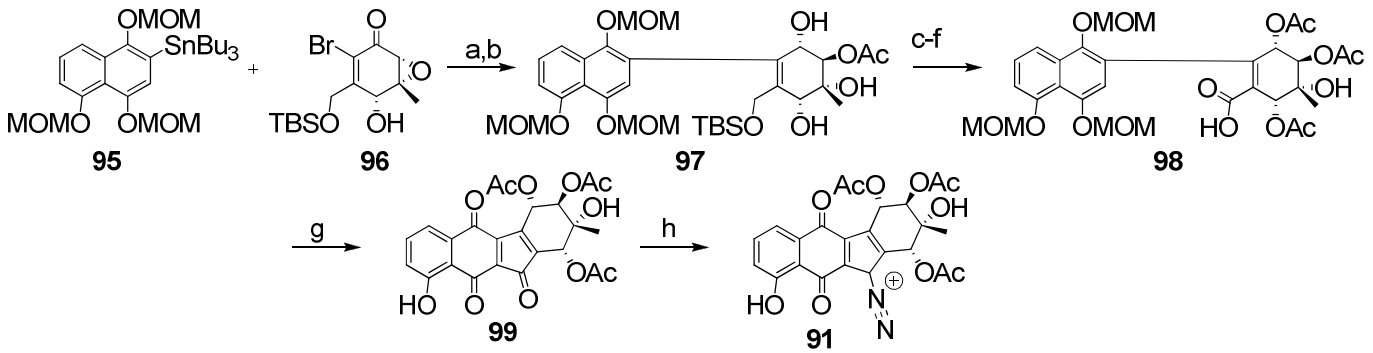
without being able to provide clear evidence for this proposal. Hence, the mechanism of action behind the antibacterial activity and cytotoxicity of kinamycins remains widely discussed.

2.4.2. Biosynthesis

Formation of the five-membered ring C and the reactive diazo group are the most intriguing biosynthetic features of kinamycins A-D (**89–92**). Gould and co-workers conducted feeding experiments on *Streptomyces murayamaensis* with isotope-labeled sodium acetate and various metabolite intermediates. The derived isotopes containing kinamycin C (**91**) and D (**92**) were subjected to NMR spectroscopic analysis to locate the distribution of isotopes.[128,129] The observed ^{13}C enrichment indicated that the skeleton of kinamycin is biosynthesized from acetate through the polyketide pathway. The oxygens at C-1, C-6 and C-7 were derived from acetate, whereas those at C-3, C-4 and C-11 from air (O_2) and that on C-2 from water. By feeding bacteria with either $CH_3{}^{13}COONa$ or $^{13}CH_3COONa$, Gould has proven that the "cyanamide carbon" of kinamycins is derived from acetate.[129] Despite the wide natural prevalence of N–N bonds, our current understanding of the biosynthetic formation of N_2 units is yet very limited and accordingly the biosynthetic pathway for the introduction of the second nitrogen of the diazo moiety of kinamycins remains unknown. A possible hydrazine-mediated pathway was suggested by enzymatic conversion of arylhydrazines to aryldiazonium salts.[130]

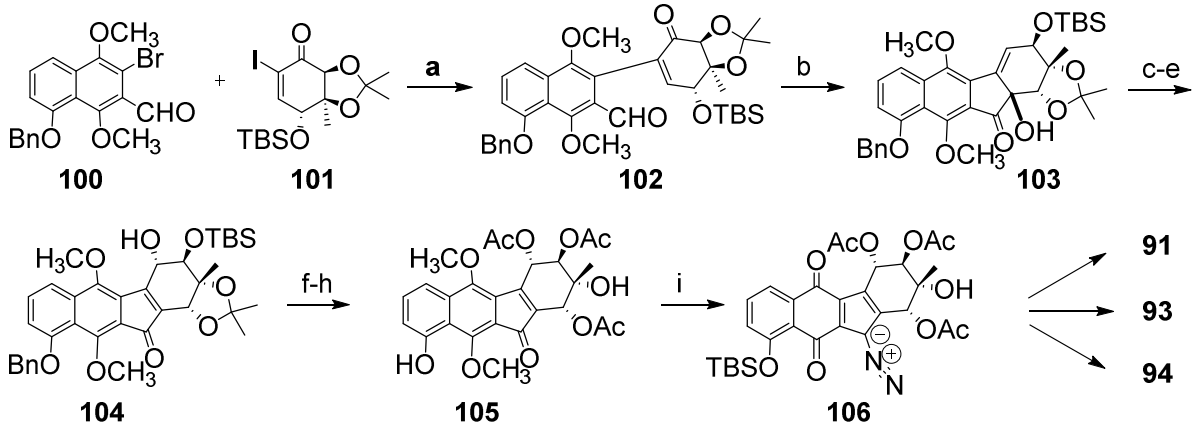
2.4.3. Total synthesis

Isolation of the first kinamycins in the early 1970s[113] did not trigger major synthetic efforts for almost twenty years. In 1990, the Dmitrienko group prepared *N*-cyanoindoles as model compounds for the synthesis of kinamycins,[131] considering them to be *N*-cyanobenzo[*b*]carbazoles. Structural revision of kinamycins in 1994[114,132,133] revealed their naturally rarely occurring benzo[*b*]fluorene skeleton connected to a diazo moiety, which insight initiated synthetic interest. The first synthesis of prekinamycin appeared in 1996.[134] Ishikawa *et al.*[135–137] achieved the regioselective construction of 4,8,9-tri oxygenated 2,3-dihydro-benz[*f*]indenone, the key intermediate in the total synthesis of kinamycin antibiotics, *via* intramolecular Friedel-Crafts acylation, followed by oxidation and Diels-Alder condensation using 4,7-dioxygenated indanone-type compounds as dienophiles. Lei and Porco performed the first enantioselective synthesis of (−)-kinamycin C (**91**) in 2006 utilizing a Friedel-Crafts acylation and a Stille coupling to assemble the central core of the molecule and a directed, asymmetric nucleophilic epoxidation to establish the stereochemistry of the D-ring (Scheme 16).[138]



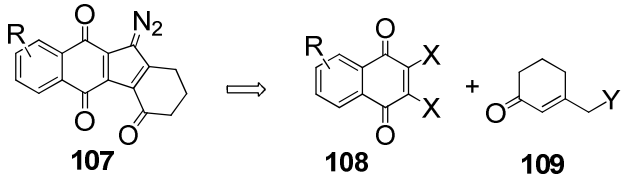
Scheme 16. Some of the key steps of the first stereoselective synthesis of kinamycin C (**91**); (a) $Pd_2(dba)_3$, $AsPh_3$; (b) Super-hydride, Ti(O*i*-Pr), *n*-Bu_4NOAc; (c) Ac_2O, pyridine; (d) Et_3N-3HF; (e) TPAP, NMO; (f) $NaClO_2$, NaH_2PO_4; (g) TFA; (h) CBr_4, then Pd/C, air; (i) TBSNHNHTBS, $Sc(OTf)_3$; (j) $PhIF_2$.[138]

The recently reported total synthesis of kinamycin C (**91**), F (**93**) and J (**94**) by Nicolaou *et al.* offers flexible route to this family of antitumour antibiotics through which structural analogues from a common congener can smoothly be established.[139] This strategy uses Ullmann coupling (step a) followed by a benzoin condensation (step b) as key steps for formation of the the pentacyclic C ring (Scheme 17). This strategy controls the stereochemistry of the D-ring through utilization of an enantiopure enone – in contrast to the Porco synthesis using asymmetric epoxidation – and installs the quinone and diazo moieties *via* cerium ammonium nitrate (CAN)-mediated oxidation.



Scheme 17. Synthesis of kinamycin C (**91**), F (**93**) and J (**94**) according to Nicolaou *et al.*:[139]
(a) $Pd_2(dba)_3$, CuI, Cu; (b) Et_3N, Rovis catalyst; (c) Ac_2O, Et_3N, SmI_2, CH_3OH; (d) Et_3N; (e) SeO_2; (f) HF, CAN; (g) Ac_2O; (h) Pd/C, H_2; (i) TBSCl, imidazole; (j)$TsNHNH_2$, aq. HCl; (k) $(NH_4)_2Ce(NO_3)_6$.

The strategy of Herzon and co-workers published year 2010 reaches kinamycin F (**93**) in twelve steps and allows generation of a variety of substituted diazofluorenes in three steps from a common precursor.[140] The retrosynthetic analysis for the construction of the C-ring of the diazofluorene core is shown in Scheme 18. The cyclization was performed in two steps: a tris(diethylamino)sulfonium trimethyldifluorosilicate-mediated 1,4-addition-elimination, followed by a Heck-type cross coupling.



Scheme 18. Retrosynthetic analysis of the formation of the five-membered ring of kinamycins by Herzon.[140]

2.5. Azaanthraquinones

Azaanthraquinones are heterocycles primarily produced by fungi and lichens. The first 1-azaanthraquinones **110–112** (Figure 8) along with bostrycoidin, fomazrine and isofomazarin were also isolated from the mycelium of *Pyrenochaeta terrestris*, the fungus responsible for the "pinkroot disease" of onions.[141] The azaanthraquinone scorpinone (**113**) was reported from *Amorosia littoralis*,[142] whereas marcanines A–E (**114–118**) from *Goniothalamus marcanii*.[143]

2.5.1. Bioactivity

Azaanthraquinones were reported to display phytotoxic,[144] antimicrobial effects against a variety of microorganism[145,146] and to inhibit cAMP phosphodiesterase.[147] Noppamas and co-workers reported[142] the

brine shrimp toxicity and human tumour cell toxicity assay guided isolation of marcanines (Figure 8),[143] a novel series of 1-azaanthraquinones, that showed high cytotoxicity against the human tumour cell lines A-549, HT-29, MCF7, RPMI and U251 (ED_{50} 0.04-3.03μM).

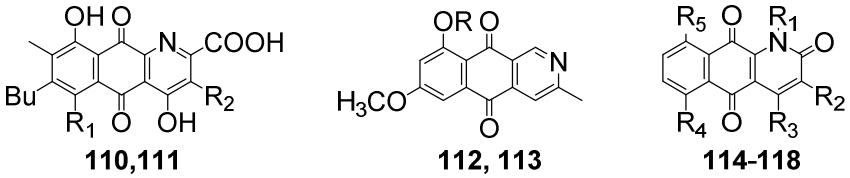
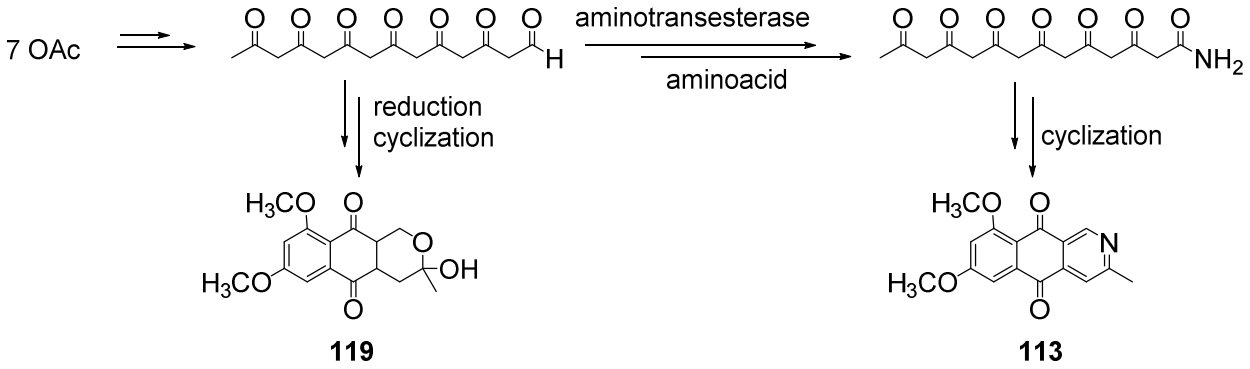


Figure 8. 1-Azaanthraquinones (**110–112**), scorpinone (**113**) and marcanines (**113–116**). For **110** R_1=OH and R_2=H, for **111** R_1=H, and R_2=OH, **112** R=H, **113** R=OCH_3. For marcanine A (**114**) $R_{1,2,4,5}$=H and R_3=CH_3; B (**115**) $R_{1,3}$=CH_3, R_2=OCH_3, $R_{4,5}$=H; C (**116**) R_1=CH_3, R_2=OCH_3, R_3=CH_2OH, R_4, R_5=H; D (**117**) R_1, R_5=H, R_2=OCH_3, R_3=CH_3, R_4=OH; E (**118**) R_{1-3}=CH_3, R_2=OCH_3, R_4=H and R_5=OH.

2.5.2. Biosynthesis

Nitrogen incorporation into a heptaketide intermediate by an aminotransferase utilizing amino acids as nitrogen source was proposed to be a likely biosynthetic route towards the nitrogeneous heterocyclic ring of scorpinone (**113**, Scheme 19).[148,149] For 1-azaanthraquinones the shikimate-acetate pathway was proposed by Goulart[150] and Arango and co-workers.[151]



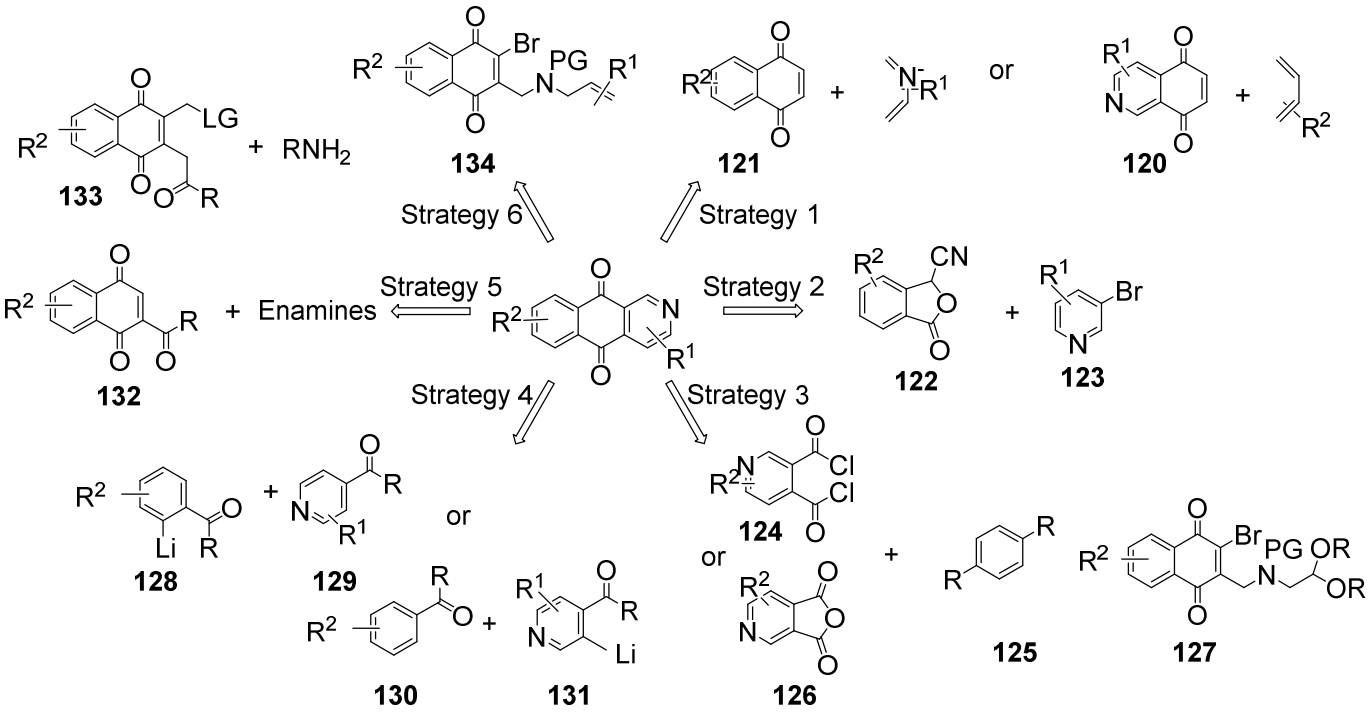
Scheme 19. Biosynthesis of 2-azaanthraquinones by enzymatic nitrogen incorporation.

2.5.3. Total synthesis

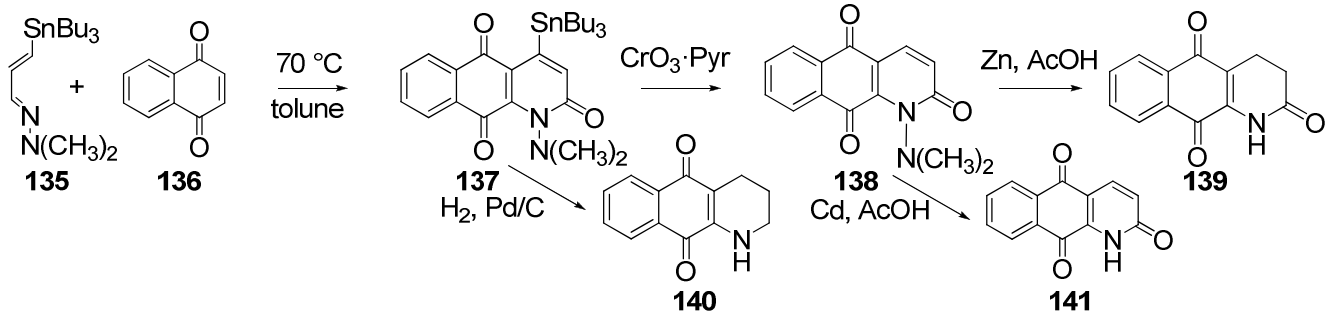
The available approaches towards 2-azaanthraquinones can be grouped into six general strategies[152] (Scheme 20): (1) those based on the Diels-Alder reaction of isoquinoline-5,8-diones (**120**) or 1,4-naphtho-quinones (**121**) with suitable 1,3-dienes and 2-aza-1,3-dienes, respectively;[153] (2) methods utilizing phthalide-annulation of cyanophthalide (**122**) and 3-bromopyridines (**123**);[154] (3) strategies making use of Friedel-Crafts reaction of an acid chloride (**124**) or acid anhydride (**125**) with 1,4-disubstituted benzenes (**126**) along with Friedel-Crafts-type intramolecular cyclization of a suitably functionalized 1,4-naphtho-quinone (**127**);[155] (4) routes using *ortho*-lithiation by reaction of lithiated aromatic amides (**128**) and pyridines (**129**) with suitable electrophiles (**130**, **131**);[156] (5) the biomimetic approach, *i.e.* addition of NH_3, primary amines or enamines to functionalize naphthoquinones (**132**, **133**) and subsequent intramolecular ring closure;[157] (6) syntheses based on intramolecular Heck reaction of 1,4-naphthoquinones (**134**).[158]

Numerous additional structurally closely related quinones were synthesized over the past decades. For example, as part of a total synthesis of the antitumour agent lavendamycin, Behforouz *et al.* prepared a series

of 7-*N*-substituted quinoline-5,8-diones from 8-hydroxy-2-methylquinoline.[159,160] 1-Azaanthraquinones were also prepared by aza-Diels-Alder reaction of 4-stannyl-1-azabutadienes with benzo-1,4-quinones,[161] followed by selective oxidation proceeding with allylic inversion (Scheme 21).



Scheme 20. Overview of the synthetic approaches towards 2-azaanthraquinones (PG=protecting group).



Scheme 21. Synthesis of 7-*N*-substituted quinoline-5,8-diones (**139–141**).[161]

2.6. Secobatzellines

Halogenated indole-4,7-quinones secobatzelline A (**142**) and B (**143**) (Figure 9), likely precursors for pyrroloiminoquinone alkaloids, were isolated from a deep-water marine sponge of the genus *Batzella*.[162]

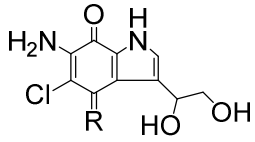


Figure 9. The structure of secobatzellines A (**142**, R=NH) and B (**143**, R=O).

2.6.1. Bioactivity

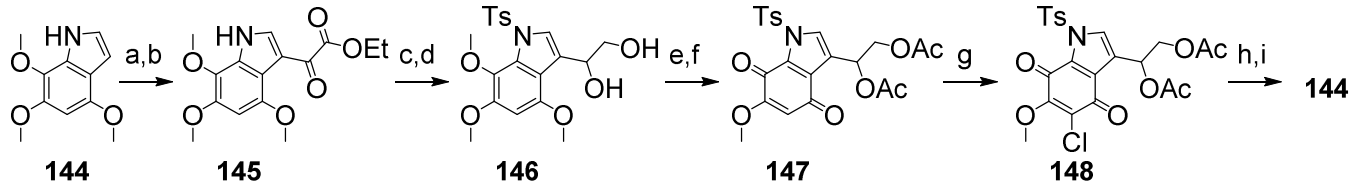
Secobatzellines A (**142**) and B (**143**) exhibited *in vitro* cytotoxicity against the murine P-388 tumour cell line (IC_{50}=0.06 and 1.22 μg/mL) and against the human lung carcinoma A-549 cell line (IC_{50}=0.04 and

2.86 μg/mL). Their diacetates showed somewhat lower antiproliferative activities (IC_{50}=1.22 and 3.83 μg/mL (P-388) and IC_{50}=2.68 and 4.68 μg/mL (A-549).[162] Moreover, they inhibit the phosphatase activity of calcineurin, a principal regulator of human immune response.[163]

2.6.2. Total synthesis

Shinkre and Velu proposed an eight-step strategy for production of secobatzelline B (**143**) from 4,6,7-trimethoxyindole (**144**),[163] which can be achieved in three steps from commercially available 2,4,5-trimethoxy-benzadehyde.[164] The key features of this route are formation of the indole-3-glyoxalyl chloride (a, Scheme 22), the one-step-reduction of indole-3-glyoxalic ester **146** with $LiAlH_4$, the $(NH_4)_2Ce(NO_3)_6$-mediated oxidation of **146** to **147** and its regioselective chlorination with a mixture of NaCl and oxone.

Whereas a large number of nitrogenous quinones were studied, so far only a few have reached clinical evaluation. Unfortunately most quinones showing promising bioactivities *in vitro* turned out to be ineffective *in vivo*, indicating the remaining lack of understanding of their mechanism of action and pharmakokinetics. The large structural heterogeneity of this group makes it likely that several different mechanisms play role in the antibacterial and antiteratogenic activity of nitrogen containing heterocyclic quinones.



Scheme 22. The total synthesis of secobatzelline B (**144**):[163] (a) $(COCl)_2$, Et_2O; (b) EtOH; (c) KH, Ts_2, THF; (d) $LiAlH_4$, Et_2O, THF; (e) Ac_2O, Et_3N, DMAP, DCM; (f) $(NH_4)_2Ce(NO_3)_6$, *n*-Bu_4NHSO_4, DCM; (g) NaCl, oxone, EtOAc, H_2O; (h) NH_4OH, EtOH; (i) NaOMe, CH_3OH.

3. Oxygen containing heterocyclic quinones

3.1. Pyranonaphthoquinones

Pyranonaphthoquinones are common secondary metabolites in a variety of bacteria, fungi and plants species. This family, also referred to as benzoisochromane quinones, commonly exists in nature as monomers, dimers and their glycosylated derivatives and was reviewed by Brimble in 1999 and 2008.[165,166]

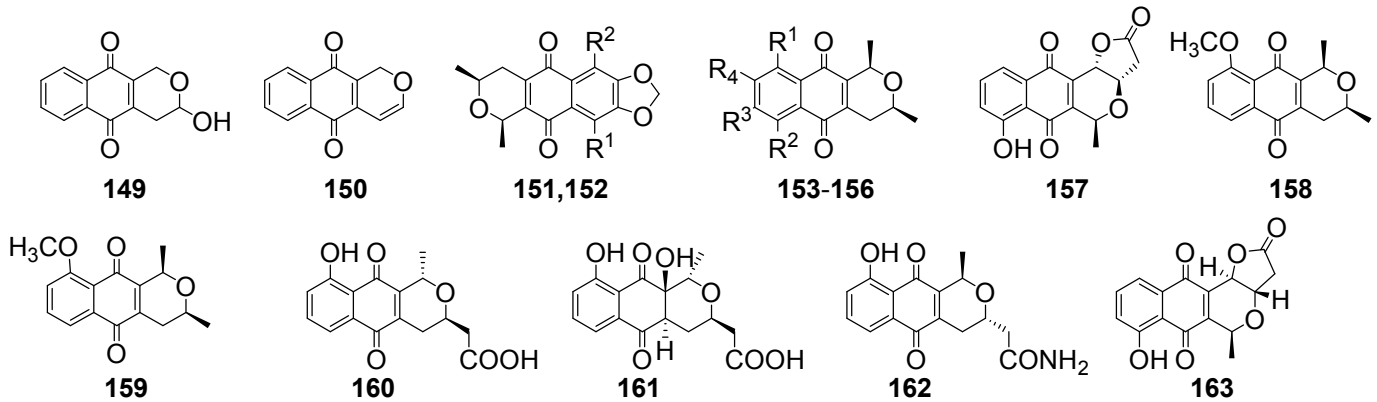


Figure 10. The structures of pyranonaphtoquinones psychorubrin (**149**), pentalongin (**150**) ventiloquinones A (**151**, $R_{1,2}$=OH), B (**152**, $R_{1,2}$=OCH_3) C (**153**, R_{1-3}=OH, R_4=OCH_3), D (**154**, $R_{1,2}$=OH, $R_{3,4}$=OCH_3), E (**155**, R_{1-4}=OCH_3), and L (**156**, R_1=OH, $R_{2,4}$=H, R_3=OCH_3), kalafungin (**157**), eleutherin (**158**), ventiloquinone L (**159**) and nanaomycines A (**160**), B (**161**), C (**162**) and D (**163**).

3.1.1. Bioactivity

The simplest naturally occurring member of this compound class is pyschorubrin (**149**, Figure 10). It was first isolated from the chloroform extract of *Psychorubria rubra*[167] and was shown to possess inhibitory activity against KB cells (ED_{50}=3.0 μg/mL). Promising antimalarial property of pyranonapthaquinones, pyschorubrin (**149**) and pentalongin (**150**) isolated from *Pentas longiflora*, was reported (EC_{50}<1 μg/mL, D6 and W2 clones of *P. falciparum*).[168] Ventiloquinones (Figure 10) were isolated from the acetone extracts of the root bark of *V. maderaspatana* and *V. calyculata*[169] and from *V. goughii*.[170] Additional antibiotic pyranonaphthoquinones kalafungin (**157**),[171] eleutherin (**158**),[172,173] ventiloquinone L (**159**).[170] Nanaomycines A-D (**160–163**) were isolated from *Streptomyces rosa*[174] and were demonstrated to exhibit inhibitory activity against mycoplasma, fungi and gram-positive bacteria. In addition, nanaomycine A (**160**) was found to inhibit platelet aggregation agent.[175]

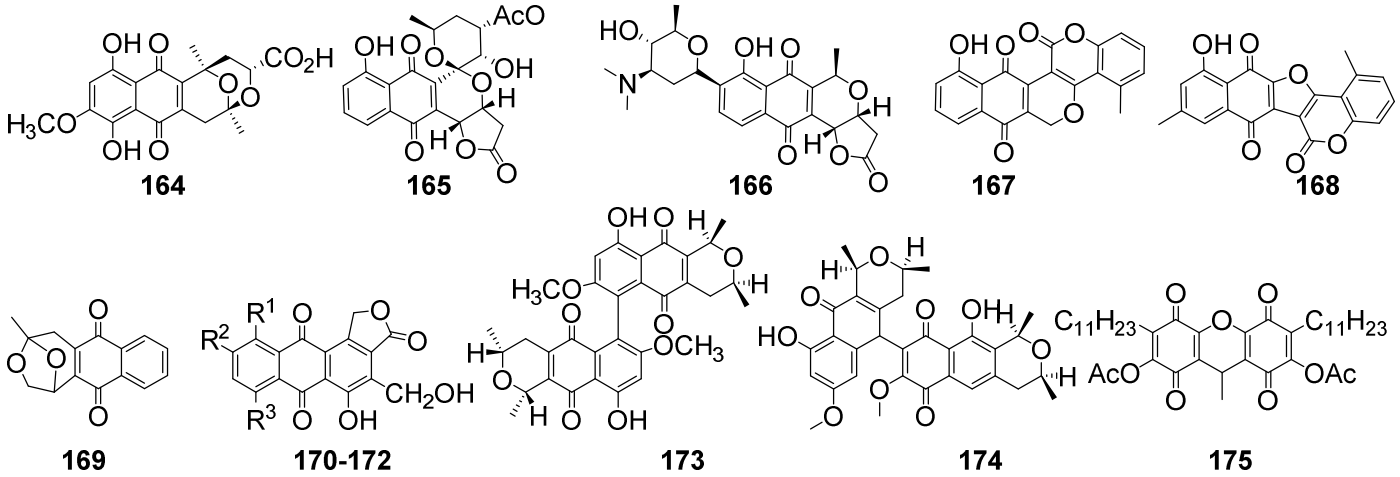


Figure 11. Pyranonaphtoquinones marticin (**164**), griseusin A (**165**), medermycin (**166**), cyclocanaliculatin (**167**), crassiflorone (**168**), isagarin (**169**), araliolactones (**170–172**, where R_{1-3}=OH, OCH_3, OAc), actinorhodins (**173**, **174**) and methylanhydrovilangin (**175**).

Structurally complex members of this family are marticin (**164**), griseusin A (**165**) and medermycin (**166**) (Figure 11), for example, which contain sugar derived hetrocyclic rings attached to the pyranonaphthoquinone skeleton,[166,176] Spironaphthoquinone griseusins, deacetylgriseusins and 2a,8a-epoxy-*epi*-deacetylgriseusin B isolated from the extract of *Nocardiopsis* were shown to show promising anticancer activities.[177] Pentacyclic quinones cyclocanaliculatin (**167**) and crassiflorone (**168**) were isolated from the Cameroonian medicinal plant *Diospyros crassiflora*.[178] Crassiflorone (**169**) was reported to possess antimicrobial activity.[179] Isagarin (**169**), reported from the East African medicinal plant *Pentas longiflora* is in use against scabies and mycosis.[180] Unusual araliolactones (**170–172**) were isolated from *Araliorhamnus vaginata* and *A. punctata* (Rhamnaceae).[181] Dimeric pyranonaphtoquinones actinorhodins **173** and **174** were reported to have antibiotic activity.[165] Additional dimeric quinones methylanhydrovilangin was reported from *M. Africana*[182] and is used in traditional Chinese medicine.

Hydroxylated quinones have high naturally abundance with structures ranging from lawsone (**176**), utilized in sunscreens, to more complex structures such as the antiplasmodial xylariaquinone A (**177**), isolated from the endophytic fungus *Xylaria sp.* and trimeric hydroxynaphthoquinone conocurvone (**178**),[183] which possess anti-HIV activity (Figure 12).[184] The chemistry of hydroxylated quinones was reviewed by Spyroudis.[185] Busseihydroquinone A (**179**) along with its prenylated derivatives (**180–183**) isolated from the

roots of *Pentas bussei* showed marginal cytotoxicity and antiplasmodial activity (Figure 13).[186] The naphthoquinones of *Rhinacantus nasutus* were reported to show promising antiproliferative activities against a variety of cancer cells (KB, Hep-2, MCF-7, HepG2, HeLa, SiHa, C-32, LLC, Colon-26, P388).[187,188]

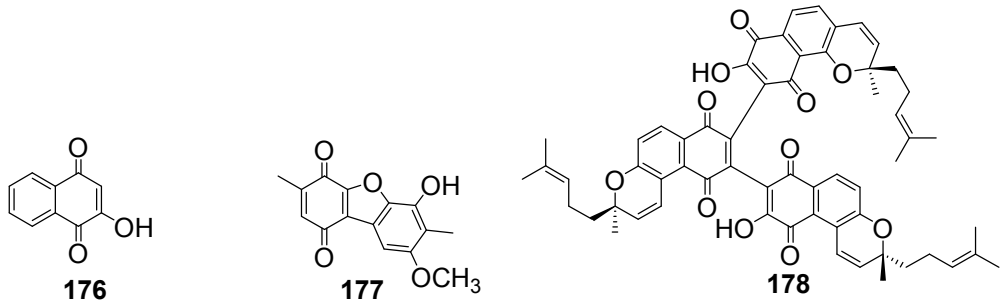


Figure 12. Lawsone (**176**), xylariaquinone A (**177**) and conocurvone (**178**).

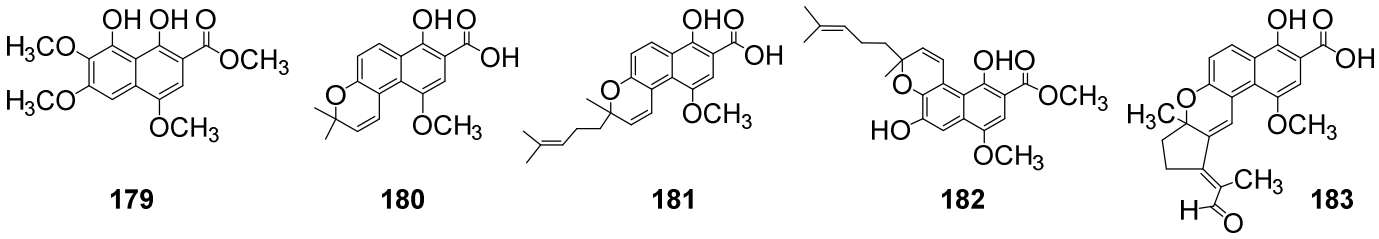


Figure 13. Naphthohydroquinones of *P. bussei*: busseihydroquinones A–D (**179–182**) and **183**.

Recently isolated griseusin analogue 3'-*O*-α-D-phorosaminyl-(+)-griseusin A (**184**, Figure 14) shows moderate activity against gram-positive bacteria.[189]

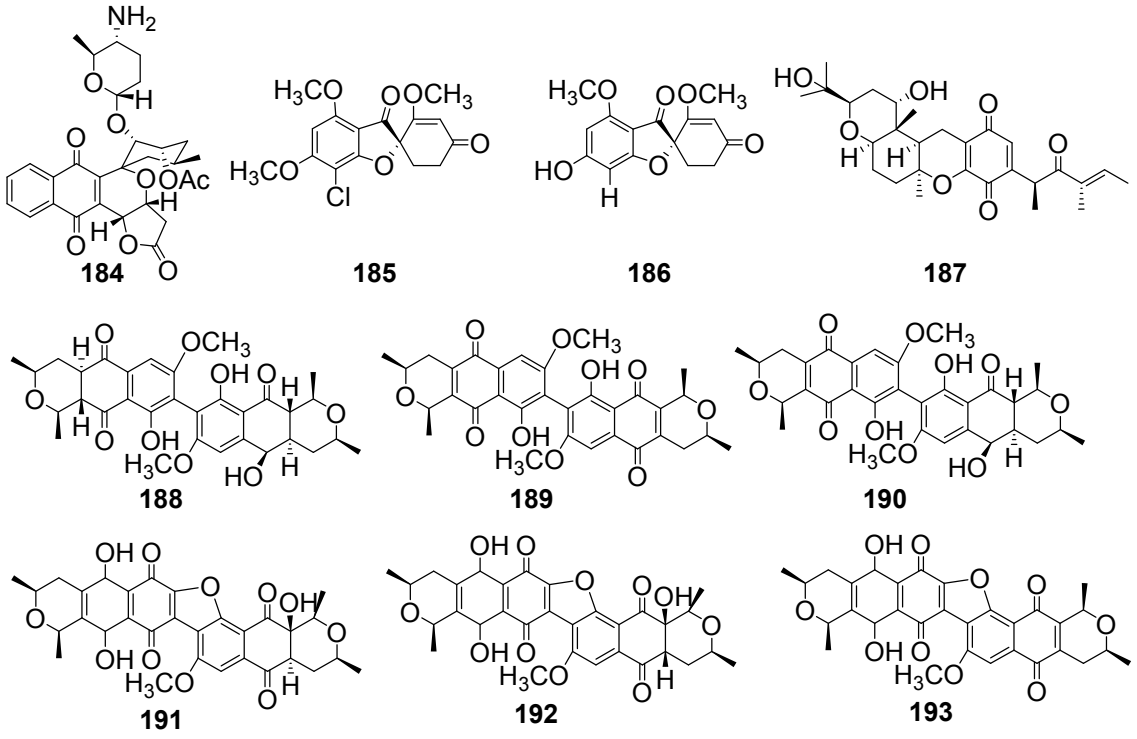


Figure 14. 3'-*o*-α-D-Forosaminyl-(+)-griseusin A (**184**), 6'-griseofulvin (**185**), 6-*O*-desmethyldechloro-griseofulvin (**186**), 2,3-didehydro-19α-hydroxy-14-epicochlioquinone B (**187**), cardinalins 1–6 (**188–193**).

Additional antibacterial griseofulvin derivatives (**185**, **186**) were reported from *Nigrospora* sp. MA75, an endophytic fungus obtained from the marine semi- mangrove plant *Pongamia pinnata*.[190] Cardianalins 1-6 isolated from *Dermocybe Cardinalis* in the mid 90's represent the first class of pyranonaphtoquinones discovered in higher order fungi. They showed promising cytotoxicity against murine leukemia, in which the tetrahydropyrane was proposed to play significant role.[191]

The quinones (**194**, **195**, Figure 15) isolated from the marine hydroid *Garveia annulata* were reported to inhibit indoleamin 2,3-deoxygenase.[192] Dialpachone (**196**) and adenophyllone (**197**) were isolated from *Heterophragma adenophyllum*, a tree common in Southeast Asia and Africa and traditionally used against viper bite and various skin diseases.[193] Anti-HIV dactyloquinones (**198–200**) were reported from *Dactylospongia elegans*.[194]

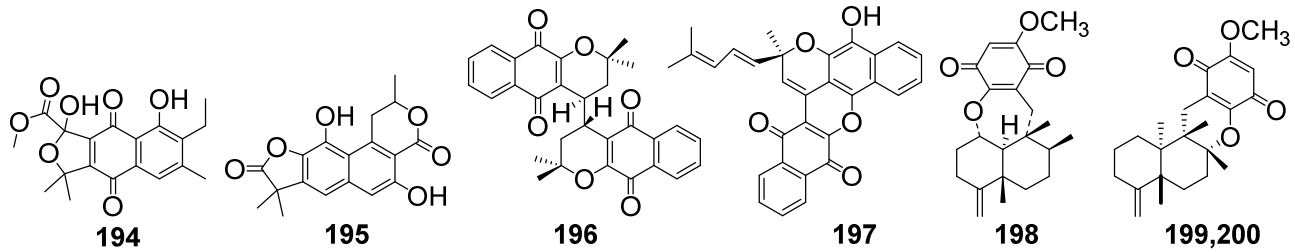
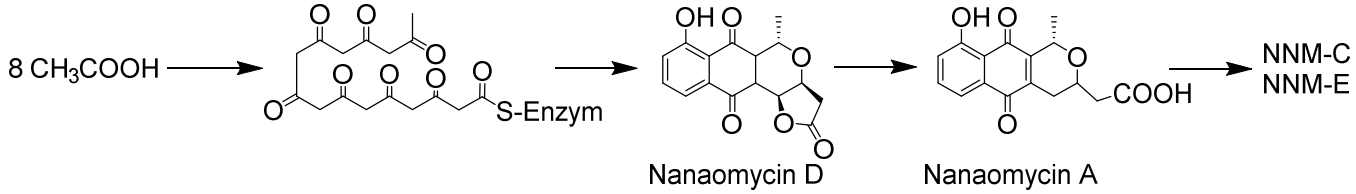


Figure 15. The structures of the quinones annulin A (**194**) and garvin C (**195**) of *Garveia annulata*, dialpachone (**196**) and adenophyllone (**197**) of *Heterophragma adenophyllum* and dactyloquinone C (**198**), D (**199**, 5-β-Me) and E (**200**, 5-α-Me) of *Dactylospongia elegans*.

3.1.2. Biosynthesis

The biosynthesis of bacterial pyranonaphtoquinones is to date believed to follow the polyketide pathway, thus the benzoquinone skeleton is built up from acetate/malonate units. Studies of the biosynthetic relationship of nanaomycines (NNMs) with cerulenin, a specific inhibitor of fatty acid and polyketide biosyntheses, revealed that the biosynthesis follows the nanaomycin D → nanaomycin A → nanaomycin E → nanaomycin B sequence (Scheme 23).[195] Similar studies of kalafungins using cerulenin supported the suggestion of their generation *via* the polyketide pathway.[196]

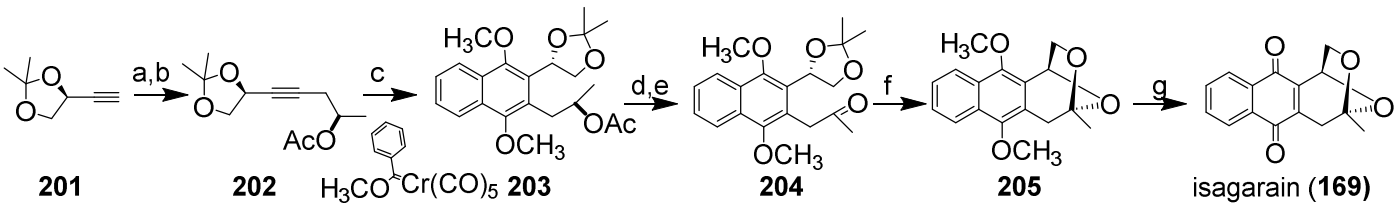


Scheme 23. The biosynthesis of nanaomycines. The first steps are common for pyranonaphtoquinones. Cyclization proceeds by linear head to tail condensation of the starter acetate and six malonates.

3.1.3. Total synthesis

Carbohydrates are frequently used sources for chiral natural products,[197] as also demonstrated by selected examples of total synthetic approaches of naphtohydroquinones. Concise enantioselective synthesis of (−)-isagarin (**169**, Figure 10) was completed in seven steps with 39.6% overall yield using Dötz benzannulation (step c, Scheme 24) and intramolecular stereospecific dioxabicyclic ketal formation as key steps.[198] The starting material **202** is available in two steps from mannitol following literature procedures.

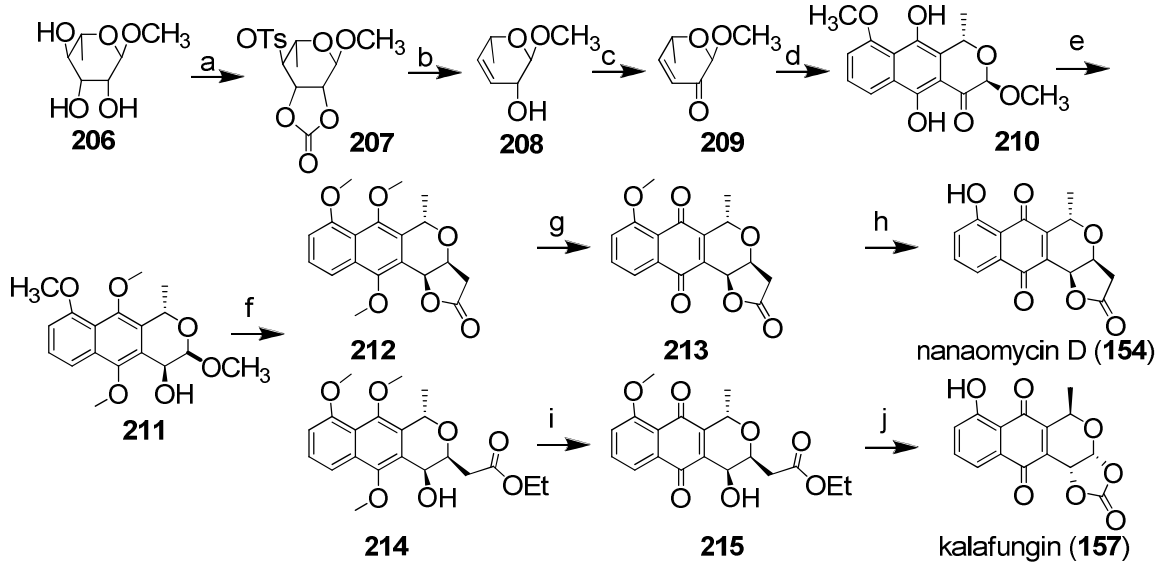
The total synthesis of kalafungin (**157**) was reported by Kraus and co-workers using a regioselective Diels-Alder reaction as a key step.[199]



Scheme 24. Stereoselective synthesis of (−)-isagarin (**168**). (a) BuLi, THF, then BF_3OEt, propyleneoxide, −78 °C; (b) Et_3N, DMAP, Ac_2O, rt; (c) THF, 45 °C, 6 h, then 0 °C, NaH, CH_3I, 0 °C; (d) DIBAL-H, DCM, 0°C; (e) IBX, EtOAc, reflux; (f) *p*-TsOH, C_6H_6, reflux; (g) $(NH_4)_2Ce(NO_3)_6$, H_2O/CH_3CN, rt.[198]

The synthesis of nanaomycin D (**154**) and kalafungin (**157**) was later achieved from a carbohydrate abundant source, methyl *L*-rhamnoside (**206**), using Michael-Dieckmann condensation (step d, Scheme 25) as a key step. The Wittig reaction in step f simultaneously affords lactone **212** and the corresponding ester **214**. The acidic isomerization of **215** provides the enantiodivergency of this synthetic strategy.[197]

The main challenge of the synthesis of spiroketal quinones is avoidance of benzoquinone formation in the spiroketalization step. Kozlowski *et al.* explored alternative strategies for spiroketalization leading to the assembly of the core of rubromycines, demonstrated on the example of purpuromycins (Figure 16).[200,201]



Scheme 25. Total syntheses of nanaomycin D (**154**) and kalafungin (**157**) following the Tatsuta protocol: (a) $ClCO_2CCl_3$, then TsCl, pyridine; (b) Zn, NaI; (c) PCC, DCM; (d) *t*-BuOLi, isobenzofuranone; (e) 3 steps; (f) Ph_3P=CHCOOEt; (g) $(NH_4)_2Ce(NO_3)_6$; (h) $AlCl_3$; (i) $(NH_4)_2Ce(NO_3)_6$ and then $AlCl_3$; (j) conc. H_2SO_4.[197]

Frenolicin B (**225**) was isolated from the culture broth of *actinomycete* (AM-3867). Its first total synthesis was reported by Kraus and co-workers.[202] This procedure followed a regioselective Diels-Alder reaction with complete regiocontrol providing **225** in 70% yield, as shown in Scheme 26.

Benzo- and/or naphtho[*c*]pyrans were frequently synthesized and studied, demonstrating the impact of the heterocyclic oxygen for bioactivity. Benzopyrans were prepared from 2-hydroxymethyl-3,6-di-methoxystyrenes by mercury-mediated oxidative ring closure and subsequent silver oxide-catalyzed oxidation.[203] Naphthoquinopyrans were prepared from benzopyrans by [4+2] cycloaddition using 1-acetoxybuta-1,3-diene (Scheme 27).[204]

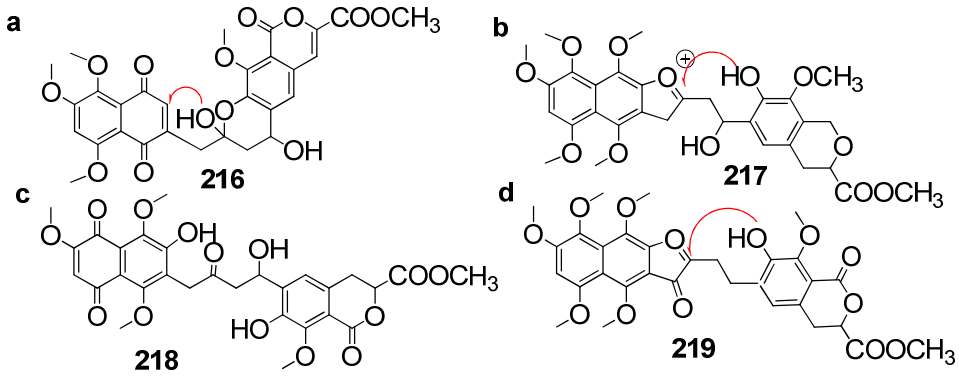
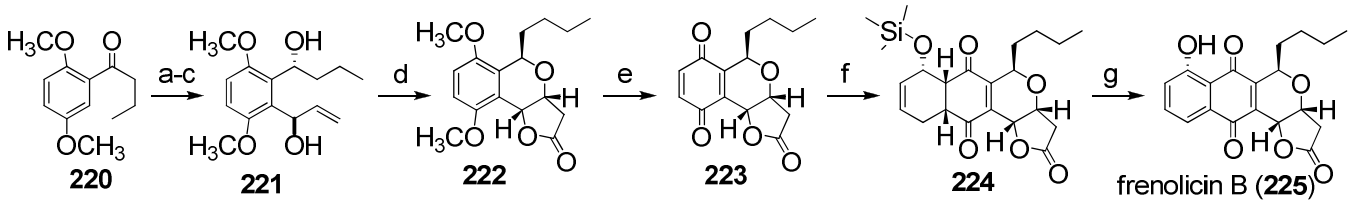
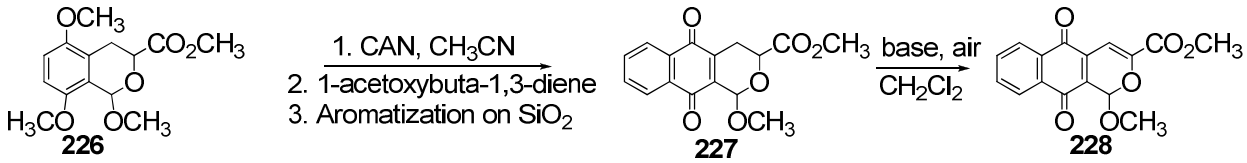


Figure 16. Spiroketalization strategies preventing benzofuran formation: spiroketalization (a) *via* hemiketal conjugate addition, (b) by removal of electron-withdrawing groups, (c) through lowering the nucleophilicity of the naphthalene, (d) by removal of benzylic protons.

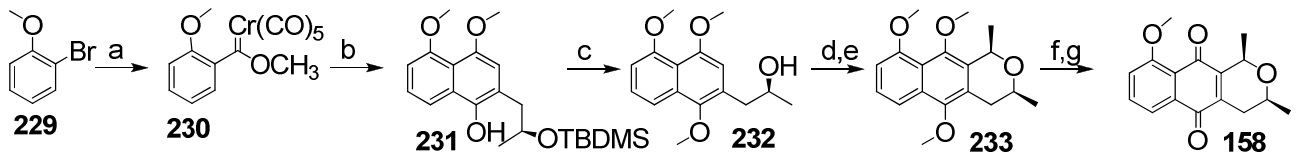


Scheme 26. The Kraus synthesis of frenolicin B (**225**): (a) (+)-Ipc$_2$BCl; (b) *n*-BuLi, 0 °C, rt; (c) acrolein, 78 °C; (d) $Pd(OAc)_2$, CO; (e) AgO, HNO_3; (f) $CH_2(CH)_2CHOTMS$, DCM, –78 °C; (g) CrO_3, H_2SO_4, acetone.[202]

Enantioselective synthesis of (+)-eleutherin (**158**) and (+)-allo-eleutherin was reported by Fernandes *et al.* in 8% overall yield.[205] The key steps of this strategy are Dötz annulation with a chiral alkyne (b) and an oxa-Pictet-Spengler reaction (f, Scheme 28). Stereoselective synthesis of (+)-ventiloquinone L (**159**) in seven steps with 13% overall yield was reported by Fernandes following similar strategy that was reported for (+)-eleutherin (**158**),[205] hence the key steps being Dötz benzannulation and oxa-Pictet-Spengler reactions.[206]



Scheme 27. Synthesis of naphthoquinopyran **228**; CAN=$(NH_4)_2Ce(NO_3)_6$.



Scheme 28. Synthesis of (+)-naphthoquinonepyran (**234**): (a) *n*-BuLi, THF, –78 °C, 5 min, then $Cr(CO)_6$ to 0 °C, then Me_3OBF_4, DCM, rt; (b) $CHCHCH_2CH(OTBDMS)CH_3$, THF, 45 °C; (c) TBAF, THF; (d) NaH, MeI, DMF, 0 °C to rt; (e) TBAF, THF; (f) $(CH_3O)_2CHCH_3$, BF_3OEt_2, THF/Et_2O; (g) $(NH_4)_2Ce(NO_3)_6$, CH_3CN/H_2O.

3.2. Furanonaphthoquinones

Numerous natural and synthetic naphthoquinones are known to be potent antitumour,[207] molluscicidal,[208] leischmanicidal,[209] antiinflammatory[210] tripanocidal,[211] antibacterial[212] and anti-

tubercular[213] agents. Herbal furanonaphthoquinones have attracted increasing attention in recent years as several compounds of this class having naphtho[2,3-*b*]furan-4,9-dione and naphtho[1,2-*b*]furan-4,5-dione skeletons have interesting biological activities.[214] Substituted naphtho[2,3-*b*]-furan-4,9-diones were reported to have higher cytotoxic activity and the activity varies with the type of substituent on parent naphtho[2,3-*b*]-furan-4,9-dione.[215]

3.2.1. Bioactivity

Antifungal (*Candida*) anthrinones were reported from Cercphora sordariodes (Figure 17).[216] Ceradrin (**234**) and its derivatives (**235**, **236**) were also reported from *Monosporascus cannonballus*.[217]

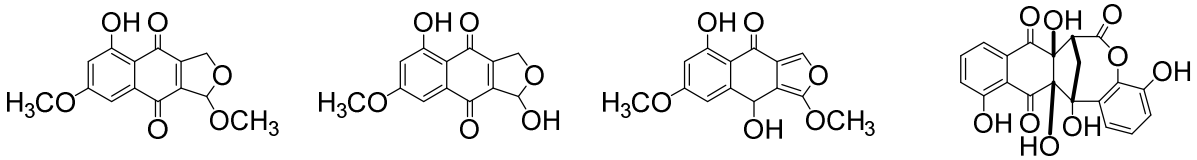


Figure 17. The structure of ceradrin (**234**), demethylceradrin (**235**), monosporascol (**236**) and engelharquinonol (**237**).

Engelharquinonol (**237**) was isolated from the antituberculotic extract of *Engelhardia roxburghian*. Oxygenated quinones discovered before the 1990's were previously reviewed in detail.[165,166] Herbal naphtho[2,3-*b*]furan-4,9-diones (**238–241**) showed promising antiproliferative activities (Figure 18).[218] 2-Acetylnaphtho[2,3-*b*]furan-4,9-dione **238** isolated from *Tabebuia cassinoides* (Lam.) (Bignoniaceae) shows significant cytotoxic activity;[218] however, three times lower than the closely related 2-methyl-naphtho[2,3-*b*]furan-4,9-dione.[219] The cytotoxicity of naphtho[2,3-*b*]furan-4,9-diones depends on their 2-substituent. Compounds **238–241** showed activity within range of ED_{50}<7 μg/mL. Introduction of 3-pyrrolin-1-yl or 2-(3-methylpiperidino) substituent, or a 7-or 8-membered ring significantly reduced the cytotoxicity of naphtho[2,3-*b*] furan-4,9-diones, whereas that of a phenoxy, isopropylamino or 2-methyl-piperidino group in the C-2 position of naphtho[2,3-*b*]furan-4,9-diones enhanced the tumour specificity. 2-Formylnaphtho[2,3-*b*]furan-4,9-dione had particularly potent activity (ED_{50}=0.09 μM).[220]

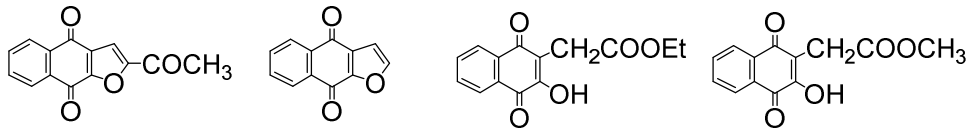
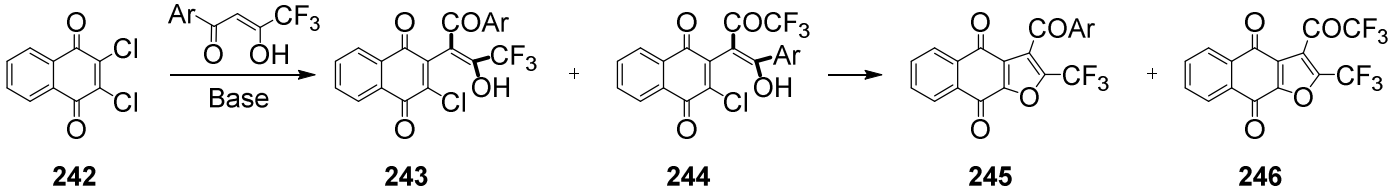


Figure 18. Herbal naphtho[2,3-b]furan-4,9-diones (**238–241**).

3.2.2. Biosynthesis

Archaebacteria and animals were reported to make use of the mevalonate pathway for generation of isoprenoid compounds. Thus, isopentenyl diphosphate (IPP) is formed from acetyl coenzyme A through mevalonate and 3-hydroxy-3-methylglutaryl-coenzyme A. In eubacteria, in apicomplexan protozoa and in plants the existence of a mevalonate-independent pathway was demonstrated.[221–223] In this route, isopentenyl diphosphate is generated from pyruvate and glyceraldehyde-3-phosphate *via* 1-deoxy-*D*-xylulose-5-phosphate and 2-C-methyl-*D*-erythritol 4-phosphate (MEP). The biosynthesis of furanonaphtoquinones of

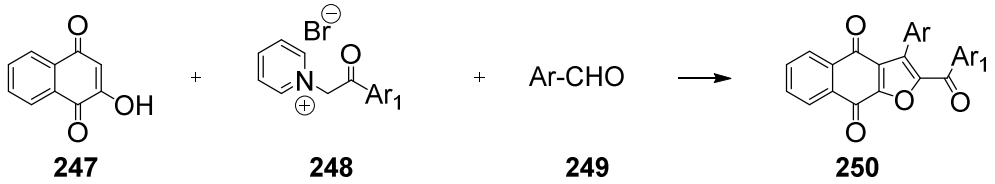
Streptomyces was studied by Bringmann and co-workers by feeding experiments applying ^{13}C-labeled precursors.[224] NMR analysis of the secondary metabolites proved the mevalonate pathway to be the dominant route of the biosynthesis of pyranonaphtoquinones; however, the MEP pathway contributed to the biosynthesis of the isoprenoid portion of the naphtoquinones.[224] Hence, the study of Bringmann *et al.* has proven that two different isoprenoid pathways may be simultaneously involved in the biosynthesis of furanonaphtoquinones in bacteria.



Scheme 29. Synthesis of naphto[2,3b] furan-4,9-diones utilizing nucleophilic substitution by activation with trifluoromethyl functionality. Base is here K_2CO_3,$(CH_3)_3(C_{16}H_{33})NBr$ in *o*-xylene.[225]

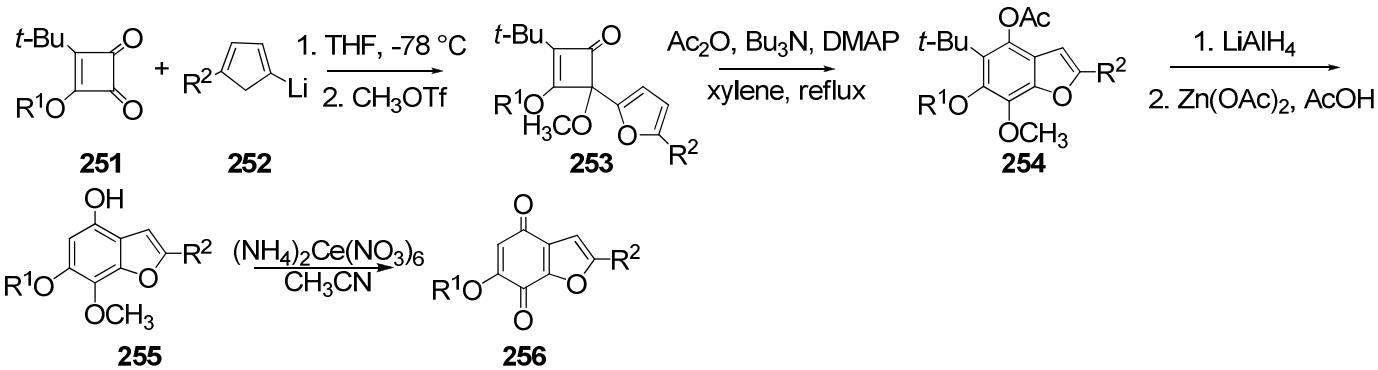
3.2.3. Total synthesis

Several synthetic approaches were reported towards the naphtho[2,3-*b*]furan-4,9-dione skeleton, the most important groups of methods being transition metal-catalyzed alkyne cyclization,[226] cerium ammonium nitrate-mediated oxidative cycloaddition,[227] nucleophilic aromatic substitution reaction (Scheme 29)[225] and one-pot multistep reactions (Scheme 30).[228]



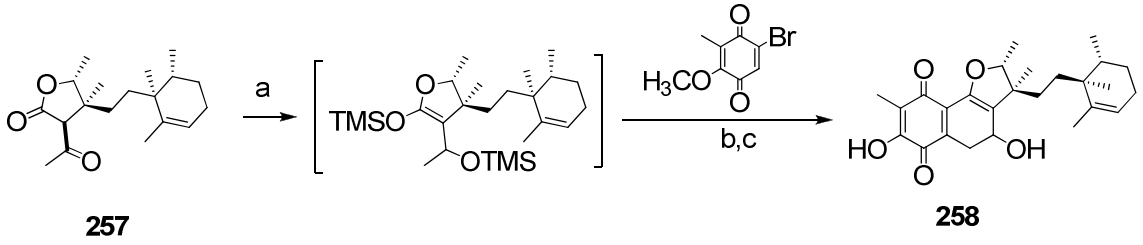
Scheme 30. Synthesis of naphto[2,3b]furan-4,9-diones by a domino protocol combining the generation of α,β-unsaturated triketone, Michael addition, intramolecular cyclization and oxidation with air. Reaction conditions: H_2O, NH_4OAc, 100 °, 10 h or 150 W, 130 °C , 20 min using microwave heating.[228]

Making use of benzanulation chemistry, Liebeskind and Liu synthesized quinones in moderate to high yields from *t*-butyl and trimethylsilyl substituted cyclobutenediones.[229] Addition of 2-lithiofurans to *t*-butyl-cyclobutenediones, followed by quenching with methyl triflate and subsequent thermolysis in the presence of acetic anhydride, provides 4-acetoxy-7-methoxybenzofurans in the sequence shown in Scheme 31.



Scheme 31. Synthesis of benzo[*b*]furandiones. R^1: CH_3, *i*-PrO, NEt_2. R^2: H,C_6H_5.[229]

Deprotection and oxidation with $(NH_4)_2Ce(NO_3)_6$ (CAN) gives benzo[*b*]furandione (**256**).[229] Importantly, the regiochemistry here is driven by the bulky *t*-butyl or trimethylsilyl substituent and hence the unsaturated carbon nucleophiles add regiospecifically to the carbonyl most distant from the $C(CH_3)_3$ or $Si(CH_3)_3$ functionality. Following the furnishment of the benzo[*b*]furandione skeleton, the *t*-butyl group is easily removable under acidic conditions.

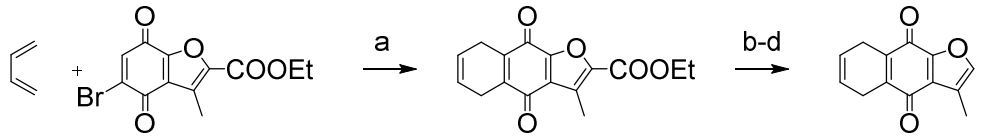


257 **258**

Scheme 32. The final steps of (+)-neomarinone (**258**) synthesis of Sestelo *et al.*:[230] formation of a 1,3-bis(siloxyl)-1,3-diene, regioselective Diels-Alder reaction, silyl enol ether hydrolysis, trimethylsiloxy elimination and subsequent aromatization in one pot. (a) LDA, TMSCl; (b) THF, rt; (c) $HClO_4$ (aq).

(+)-Neomarinone (**258**), isolated from the fermentation broth of actinomycetes, showed moderate antibiotic and antiproliferative activity. Its stereoselective synthesis was reported by Sestelo *et al.* utilizing (*R*)-lactate and (*R*)-3-methylcyclohexanone as chiral building blocks.[230] The two quaternary stereocentres were in this strategy furnished by diastereoselective 1,4-conjugate addition and enolate alkylation whereas the furanonaphtoquinone skeleton was built up *via* a regioselective Diels-Alder reaction (Scheme 32).

Regioselective Diels-Alder condensation (Scheme 33) was the key step in the total synthesis of maturinone (**262**), reported by Fillion *et al.* (16% overall yield).[231] An advantage of this strategy is the regiocontrol of the electrocyclic reaction by introduction of a bromine into the quinoid starting material (**260**), which in turn can be generated from phenolic precursors upon bromination and CrO_3-mediated oxidation. This route is likely to be applicable for the generation of maturinone analogues.



259 **260** **261** **262**

Scheme 33. Synthesis of maturinone (**262**): (a) $NaHCO_3$, DCM, rt; (b) KOH, EtOH, reflux; (c) neutralization with HCl (aq); (d) Cu, quinoline, 200 °C.

4. Sulfur containing hetrocyclic quinones

Sulfurous natural products have most often been isolated from marine sources. Caldariellaquinone (**261**, Figure 19) is one of the most well-studied examples of this substance group that was reported from the thermophillic, acidophilic bacterium *Caldariella acidophila*.[232] Caldariellaquinone is also a major component of the extract of *Sulfolobus* species[233,234] and its chemistry has previously been reviewed.[10]

4.1. Bioactivity

In similarity to other quinones, the sulfur containing ones were also reported to possess significant cytotoxicity and hence are potential anticancer agents. Conicaquinones A (**264**) and B (**265**) were isolated from the methanol extract of *Aplidium conicum*, a marine ascidian, and observed to show cytotoxicity

(IC_{50}>5 μg/ml) on rat glioma C6 cell assay; however only marginal effect on rat basophilic leukemia (RBL-2H3) cells.[235]

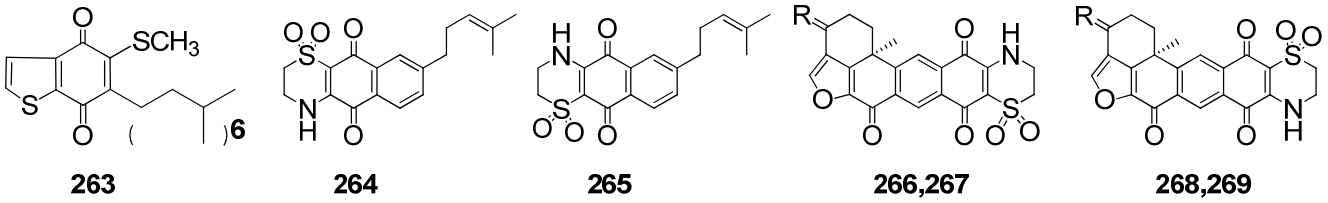


Figure 19. Caldariellaquinone (**263**), conicaquinones A (**264**) and B (**265**), (+)-adociaquinones A (**266**, R=H_2) and B (**268**, R=H_2), (+)-3-ketoadociaquinones A (**267**, R=O) and B (**269**, R=O).

Adociaquinones A (**266**) and B (**268**) and 3-ketoadociaquinones A (**267**) and B (**269**) were isolated from Xestospongia and showed inhibitory activity against human protein-tyrosine phosphatase that plays a chief role in the regulation of the cell cycle[236–238] and were found cytotoxic on P388, HCT, KB16 and HEP-3B cell lines.[236] 3-Ketoadociaquinones inhibited the protein farnesyltransferases of the yeast *Saccharomyces cerevisiae* (IC_{50}=1.48 and 3.75 μM) and of human (IC_{50}=4.19 and 9.27 μM) and showed antiplasmodial activity against the FcB1 and 3D7 *Plasmodium falciparum* strains (IC_{50}=1–4 μM).[237] Adociaquinones were reported from the tropical marine sponges *Adocia* [239] and from *Petrosia alfiani*[240] and were observed to selectively inhibit the iron chelator-induced HIF-1 activation in T47D cells (IC50 ~0.2 μM).[240] Mechanistic studies revealed that adociaquinones promote oxygen consumption without affecting the mitochondrial membrane potential. The ascidiathiazones **270**, **271** (Figure 20) of *Aplidium* sp. inhibited the superoxide production of human neutrophils *in vitro* (IC_{50}=1.55, 0.44 μmol/ml) and *in vivo* (gout, IC_{50}=25.6 μmol/ml).[241] (+)-Mevashuntin (**272**) was isolated from *Actinomycetes* upon inhibition of its HMG-CoA reductase with mevalotin.[242] Thiplidaiquinones A (**273**) and B (**274**) were isolated from the ascidian *Aplidium conicum* and observed to induce apoptosis by triggering reactive oxygen species.[243]

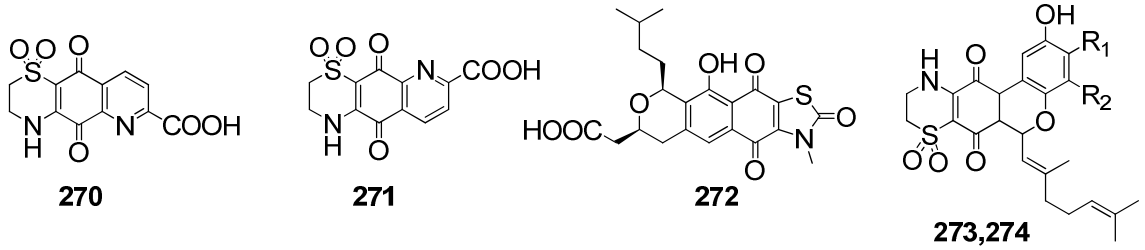


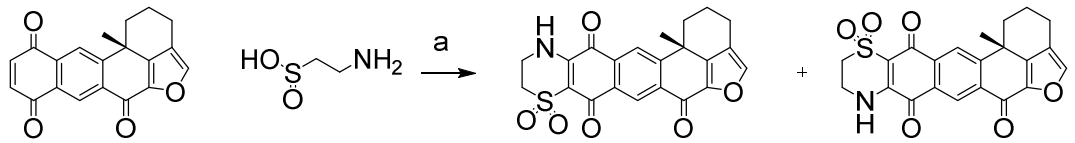
Figure 20. The structure of ascidiathiazones A (**270**) and B (**271**), (+)-mevashuntin (**272**) and (+)-thiaplidiaquinones A (**273**) and B (**274**).

4.2. Biosynthesis

The biosynthesis of caldariellaquinone (**263**) was studied in *Sulfolobus* by measuring the incorporation of isotopically labeled tyrosines. Feeding a series of ^{2}H or ^{13}C-labeled tyrosines followed by mass spectrometric tracing of the extent and position of the isotopes revealed that all but the C1-carbon of benzo[b]thiophen-4,7-quinone **263** is derived from tyrosine.[244] Incorporation of sulfur most probably proceeds very early in the biosynthetic route through a sulfur containing derivative of tyrosine. The biosynthesis of sulfur containing natural products has been reviewed in detail by Parry,[245] that of isoprenoid quinones by Nowicka and Kruk.[32]

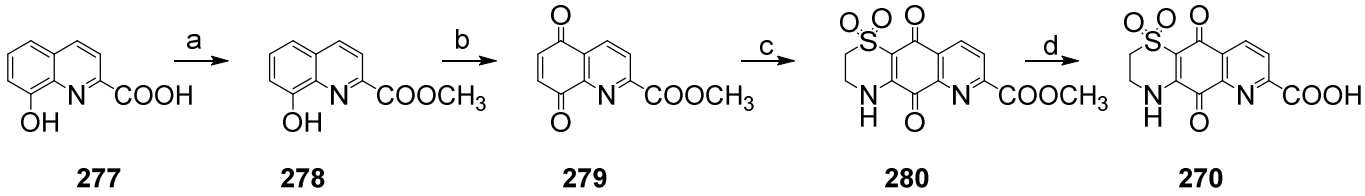
4.3. Total synthesis

The total synthesis of (+)-adociaquinones A (**266**) and B (**268**) by Harada *et al.*[246] starting from xestoquinone (**275**) available through the procedure of Schmitz.[239] The key step, cyclization with hypotaurine (**276**), of the reaction root is shown in Scheme 34.



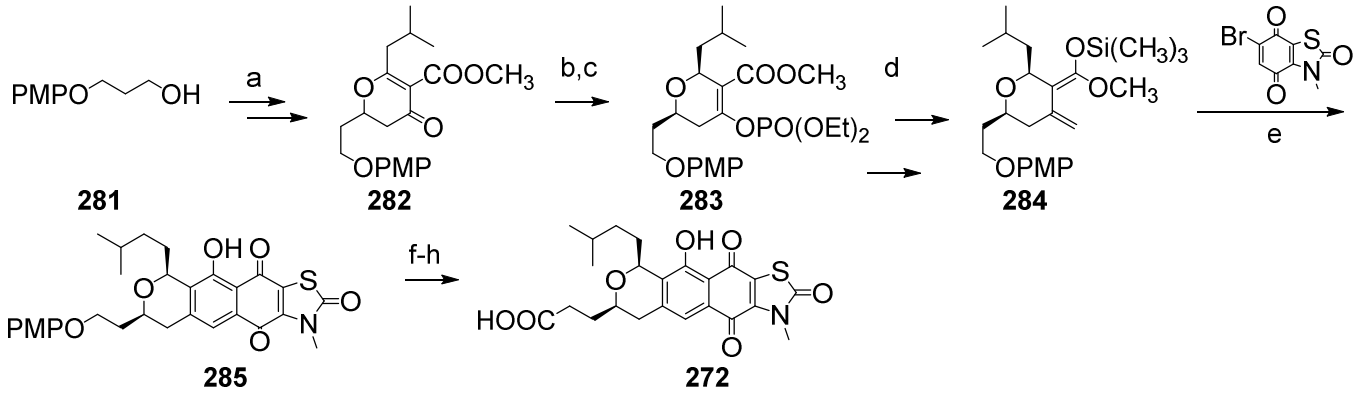
Scheme 34. The synthesis of (+)-adociaquinones A (**266**) and B (**268**): (*a*) EtOH/CH_3CN/H_2O, 40 °C.

Ascidiathiazones A (**270**) and B (**271**) were synthesized by Copp *et al.*[241] from commercially available 8-hydroxyquinoline-2-carboxylic acid (**277**). The key steps of this synthesis was oxidation with Fermy's salt (step b, Scheme 35) cyclization with hypotaurine (**276**, step c) in similarity to the protocol of Harada towards (+)-adociaquinones.[246] Importantly, here the correct regioisomer was produced in a 10:1 ratio.



Scheme 35. Synthesis of (+)-ascidiathiazone A (**270**) by Copp:[241] (a) $SOCl_2$, CH_3OH; (b) $K_4[ON(SO_3)_2]$ (Fremy's salt); (c) hypotaurine (**276**); (d) HCl; (e) KOH.

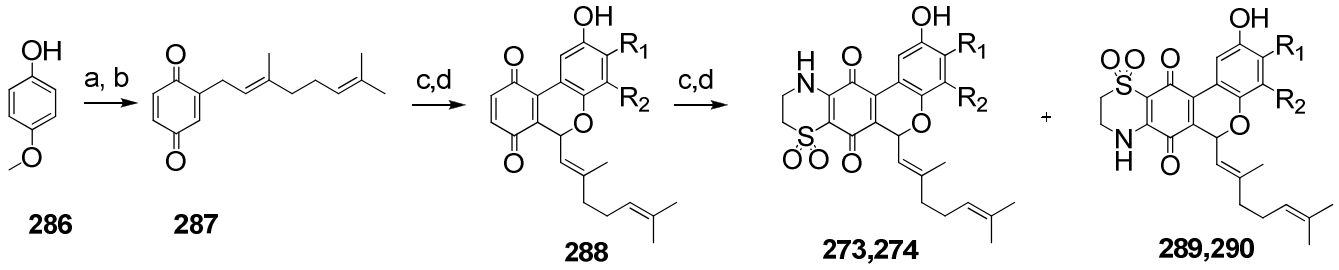
(+)-Mevashuntin (**272**) was prepared in a convergent eleven steps strategy from 3-(4-methoxy-phenoxy)propanol (**281**) by Moody and co-workers.[247] The *syn* stereochemistry of the two pyrane substituents was introduced by hydrogenation on Pd/C (step b, Scheme 36), whereas tetracyclic skeleton was assembled by a regioselective Diels-Alder condensation (step e).



Scheme 36. The key steps of the synthesis of (+)-mevashuntin (**272**): (a) 4 steps; (b) H_2, Pd/C, CH_3OH; (c) NaH, $ClPO(OEt)_2$, THF; (d) 2 steps; (e) Et_3N, DCM, 0 °C; (f) AgO, HNO_3, dioxane; (g) Jones' reagent, acetone; (h) $TMSCHN_2$, toluene, CH_3OH.[247]

Thiaplidiaquinones A (**273**) and B (**274**) were synthesized in a biomimetic strategy by Copp *et al.*[248] and hence by addition of hypotaurine (**276**) to a pyranoquinone, which in turn may be furnished through an

aza-6π-electrocyclization (Scheme 37). The final cyclization step, which is similar to that applied in the total synthesis of **266**, **268**, **270** and **272**, provides a mixture of four isomers, with **273** in 21% and **274** in 9% yield. Synthetic strategies towards various benzoquinones have been recently reviewed by Pardasani and co-workers.[249]



Scheme 37. Synthesis of thiaplidiaquinones A (**273**) and B (**274**): (a) NaH, geranyl bromide, Et_2O, reflux; (b) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O; (c) Et_3N, DCM; (e) SiO_2; (f) hypotaurine (**276**); CH_3CN/EtOH.

5. Quinones and cancer

A common feature of heterocyclic quinones is that they frequently show promising antiproliferative activity, which has often been associated to their ability to inhibit DNA topoisomerase-II.[250] However, several additional biochemical pathways may contribute to their overall bioactivity. Quinones undergo enzymatic reduction to give semiquinone radicals and hydroquinones, the driving force being formation of a fully aromatic system.[251] The one electron reduction is catalyzed by cytochrome P450 reductase, mediated by NADPH and yields unstable semiquinones. Under aerobic conditions, semiquinone radical anions reconvert into quinones by generating superoxide radical anions ($^{\cdot}O_2^-$) from O_2. Superoxide is converted to hydrogen peroxide by superoxide dismutase, which may be further converted to hydroxyl radical (HO) *via* the Fe-mediated Fenton reaction. This process is named 'aerobic redox cycling'. The hydroquinone formed *via* two-electron reduction may be excreted by a detoxification mechanism or may undergo comproportionation with the parent quinone to yield semiquinone radical anions. Both the semiquinone and the superoxide radical anion can generate hydroxyl radicals. These highly reactive species may attack DNA or other cellular macromolecules, such as lipids and proteins, leading to cell damage or DNA breakage (Figure 21).[252–254]

The two-electron reduction of quinones is catalyzed by NAD(P)H:quinone oxidoreductase (NQO1)[255,256] and generates hydroquinones (QH_2). This enzyme reduces reactive quinones, which in turn are toxic, and hence by-pass the creation of toxic intermediates. Whether the two electron reduction leads to detoxification or to activation of oxidative stress depends on the rate of autoxidation of the formed hydroquinone.[257] If the autoxidation rate is low, conjugation may occur before oxidation. As a consequence, the two-electron reduction will lead to detoxification and an increase in the NQO_1 activity. If, however, the hydroquinone is rapidly oxidized, only a minor fraction may be conjugated and hydroquinone formation results in activation. In this case, an enhanced tissue level of NQO_1 is expected to increase the toxicity of quinones.[257] In an attempt to improve the anticancer properties of quinones substituted 8-aminopyrimido[4,5-c] isoquinolinequinones were synthesized,[112] *N*-alkylamino-, phenylamino- and alkyphenylamino derivatives showing most promising antitumour activities.

Quinones with fused aromatic rings were proposed to exhibit cytostatic activity *via* DNA intercalation, which causes reading errors during the replication process. In addition to the primary nucleic acid intercalation, further modulation by binding to additional substrates, *e.g.*, topoisomerase I/II, may take place.

A positive charge, generally needed for their bioactivity, is usually provided by a nitrogen[258] making the number and positions of nitrogens especially important for anti-cancer applications.[259]

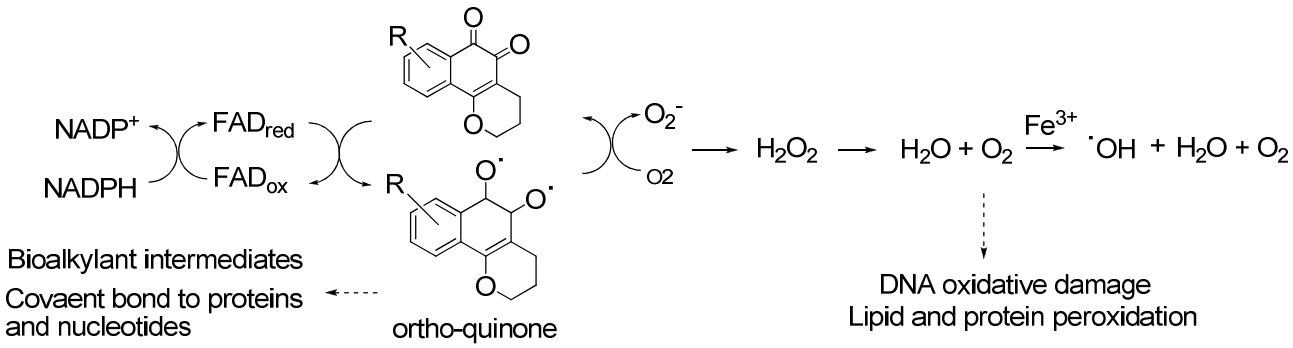


Figure 21. Representation of the redox cycle and generation of metabolites by quinones.[254]

6. Concluding remarks

Traditionally, natural products were isolated *via* bioassay guided fractionation. Besides the strengths of this methodology in providing bioactive substances, it suffers from the weakness of frequent reisolation of known metabolites. Chemical screening of crude plant extracts, a recent technology utilizing the advances of analytical techniques (HPLC-NMR/MS) is a complementary strategy allowing rapid identification of novel substances in extracts and their targeted isolation. It enables recognition of known metabolites at an early stage thereby avoiding costly and time-consuming isolation of already known constituents.

Despite the large number of reports on bioactive heterocyclic quinones, so far only a few have reached clinical evaluation. As shown above, synthetic methodologies were developed to generate hetrocyclic quinones; however, production of derivatives with a chemically diverse substitution pattern remains a challenge. Enantiodivergent synthesis was achieved for a few substances, such as (−)-isagarin and (−)-kinamycin C, whereas synthetic routes to a numerous important substance groups has yet to be developed. The genus *Steptomycetes* proved to be an excellent source of nitrogen containing hetrocyclic quinones indicating the high potency of studies of herbal and bacterial extracts in the search for novel bioactive substances. Natural products of marine origin were observed to often possess less common substituents (halogens) and a larger propensity of heterocyclic rings. In addition, they often show promising antiteratogenic effect. Although the anticancer and antimicrobial activities of a number of substances were studied, detailed structure-activity relationship information is yet barely available for heterocyclic quinones. Despite the vast amount of work already performed on this substance family, the intriguing chemical structure and potential biological activities of heterocyclic quinones is expected to remain to raise considerable interest.

Acknowledgment

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PHENYLENE-THIOPHENE POLYMERS AND OLIGOMERS FOR ORGANIC ELECTRONICS: SYNTHESIS, PROPERTIES AND APPLICATION IN DEVICES

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Abstract. *Several organometallic methods are used to synthesize π-conjugated molecules and polymers with alternating thiophene-dialkoxyphenylene units in the conjugated backbone. Here we describe our approaches to the synthesis of materials based on the dialkoxyphenylenethienylene structural motif via palladium catalyzed cross-coupling reactions of organomagnesium or organoboron reagents with aryl halides. The properties of the resulting compounds and their applications in (opto)electronic devices (organic field effect transistors, resistive gas sensors, field effect chiral sensors, photoelectrochemical cells and bulk-heterojunction solar cells) are also discussed, highlighting the role of the synthetic logic in the design of multifunctional organic materials.*

Contents

1. Introduction

Applications of π-conjugated polymers[1] and oligomers[2] as active materials in thin film opto-electronic devices such as organic light emitting diodes (OLEDs),[3] organic field effect transistors (OFETs),[4] solar

cells[5] and chemical/biological sensors[6] have raised enormous industrial and academic interest over the last twenty years. In fact, plastic electronics largely benefits from the possibility to combine in a single material the optical and electrical properties of semiconductors with the easy and low cost processability of polymeric and molecular compounds. In addition, the structural variety of organic chemistry offers virtually unlimited options for tailoring and optimizing properties at the molecular level for targeted applications.

In the wide pool of organic semiconductor structures, thiophene based polymers and oligomers, including oligo- and poly(arylenethienylene)s (OATs and PATs) have been widely investigated because of their excellent electrical and optical properties and good processability.[7]

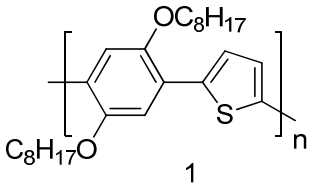
Dialkoxy functionalized PATs and OATs can be conveniently synthesized by various procedures, most commonly based on direct Csp^2–Csp^2 bond forming cross-coupling reactions,[8] involving aryl halides and organometallic reactants such as organoboron (Suzuki Miyaura coupling), organotin (Stille coupling), organozinc (Negishi coupling) and organomagnesium (Kumada coupling) derivatives.[9]

This article surveys our recent contributions on dialkoxyarylenethienylene based polymers and molecules, covering their synthesis, properties and applications in field effect transistors, photovoltaic devices and chemical sensors. The suitability of several thiophene organometallic reagents allows the synthesis of dialkoxyarylenethienylene polymers and molecules by various possible reactions, thus offering the possibility to select the experimental protocols that better tolerates specific functional groups in the cross coupling partners, leading to final products with chemical structure tailored for targeted applications.

The discussion on this specially versatile class of molecular and polymeric semiconductors will give the opportunity to show the synthetic logic underlying the choice of structures and the criteria of molecular design in organic electronics, emphasizing the key role of organic synthesis in the progress of this important scientific and technological field.

2. Poly(dialkoxyphenylenethienylene): from synthesis to devices

Our investigation on dialkoxyarylenethienylene material started in 2002[10] with the synthesis of poly(2,5-dioctyloxy-1,4-phenylene-*alt*-2,5-thienylene) (POPT) **1** (Figure 1), a quite simple copolymer alternating 2,5-dioctyloxy-1,4-phenylene and 2,5-thienylene moieties. The linear alkoxy chains on the phenylene units confer solubility to the polymer in common organic solvents, allowing easy thin film processing from solution.



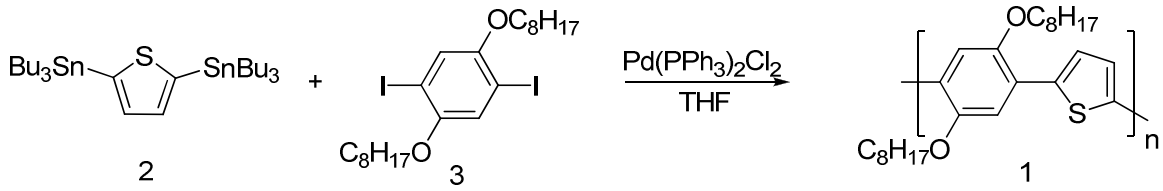
1

Figure 1. Poly(2,5-dioctyloxy-1,4-phenylene-*alt*-2,5-thienylene) (POPT) **1**.

2.1. Synthesis of poly(2,5-dioctyloxy-1,4-phenylene-*alt*-2,5-thienylene) 1 (POPT)

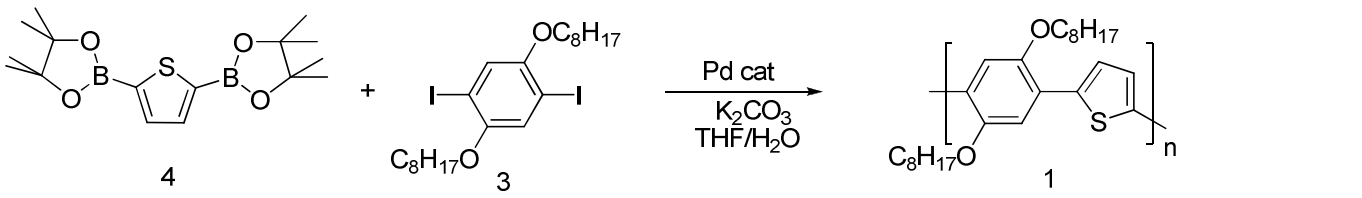
Polymer **1** can be synthesized by various cross coupling reactions. It was early synthesized by Z. Bao *et al. via* the Stille cross-coupling of 2,5-bis(tributylstannyl)thiophene **2** with 1,4-diiodo-2,5-bis(octyloxy-benzene) **3** (Scheme 1).[11]

However, the well-known toxicity of organostannanes stimulated the research on alternative synthetic methods based on more benign and environmentally friendly reagents, such as the Suzuki-Miyaura reaction.



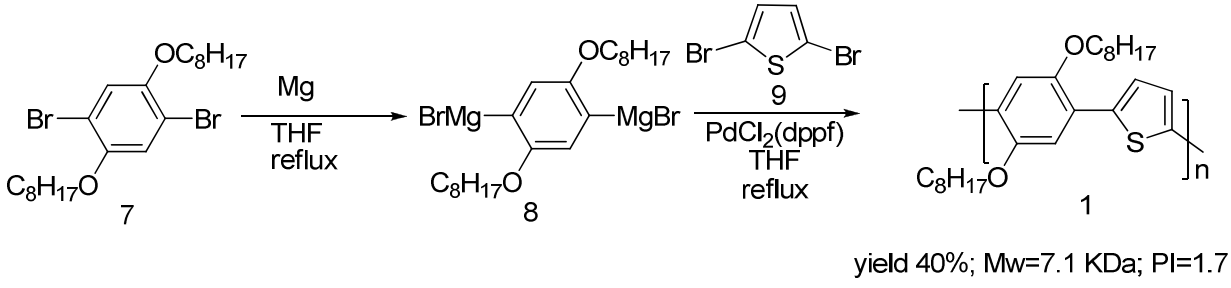
Scheme 1. Synthesis of POPT **1** by the Stille cross-coupling.

In fact, **1** can be also prepared by polymerization of the bis(pinacolato)diboron derivative **4** with 1,4-diiodo-2,5-bis(octyloxybenzene) **3**, according to Scheme 2.[12] A systematic study comparing **4**, its dioxaborinane analogous **5** and the diboronic acid **6** revealed a better stability of **4**, especially in consideration of the easy hydrolytic deboronation process that limits the use of **5** and **6** in the polymerization reaction with **3**. Improvement in the reaction yield using **4** was achieved employing ligandless palladium(II) acetate $Pd(OAc)_2$ as the palladium precursor: a still debated triphenylphosphine inhibitory effect on the reaction occurs with the most common tetrakis(triphenylphosphine)palladium(0) $Pd(PPh_3)_4$ catalyst. In any case, as argued from MALDI-TOF mass spectra, hydrolytic deboronation is still the main chain termination process even when $Pd(OAc)_2$ is used, while undesired chain termination *via* phenyl capping of the growing chains occurs in the presence of free triphenylphosphine in the reaction medium.



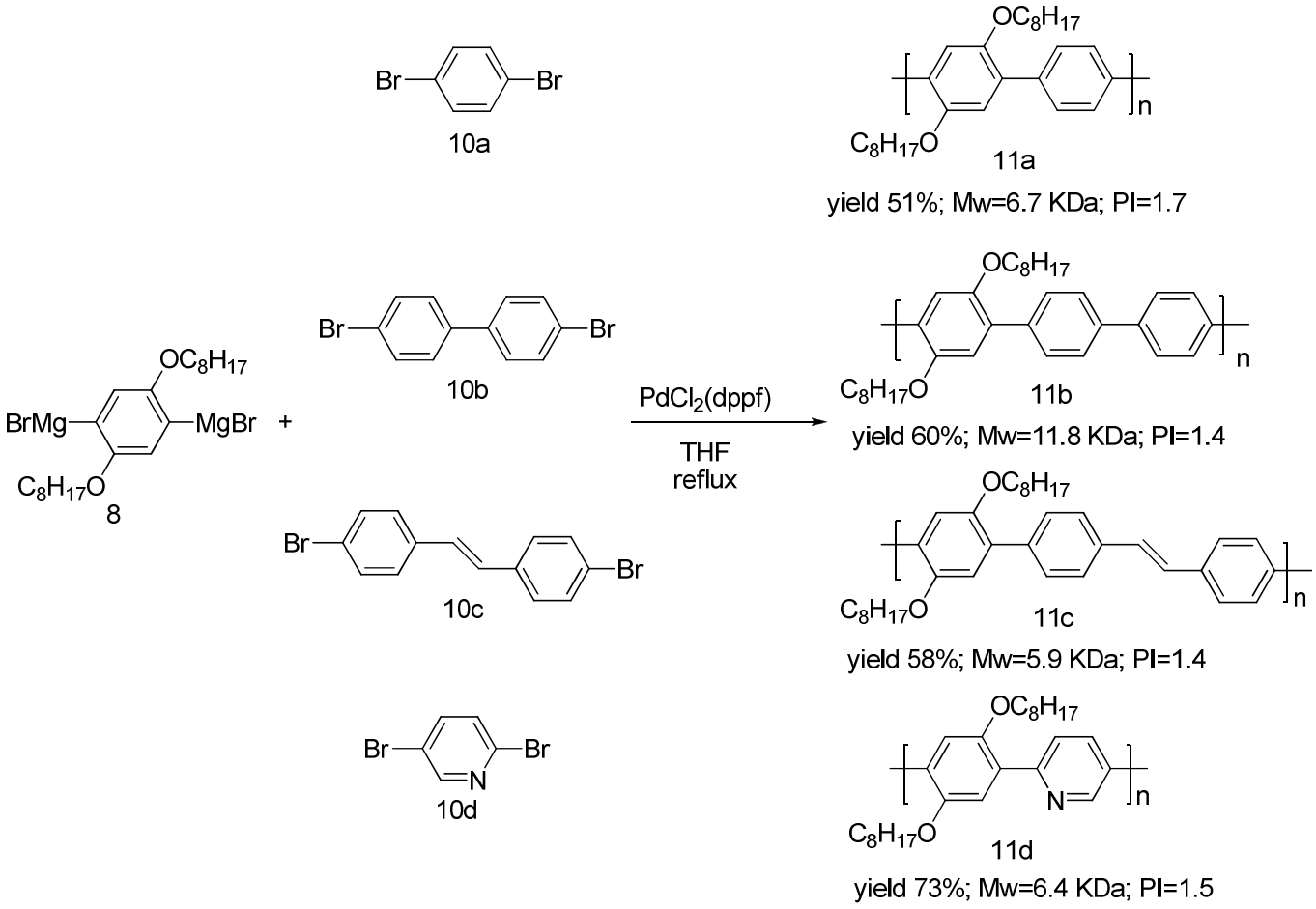
Scheme 2. Synthesis of **1** by the Suzuki-Miyaura cross-coupling.

We proposed a simple protocol for the synthesis of **1**, as a convenient alternative to the methods previously reported.[11,12] It is based on the Pd-catalyzed polymerization of bis-organomagnesium reagent **8**, derived from 1,4-dibromo-2,5-bis(octyloxy)benzene **7**, with 2,5-dibromothiophene **9** (Scheme 3).[10]



Scheme 3. Synthesis of **1** by cross-coupling of bis-Grignard reagent **8** with 2,5-dibromothiophene **9**.

This protocol is straightforward and it is based on a non-toxic organometallic reagent **8** that can be simply prepared from the easily accessible dibromo-derivative **7**. The protocol was readily extended to the preparation of several conjugated polymers in good yields, thus demonstrating its versatility and generality (Scheme 4).



Scheme 4. Polymerization reactions between **8** and the dihalides **10a–d**.

The $PdCl_2$(dppf) (dppf: 1,1′-bis(diphenylphosphino)ferrocene) complex led to the highest yield in comparison to other Pd catalysts.[10] According to the generally accepted mechanism for these polymerizations,[13] a small amount of **8** is consumed during the initial Pd(II) reduction to the effective catalytic Pd(0) species: this would result in an imbalance between the organomagnesium and the electrophile monomers molar ratio and, as a consequence, in a decrease of the degree of polymerization. Therefore, a proper (1–2%) excess of the bis-Grignard reagent **8** in all polymerization reactions reported in Schemes 3 and 4 had to be employed to adjust the reaction stoichiometry.

Molecular mass values (Mn and Mw) and degree of polymerization (DP) of polymer **1** as determined by both Gel Permeation Chromatography (GPC) and MALDI-TOF mass spectrometry are reported in Table 1. The low molecular weights of **1** are likely due to its limited solubility in the reaction solvent, but they are comparable to molecular weights of the same polymer prepared by different reaction protocols.

The differences between the mass values determined by MALDI-TOF MS and GPC are explained as follows: on one hand the quite different hydrodynamic behaviour of conjugated polymers, which are rigid rod-like molecules rather than polydisperse coils as the standard polystyrene, determines an overestimation of Mn and Mw measured by GPC.[14] On the other hand, MALDI-TOF suffers from mass discrimination

phenomena at the higher molecular mass end[15] and, as a consequence, underestimation of molecular masses is expected with this technique.

Table 1. Comparison of molecular mass and degree of polymerization values for **1** determined by GPC-HPLC and MALDI-TOF MS

	GPC	MALDI-TOF
M_n (KDa)	4.3	4.0
M_w (KDa)	7.1	5.3
M_w/ M_n	1.7	1.3
DP	10	10

However, the polydispersity index (M_w/M_n) determined by both techniques (1.7 by GPC, 1.3 by MALDI-TOF) is indicative of a narrow distribution of chain lengths. The MALDI-TOF spectrum of polymer **1** reported in Figure 2 shows a uniform distribution of chains with all the possible terminations. An important advantage of the Grignard polymerization, with respect to the two other organometallic routes above discussed,[11,12] is represented by the absence of polymer chains terminating with organometallic moieties or phosphine defects.

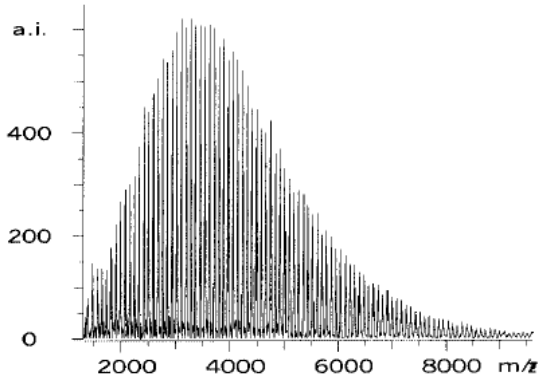
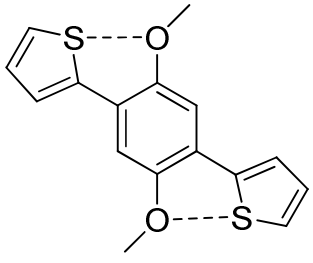


Figure 2. MALDI-TOF spectrum of **1**. Reprinted with permission from *Eur. J. Org. Chem.* **2002**, 2785. Copyright 2013 Wiley.

2.2. POPT as organic semiconductor for thin film transistors

Crystallographic data for the methoxy substituted analogous compound **12** (Figure 3) demonstrated a quasi-planar conformation of the bis(thienyl)benzene backbone with a non-covalent intramolecular S–O interaction in the solid state. Effective conjugation was also highlighted in the gas phase by UV/photoelectron spectroscopy and theoretical calculations (DFT).[16]



12

Figure 3. Intramolecular S–O interactions in compound **12**.

High field-effect charge mobility is generally found in organic polyconjugated materials with planar molecular conformation, usually corresponding to extended effective π-conjugation of the polymer chains and orderly packed thin films where strong π–π interchain interactions are established in the charge transport direction. Thus, considerations based on model compound **12**, suggested **1** as a promising material for field-effect transistor application, where good charge mobility is a key requisite. Charge transport studies on thin films of **1** prepared with different techniques[17] showed critical dependence of field effect behaviour on the deposition method, indicating that the planarization of the molecular skeleton in **1** is affected by the deposition conditions.

In particular, solution methods such as drop casting and spin coating, which are suitable for large-scale processing, cannot generate well organized self-assembled thin films of **1**. Conversely, layer-by-layer assembly procedures, *i.e.* the Langmuir-Schäfer (LS; horizontal transfer) and Langmuir-Blodgett (LB; vertical transfer) techniques, offer better reproducibility and control over film thickness and molecular packing.[18]

POPT **1** was deposited by chloroform solution casting in an N_2 atmosphere on a silicon wafer covered by thermal silicon dioxide (Si/t-SiO_2). For the LS deposition on the same substrate, the polymer molecules were spread as a chloroform solution at the air-water interface and, after solvent evaporation, they were laterally compressed until a uniform layer was formed. As the compression process was completed, the film was deposited through the horizontal transfer of several subsequent layers.

Organic thin film transistors (OTFTs) were fabricated using both the solution cast and LS deposited polymer **1** films as the active layers in a typical bottom-gate, top-contact device architecture reported in Figure 4. Here the gate (G) contact gold pad is deposited directly on the conducting silicon substrate, whereas the gold source (S) and drain (D) contacts are defined by thermal evaporation through a shadow mask, directly on the polymer films.

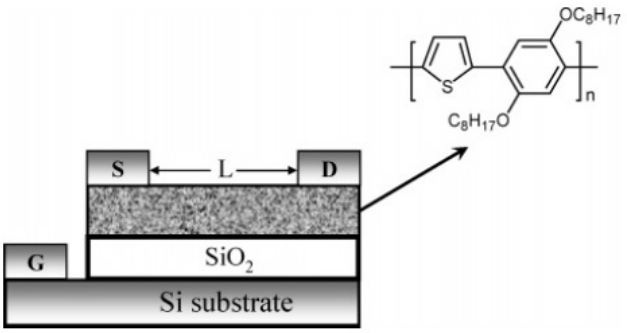


Figure 4. Schematic diagram of OTFT device based on cast or LS active thin film of **1**. Reprinted with permission from *Chem. Mater.* **2006**, *18*, 778. Copyright 2013 American Chemical Society.

The devices were operated in the common source mode and both V_{ds} and V_g biases were imposed negative with respect to the grounded source because polymer **1** was expected to be a p-type semiconductor.[19] The current-voltage (I_{ds}-V_{ds}) characteristics measured in the 0−100 V range (Figure 5a,b) demonstrate that the cast film behaves like a resistor, since no current modulation can be observed in the corresponding device when the gate bias is ranged between 0 and −100 V (Figure 5a). The LS film based device shows remarkably different electrical characteristics, always exhibiting a source-drain current modulation with the gate bias (Figure 5b), which is a typical transistor behaviour.

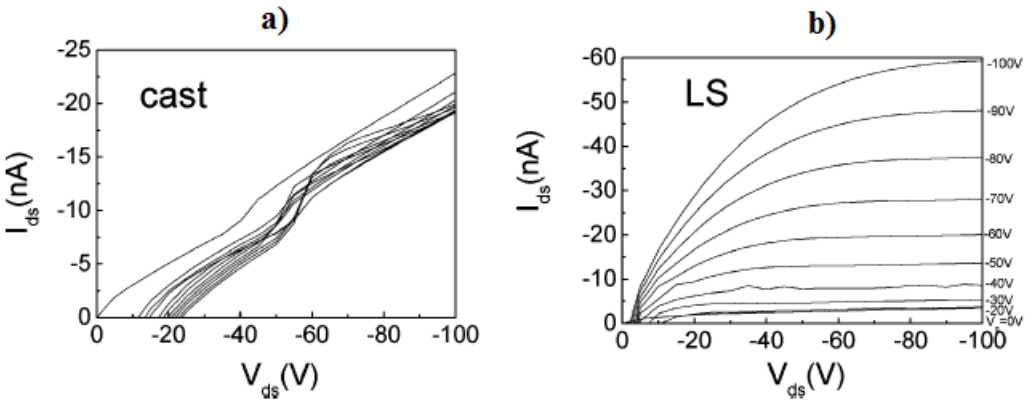


Figure 5. Current-voltage characteristics of OTFTs based on cast (a) and LS (b) thin films of polymer **1**. Reprinted with permission from *Chem. Mater.* **2006**, *18*, 778. Copyright 2013 American Chemical Society.

The UV-vis absorption spectra of **1** as cast and LS films are shown in Figure 6. The absorption band of the LS film, relevant to the π–π* optical transition of polymeric chains, is 14 nm red-shifted with the full width at half-maximum (fwhm) 50 nm narrower than the cast film: this indicates that a more extended and less dispersed average conjugation length is retained by the polymer chains when the floating layer is transferred from the air-water interface to the substrate as LS film. This evidence could be explained considering that the electrostatic interaction of the sulfur and oxygen atoms of the polymer backbone with the water subphase forces the molecules to lie flatter on the polar surface, reaching a more planar, though energetically unstable, conformation. Moreover, the long *n*-octyl branches of the side chains are likely pulled upwards or, in any case, far from the water surface. The difference in effective conjugation length, together with better π–π interactions in the solid state can account for the superior electrical performances of the LS cast thin films.

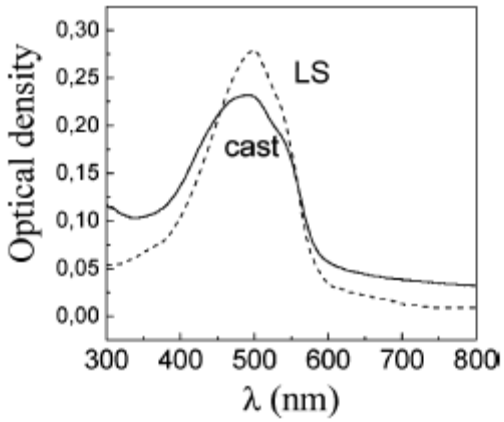


Figure 6. UV-vis spectra of a cast film (solid line) and a 10 horizontal transfer LS (dashed line) film of polymer **1**. Reprinted with permission from *Chem. Mater.* **2006**, *18*, 778.
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The differences between the cast and the LS thin films of **1** were also evidenced by comparison of their surface morphologies observed *via* tapping-mode scanning force microscopy (SFM): in particular, the root-mean-square roughness, on a scale of about 30 μm, falls in the range of 50–70 nm for the cast films while it goes down to 30–40 nm for the LS films. Also on a smaller scale (2–5 μm), differences are evident in the morphology of the two films, with the LS film showing a much more regular and granular-type structure (Figure 7).

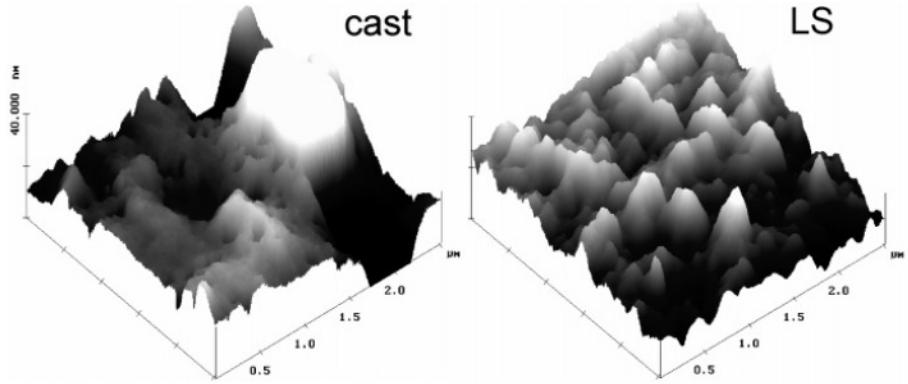


Figure 7. Scanning force microscopy images of **1** drop cast and LS films. Reprinted with permission from *Chem. Mater.* **2006**, *18*, 778. Copyright 2013 American Chemical Society.

Further studies compared electrical behaviour of LS films in OTFT devices prepared by transferring the semiconductor on hydrophobic and hydrophilic substrates: t-SiO_2 functionalized with hexamethyl-disilazane (HMDS) and bare t-SiO_2, respectively.[20] Two series of LS films of increasing thickness were deposited by varying the number of horizontally transferred active monolayers of **1** on either t-SiO_2/HMDS or bare t-SiO_2 substrates and their morphology and electrical properties in OTFT devices were investigated. In particular, the conductance values of devices based on t-SiO_2/HMDS substrate resulted substantially thickness independent while field-effect conductance of bare t-SiO_2 based transistors varied of one order of magnitude as the active layer thickness increased from 5 to 50 LS transfers: in this series, the best field-effect charge mobility was observed for the 50 LS layer device (6×10^{-6} $cm^2/V\cdot s$), while lower values in the 10^{-7} $cm^2/V\cdot s$ range are recorded for thinner films. The different behaviour of the two series of devices can be correlated to the different organization of the very first layers of **1** chains which are in direct contact with the gate dielectric. In particular, AFM images of the first layer of **1** deposited on both substrates confirm that the polymer organization is notably heterogeneous on the hydrophilic t-SiO_2 surface while it exhibits nanograins with a quite compact and regular texture on the hydrophobic methyl functionalized t-SiO_2/HMDS.

2.3. POPT as active material for resistive gas chemical sensors

The good electrical properties of LS films of **1** were exploited in gas sensing devices, also in comparison with similar polymers bearing vinylene units instead of thiophene rings in their conjugated backbone.

The electrical conductivity of semiconducting polymers can be affected over many orders of magnitude by exposure to specific gaseous species.[21] Sensors based on organic semiconductors thin films offer important advantages over those based on the inorganic counterparts given by the enormous structural versatility of the organic materials and by their reversible redox chemistry in response to different environments.[22] Moreover, the chemistry of polymer sensing layers occurs at lower working temperatures with respect to metal oxide semiconductors and organic polymer based sensors are low power consuming and can be easily fabricated in a handheld portable version. These benefits justify the recent intense interest in organic semiconductors as promising gas sensitive materials to monitor the quality of atmosphere, *e.g.* work and domestic ambient. Polymeric thin films processed by various deposition methods such as spin coating, thermal evaporation, Langmuir-Schäfer and Langmuir-Blodgett techniques[23] have been reported so far to respond reversibly in few seconds to several gaseous analytes and to be sensitive at the parts per

million level to volatile organic compounds[24], but also to low levels of reactive gases such as ammonia and nitrogen dioxide.[25]

The sensing mechanism is related to the intrinsically insulating nature of organic conjugated polymers which in the electronic ground state possess a forbidden energy gap between filled and empty energy levels. Their conducting behaviour in thin films arises after doping processes and, in the case of gas sensitive active polymers, the doping mechanism can be ascribable to the interaction between gas molecules and the surface of the active polymer layer. This doping mechanism generates extra charges in the polymer chains inducing the formation of charged defects associated with the appearance of electronic states in the polymer energy gap. After this kind of doping, conjugated polymers generally exhibit p-type behaviour and it is reasonable to expect that oxidizing or reducing gases, such as NO_2 or NH_3, respectively, will cause an increase or decrease in the polymer conductivity, as a consequence of the formation of additional free carriers within the polymer electronic band structure.

Aiming to explore the suitability of various classes of organic semiconductors as active layers in resistive gas sensors, the performances of thin films of dialkoxy-poly(*p*-phenylenevinylene)s (PPVs) **13** and **14**, synthesized in our laboratories, were investigated (Figure 8).[26] In particular, cast films of these polymers showed a rather limited variation of their electrical conductivity when exposed to NO_2, whereas Langmuir Blodgett deposited films did not show any sensitivity toward all the gases tested including NO_2, CO, NO, SO_2, NH_3.

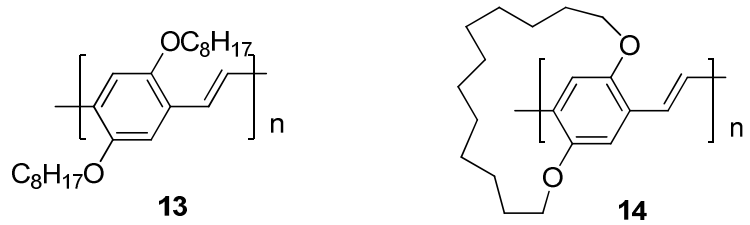


Figure 8. Chemical structures of poly(2,5-dioctyloxy-1,4-phenylenevinylene) **13** and poly [2,15-dioxabicyclo[14.2.2]icosa-1(19),16(20),17-trien-17,19-ylenevinylene] **14**.

On the contrary, polymer **1**, which contains thiophene instead of vinylene units, led to excellent results in terms of sensitivity and selectivity of the corresponding sensing devices toward NO_2 toxic gas.[27]

As shown in the inset of Figure 9, by exposing the Langmuir-Schäfer active layer of polymer **1** to a gaseous flux of dry air containing NO_2 at ppm levels, the doping process of the sensitive polymer occurs upon the interaction with NO_2 and is completely reversible. Moreover, the response of the sensing layer increases by increasing the working temperature of the device, reaching the highest value in the range between 60 and 80 °C (Figure 9). Here, the response is defined as $\Delta I/I=(I_{gas}-I_{air})/I_{air}$, where I_{air} is the electrical current measured at the electrodes by fixing a voltage of 5 V, and I_{gas} is the electrical current of the sample in the presence of test gas. The effectiveness of this sensor is also confirmed by observing that its response $\Delta I/I$ linearly increases with the NO_2 concentration in the range 2.5−10 ppm at the investigated working temperatures (see inset of Figure 9).

To explore the sensitivity threshold of the gas sensor made with the LS deposited **1**, experimental tests were performed at the temperature of maximum response exposing the active layer to a flux of dry-air containing 50 ppb of NO_2: Figure 10 confirms that, also at this very low analyte concentration, the response is completely reversible and exclusively related to the interaction of the active layer with NO_2.

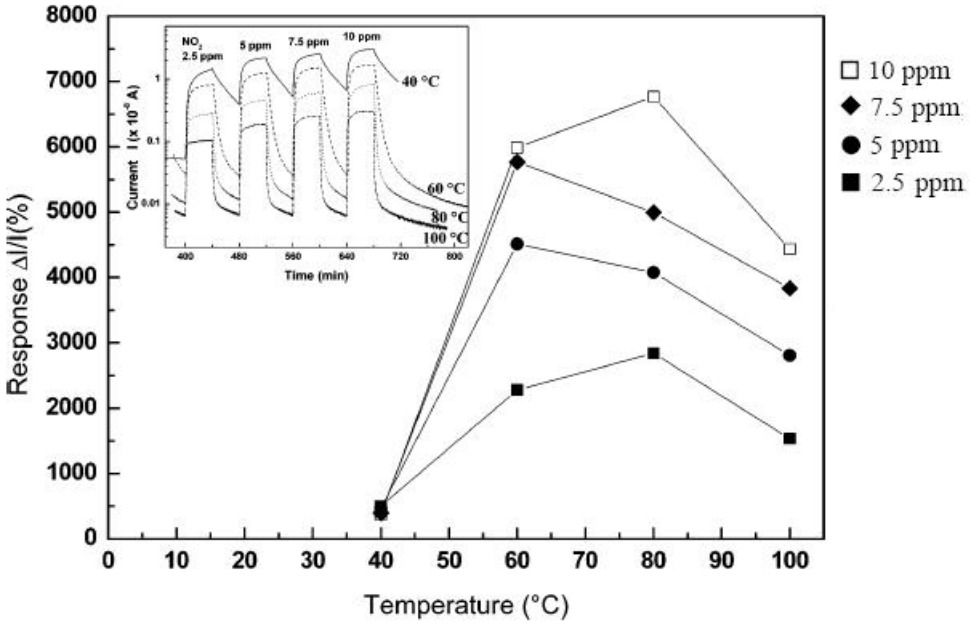


Figure 9. Response of the sensing layer as a function of the working temperature for different NO_2 concentrations. In the inset the dynamic responses at different NO_2 concentrations are reported in dry-air, keeping the sensing layer at different working temperatures. Reprinted with permission from *J. Am. Chem. Soc.* **2003**, *125*, 9055. Copyright 2013 American Chemical Society.

Measurements were also carried out in the presence of potential interfering gases, such as ammonia, carbon monoxide, or sulfur dioxide in order to evaluate the selectivity of this sensor: the results show evidence of the high selectivity of the sensing layer to very low concentrations of NO_2 (1 ppm), even in the presence of mixtures containing large concentrations of other gases (100–200 ppm).

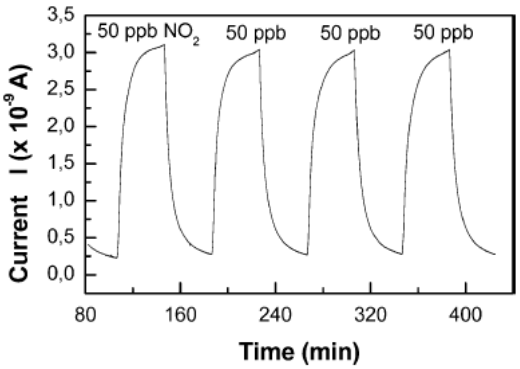


Figure 10. Dynamic response of the sensor in the presence of low NO_2 concentration (50 ppb). Reprinted with permission from *J. Am. Chem. Soc.* **2003**, *125*, 9055. Copyright 2013 American Chemical Society.

2.4. Heterostructures based on POPT and carbon nanotubes

Single-walled carbon nanotubes (SWNTs), carbon allotropes with a cylindrical geometry, have elongated shape with a length to diameter ratio of up to $\approx 3 \cdot 10^7$:1 and can also reach lengths of up to several millimeters.[28] Recent research has demonstrated the application of carbon nanotubes in nanoelectronics,[29] field-effect transistors,[30] chemical sensors[31] and in the photoactive layers of organic photovoltaic cells.[32] However, their poor solubility, due to van der Waals forces which aggregate individual pristine carbon nanotubes in bundles, makes them not directly processable for devices.[33] A possible way to overcome this issue consists in covalently binding soluble groups to their nanostructures, although this strategy often induces deep alterations of the desired electronic properties of pristine carbon nanotubes.[34]

An effective alternative approach involves the non covalent functionalization with organic polymers able to wrap around carbon nanotubes preventing their aggregation, without modifying their π-electronic system. The best candidates as effective suspenders are flexible conjugated polymers bearing a highly delocalized π-electron system.[35]

On this ground, the conjugated polymer **1** was successfully tested as a suspender of SWNTs in organic solvent (1,2-dichloroethane) and the resulting suspension was transferred from the air-water interface to solid substrates by LB technique.[36] Other examples of organic polymers employed to solubilize and process nanotubes in thin films by LB procedure were already reported in the literature,[37] but the use of a conjugated polymer such as **1** in this procedure, with the original aim of obtaining a donor-acceptor photoactive film, had not been explored yet.

AFM images were acquired on LB films of the sole polymer **1** (Figure 11a) and of **1**/SWNTs (Figures 11b,c) transferred on glass substrates at different surface pressures (6 and 24 mN/m, respectively). The film of **1**/SWNT deposited at lower surface pressure shows both globular and tubular structures (Figure 11b) whereas control films of **1** showed a globular morphology. On the contrary, only tubular morphology was evidenced for the LB **1**/SWNT film deposited at higher surface pressure with a surprisingly high degree of parallel, oriented tubular structures having average 100 nm diameter and an orientation perpendicular to the film compression. Considering that the diameter of a single-walled carbon nanotube is on the average 1 nm, it was deduced that a non covalent interaction occurs between polymer **1** chains and bundles of SWNTs rather than individual SWNTs: this hypothesis was confirmed by AFM images of **1**/SWNT bundles after exposure to soft X-rays that selectively remove the polymer shell.

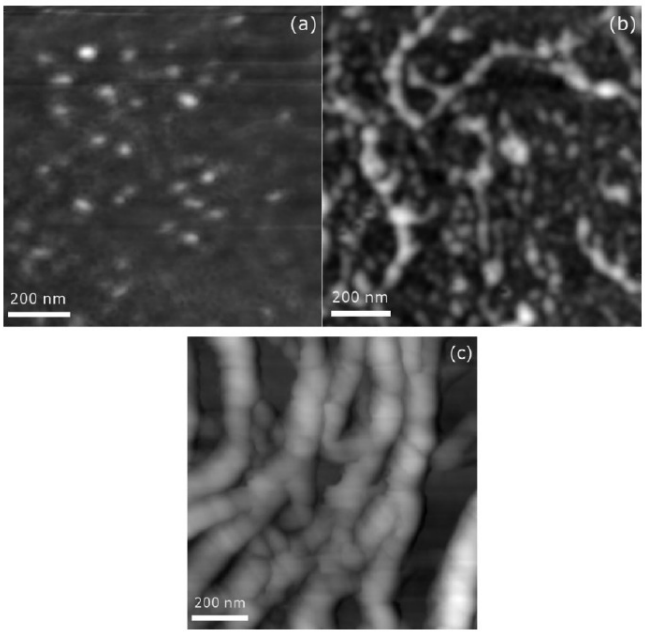


Figure 11. AFM images of (a) polymer **1** LB film at 17 mN/m, (b) **1**/SWNT LB film at 6 mN/m, (c) **1**/SWNT LB film at 24 mN/m. Reprinted with permission from *Adv. Funct. Mater.* **2010**, *20*, 2481. Copyright 2013 Wiley.

Nanostructured cathodes for photo-electrochemical cells were fabricated depositing **1**/SWNT films by LB technique on a indium tin oxide (ITO) substrate with different thicknesses (*i.e.* different numbers of **1**/SWNT monolayers). Photo-electrochemical devices were fabricated in the sandwich-type architecture ITO/(**1**/SWNT)$_n$/I^-,I^-_3/Pt-FTO where n represents the number of monolayers composing the active film: a

solution of 0.5 M LiI and 0.01 M I_2 in acetonitrile was used as the electrolyte and a fluorine doped tin oxide (FTO) coated with Pt was employed as the anode, in accordance with a literature procedure.[38] The best results were recorded for the device made with the 55 LB stacked layers photocathode: in particular, the maximum incident photon to current efficiency (IPCE) was 1.97% and the current-voltage (I–V) characterization showed an open circuit voltage (V_{oc}) of 0.18 V, a short-circuit current (ISC) of 85.8 mA, a fill factor (FF) of 40.0% and a power-conversion efficiency (η) of $6.23 \cdot 10^{-3}$%.

The absorption spectra of the devices exhibit a maximum around 460 nm, resembling both the absorption peaks of a suspension of **1**/SWNT in 1,2-dichloroethane solution and of the device with configuration ITO/(**1**)$_n$/I^-,I^-_3/Pt-FTO fabricated with a Langmuir Schäfer film of the sole polymer **1** instead of the LB **1**/SWNT film (Figure 12a).

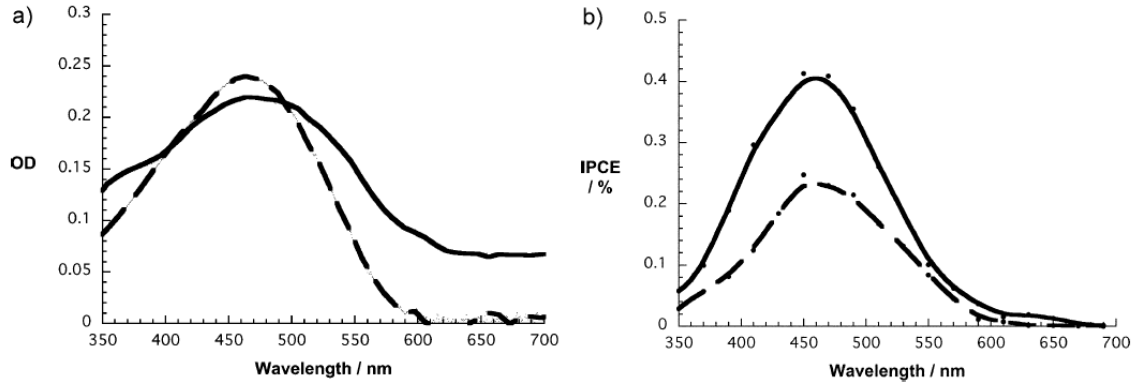


Figure 12. (a) Absorption and (b) IPCE spectra of ITO/(**1**/SWNT)$_{25}$/I^-/I^-_3/Pt-FTO (solid line) and ITO/(**1**)$_{25}$/I^-/I^-_3/Pt-FTO (dashed line). Both devices were fabricated using the same number of monolayers (25). Reprinted with permission from *Adv. Funct. Mater.* **2010**, *20*, 2481. Copyright 2013 Wiley.

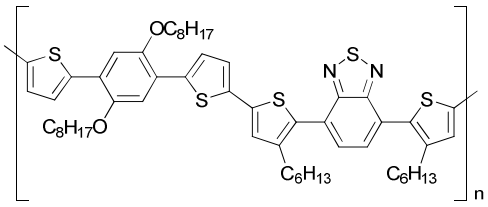
This suggests that the main active component in all photo-electrochemical cells is polymer **1** and its photoexcitation is followed by a rapid charge separation to oxidized **1** and reduced I^-_3 electrolyte. Then, a cascade of hole-transfer processes occurs from **1** to SWNTs and from SWNTs to ITO. The role of SWNTs in this transfer is relevant because their hole-mediating function bridges the high energy gap existing between polymer **1** and ITO. This key role was also demonstrated comparing the incident photon to current efficiency (IPCE) spectra in Figure 12b recorded for two devices with configurations ITO/(**1**/SWNT)$_{25}$/I^-/I^-_3/Pt-FTO and ITO/(**1**)$_{25}$/I^-/I^-_3/Pt-FTO. Indeed, despite the similarity of the corresponding absorption spectra shown in Figure 12a, the photocurrent observed for the device containing SWNTs in the active layer is 40% higher than that recorded for the device made with the sole polymer **1** (Figure 12b).

3. Poly(arylenethienylene)s containing benzothiadiazole and dialkoxyphenylene-thiophene units for polymer solar cells

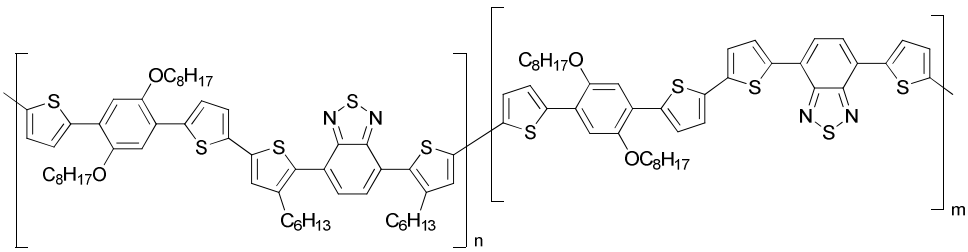
Organic photovoltaics has recently attracted great academic and industrial interest since it offers the possibility to produce semitransparent large area photovoltaic panels with performances independent on the light incident angle and with low plant production costs due to the cheap printing or coating processing techniques.[39,40]

In particular, bulk-heterojunction (BHJ) polymer solar cells[41] are among the most promising organic photovoltaic devices because of their quite simple architecture. Their active layer is composed of a blend of an organic conjugated polymer acting as the donor (D), while the acceptor (A) is most commonly a fullerene

derivative such as [6,6]-phenyl-C61-butyric acid methyl ester (PCBM).[42] In particular, charge generation occurs in the BHJ layer at the interface between D and A and a requisite to achieve good device performances is the correct alignment of the valence energy levels of donor and acceptor also with respect to the metal contacts. Therefore, many efforts are presently focused in the search of the best performing donor and acceptor couple, with special attention to the design of donor materials when C60 is fixed as the acceptor. The best candidates for this purpose are conjugated polymers and molecules with a low band gap (lower than 2eV), since they can absorb effectively a large portion of the solar spectrum.[43] A common approach to the preparation of low band gap polymers consists in the design of conjugated architectures whose extended π conjugation comprises the alternation of electron-rich and electron-poor units along the polymer backbone.[44] With this respect, polymers containing the electron-donating 2,5-dialkoxyphenylene unit combined with thiophene rings and electron-poor units showed promising properties for near infrared photon to electron conversion, though with low overall power conversion efficiencies.[45] Considering the possibility to use the 2,5-dialkoxyphenylene moiety as electron-donating unit in push-pull conjugated polymers and the encouraging results obtained on **1** in many optoelectronic applications, we decided to re-elaborate polymer **1** structure in a low band gap polymer backbone. In this context, the low band gap poly(arylenethienylene)s **15** and **16** (Figure 13) were investigated.[46] Polymer **15** skeleton is composed of an alternation of thiophene-benzothiadiazole-thiophene (TBzT) and thiophene-bis(*n*-octyloxy)phenylene-thiophene (TPhT) moieties; the thiophene rings in TBzT also bear pendant *n*-hexyl chains in order to ensure the polymer solubility. Polymer **16** is instead a random copolymer, combining the repetition unit of **15** with a similar one which does not bear alkyl functionalization in TBzT: this structural difference allows diluting the most planar (but insoluble) repeating units in a soluble polymeric chain, improving the overall absorption properties of the resulting macromolecular structure.



15



16

Figure 13. Chemical structures of polymers **15** and **16**.

3.1. Synthesis of low band gap poly(arylenethienylene)s

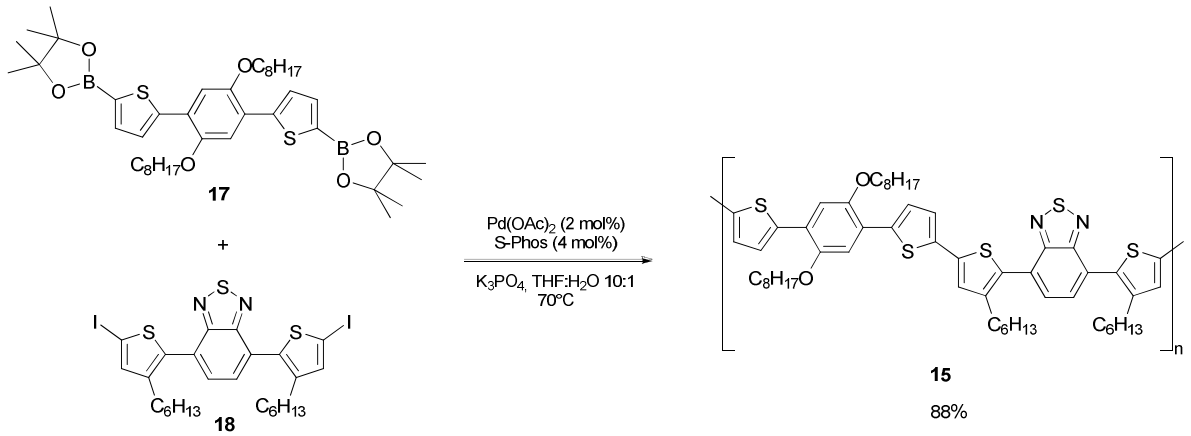
The synthesis of **15** and **16** is entirely based on the Suzuki-Miyaura cross-coupling reaction: this process was firstly used for the preparation of the building blocks **17**, **18** and **19** (Scheme 8) and then for

their polymerization reactions leading to **15** and **16** (Schemes 5 and 6). As previously reported for the synthesis of regioregular poly(3-alkylthiophene)s[47] and of **1** (see Scheme 2), the use of Suzuki cross-coupling reactions involving thiophene derivatives with a boron substitution on the α-position to the sulfur atom largely suffers of deboronation processes induced by the transition metal complex catalyst (usually a Pd complex with phosphine ligands). This drawback justifies the general choice of alternative synthetic methods, mainly based on the Stille, Kumada or Negishi cross-coupling reactions involving different organometallic derivatives of thiophene, which are usually preferred to the Suzuki reaction,[48] although often experimentally more difficult.

A possible way to overcome the drawback related to the Suzuki coupling of thienylboronic reagents consists in the use of phosphine-free palladium catalysts or microwave assisted reaction protocols that speed up the Suzuki process, reducing by-products formation.[47,49] Alternatively, a catalytic complex formed *in situ* by $Pd(OAc)_2$ and an electron-rich phosphine, namely the Buckwald's ligand 2-dicyclohexylphosphino-2′,5′-dimethoxybiphenyl (S-Phos), was recently reported to enhance the Suzuki polymerization yields of regioregular poly(3-alkylthiophene)s with respect to those achieved by more common palladium-phosphine complexes.[50] This result is in agreement with the general observation that the Pd complex with S-Phos ligands is considered one of the most active and long-living catalysts in Suzuki cross-coupling processes, speeding considerably up the oxidative addition step and showing good outcomes also in the presence of pinacol boron derivatives.[51]

Therefore, the effectiveness of this catalyst was investigated for both polymerization reactions leading to copolymers **15**, **16** and for the preparation of the polymerization partners. In particular, a screening of the experimental conditions for the synthesis of polymer **15** (Table 2) revealed that the best results can be achieved carrying out, at 70 °C, the Suzuki reaction between monomers **17** and **18**, in the presence of the base K_3PO_4, the catalyst generated *in situ* from $Pd(OAc)_2$ and S-Phos, working without the use of any phase transfer agent in heterogeneous medium THF/water combined in 10:1 volumetric ratio (Scheme 5, entry 3 in Table 2).

Application to the synthesis of **15** of the experimental protocol reported in the literature for the synthesis of poly(3-alkylthiophene)s involving the ligandless $Pd(OAc)_2$ catalyst in a mixture of an organic solvent (toluene or THF), ethanol and water (entry 1) led to very low yield of a low molecular weight **15**. On the contrary, the use of $Pd(OAc)_2$ and S-Phos independently on the solvent employed and on the heating system applied (thermal or microwave) gave remarkable results.



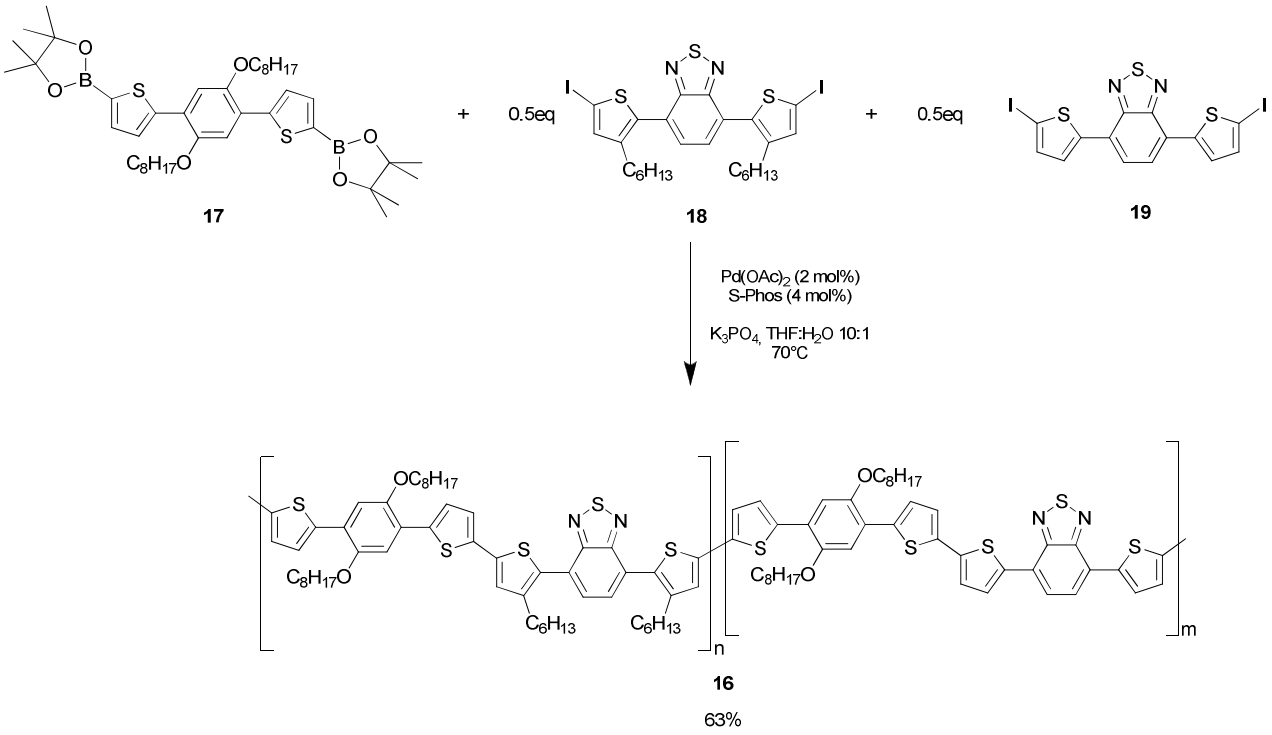
Scheme 5. Synthesis of polymer **15** *via* Suzuki cross-coupling.

Table 2. Screening of the experimental conditions for the synthesis of polymer **15**.

Entry	Catalyst	Base	Solvent	Temperature (°C)	Yield (%)	M_n (KDa)	M_w (KDa)
1	$Pd(OAc)_2$	K_3PO_4	Toluene (or THF):EtOH:H_2O	80–90	11	3.3	5.2
2	$Pd(OAc)_2$/S-Phos	K_3PO_4	Toluene:H_2O 10:1	90	75	5.4	8.5
3	$Pd(OAc)_2$/S-Phos	K_3PO_4	THF:H_2O 10:1	70	91	18.0	30.0
4	$Pd(OAc)_2$/S-Phos	K_3PO_4	THF:H_2O 10:3	130 for 40 min[a]	98	8.0	14.6

[a] Carried out in a microwave oven with a power of 180W.

Average molecular weights (GPC) of the isolated chloroform soluble fraction of **15** increased with increasing of the crude product solubility in the polymerization solvent ranging from toluene/water to THF/water 10:3 to THF/water 10:1 (entries 2–4 in Table 2). Therefore, the solvent mixture reported in entry 3 of Table 2 was considered the most suitable for obtaining high molecular weight materials and the use of THF/water 10:1 was eventually extended to the synthesis of polymer **16** (Scheme 6).



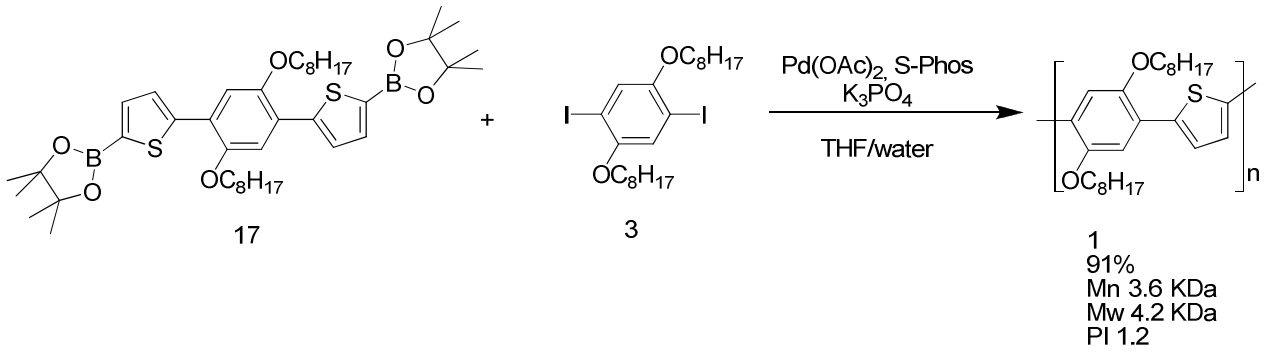
Scheme 6. Synthesis of polymer **16** *via* Suzuki cross-coupling.

The reduced presence of alkyl chains in **16** resulted in lower yield of the chloroform soluble fraction and, more in general, limited the solubility of this material in common organic solvents. A soluble fraction of **16** in chlorobenzene could be recovered in 63% yield, showing average molecular weights *M*n ~ 6.3 kDa and *M*w ~ 10.0 kDa.

The same polymerization protocol was extended to the synthesis of **1**, already discussed in paragraph 2.1, to have a reference material for proper comparison (Scheme 7). Interestingly, the yield of **1** with this experimental protocol is the highest ever reported.

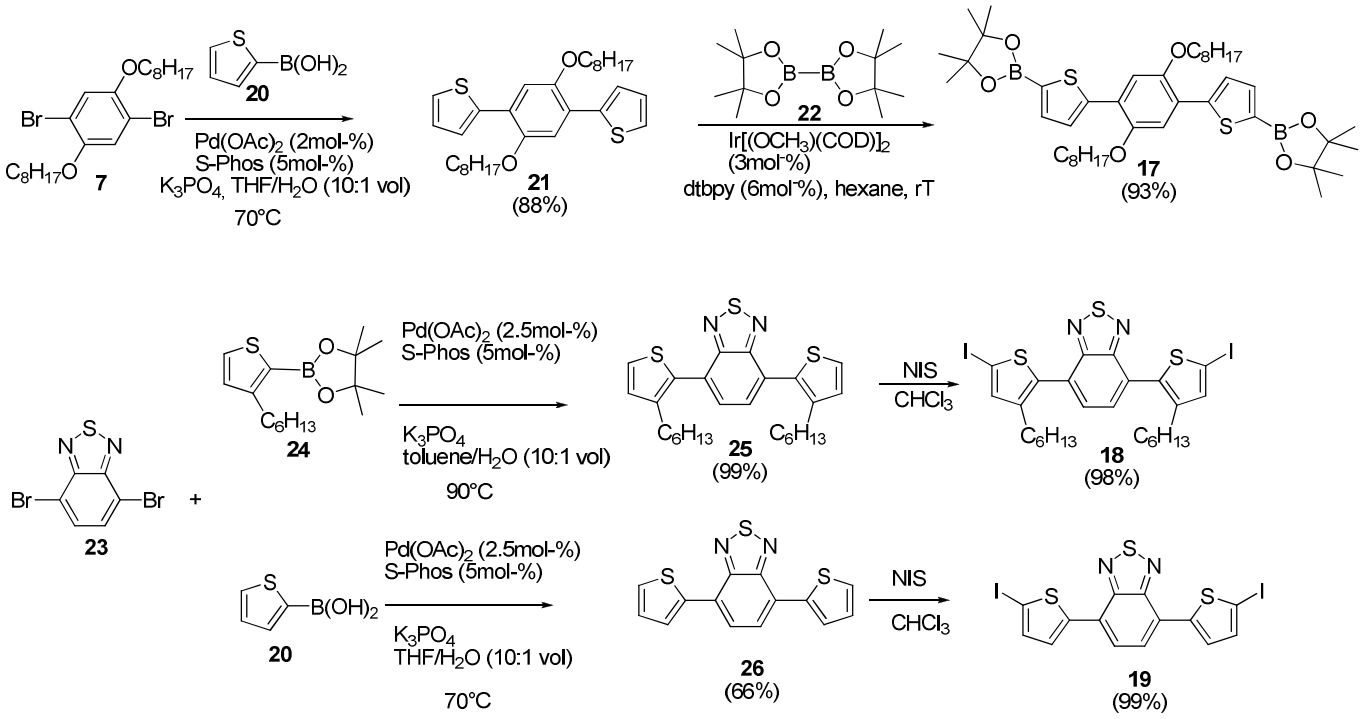
Similar experimental conditions of Suzuki cross-coupling were also used for the preparation of the reactive monomers (Scheme 8). Bis-pinacolboronic ester **17** was obtained in two steps, the first based on the Suzuki coupling of 1,4-dibromo-2,5-di(octyloxy)benzene **7** with 2-thiopheneboronic acid **20** leading to **21** in

88% yield. The same synthesis performed with $Pd(PPh_3)_4$ as the catalyst afforded **21** in only 10% yield, confirming the inhibitory effect of PPh_3 on the reaction. The almost quantitative boronation of **21** was then carried out with bis(pinacolato)diboron **22** in hexane, using $Ir[(OCH_3)(COD)_2]$ and 5,5′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as the catalysts.[52]



Scheme 7. Synthesis of **1** by our Suzuki approach.

4,7-Dibromo[2,1,3]benzothiadiazole **23** reacted with the thienylboronic derivatives **24** or **20** under similar Suzuki cross-coupling conditons and the corresponding products were subjected to quantitative iodination reaction leading to **18** and **19**, respectively (Scheme 8).



Scheme 8. Synthesis of the monomers **17–19**.

3.2. Application of low band gap poly(arylenethienylene)s in bulk-heterojunction solar cells

The UV-vis absorption spectra of **15** and **16** films (Figure 14b) are red-shifted with respect to the corresponding spectra in dilute chloroform solution (Figure 14a), due to intermolecular interactions in the solid state. The red-shift is more pronounced in **16** than in **15**, likely due to the more planar structure of **16** where less distorting alkyl chains are attached to the conjugated backbone.

The HOMO energy levels of **15** and **16** were determined from the oxidation potentials (E_{ox} in Table 3) measured by cyclic voltammetry of thin films of both polymers (Figure 15), using as reference the redox

couple ferrocene/ferrocenium, whose energy level was assumed to be −4.8eV.[53] Voltammograms of **15** and **16** were measured on a platinum working electrode in acetonitrile with $TBAPF_6$ 0.1M supporting electrolyte, using an Ag/AgCl reference electrode.[54] The UV-vis absorption onsets furnished the optical band gap values reported in Table 3 for the two polymers. Hence, the LUMO energy level was estimated by difference between the HOMO energy level obtained electrochemically and the optical band gap. The data derived from electrochemical and optical measurements are summarized in Table 3. The low band gap values (1.9 eV and 1.7 eV for **15** and **16**, respectively) together with the proper alignment of the energy levels with respect to the energy levels of the PCBM acceptor make both polymers suitable as donor materials for bulk heterojunction (BHJ) solar cells.[39]

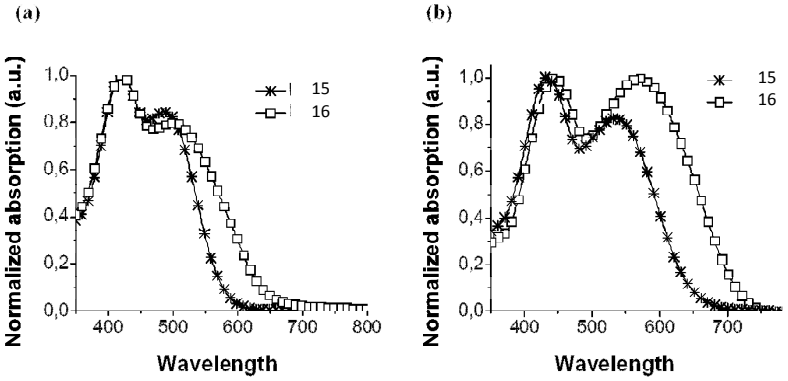


Figure 14. Normalized absorption spectra of **15** and **16** in (a) $CHCl_3$ solution and (b) spin-coated film on quartz substrate. Reprinted with permission from *Sol. Energy Mater. Sol. Cells* **2011**, *95*, 3490. Copyright 2013 Elsevier.

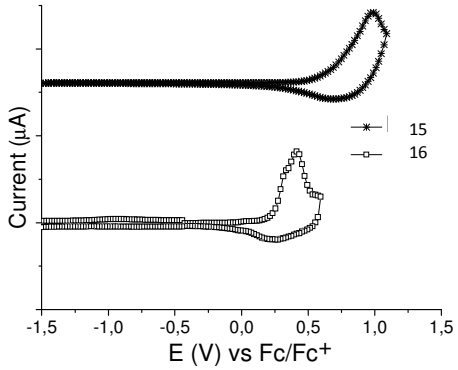


Figure 15. Oxidation cyclic voltammograms of **15** and **16** films cast on a platinum electrode. Potentials are given with respect to $E°_{Fc/Fc+}$. Reprinted with permission from *Sol. Energy Mater. Sol. Cells* **2011**, *95*, 3490. Copyright 2013 Elsevier.

Table 3. Optical and electrochemical data of **15** and **16**. Reprinted with permission from *Sol. Energy Mater. Sol. Cells* **2011**, *95*, 3490. Copyright 2013 Elsevier.

	λ_{max} ($CHCl_3$) (nm)	λ_{max} (film) (nm)	E_{ox} (film) (V)	Optical band gap (film) (eV)	HOMO (eV)	LUMO (eV)
15	488	533	0.60	1.9	−5.4	−3.5
	422	431				
16	500	572	0.23	1.7	−5.0	−3.3
	422	445				

A series of BHJ solar cells was fabricated using ITO/PEDOT:PSS as the anode, calcium/aluminum as the cathode and various spin coated active layers of **15**:PCBM and **16**:PCBM blends. The acceptor used was PC[60]BM. The best performances were obtained when the layers were casted from chloroform in a blend weight ratio 1:2 of polymer with respect to the acceptor PC[60]BM.

The current-voltage (IV) characteristics of the two best solar cells prepared are reported in the Figure 16, while the device parameters are summarized in Table 4. **15** showed better performance than **16** in terms of open circuit voltage (V_{oc}=0.87) and photocurrent efficiency (PCE=1.2%). In this case, the high V_{oc} value can be attributed to a very good alignment of **15** HOMO level with respect to the LUMO of PCBM.

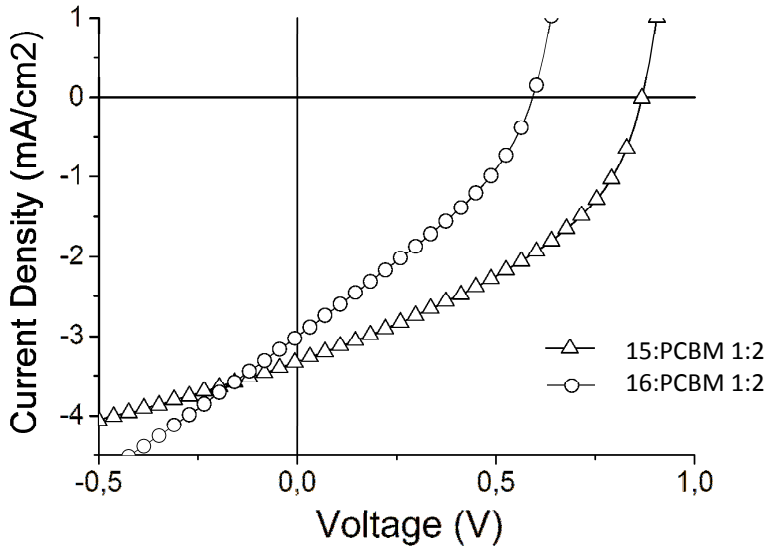


Figure 16. Current-potential characteristics of not optimized devices prepared with blends of **15**:PCBM and **16**:PCBM (1:2 weight ratio) casted from chloroform. Reprinted with permission from *Sol. Energy Mater. Sol. Cells* **2011**, *95*, 3490. Copyright 2013 Elsevier.

Table 4. Photovoltaic responses of polymers **15** and **16**.

Blend	PCE (%)	FF	Voc [V]	Jsc [$mAcm^{-2}$]
15:PCBM 1:2	1.2	0.41	0.87	3.3
16:PCBM 1:2	0.6	0.33	0.60	3.0

The solar cell fabricated using polymer **16** as the donor material in the active layer in the same conditions showed globally lower photovoltaic performances (V_{oc}=0.60 and PCE=0.6%), despite the broader absorption spectrum of **16**. This can be explained as follows: on one hand, the absence of alkyl chains in the second repeating unit of **16** induces planarization of polymer chain with respect to **15**, raising the HOMO energy level of **16**. This results in a lower value of the open circuit voltage for the device made with the blend **16**-PCBM. Moreover, the IPCE spectrum of **16**:PCBM shows limited photons to electrons conversion at the highest wavelengths (Figure 17b) with respect to the IPCE spectrum measured for the device containing **15** and PCBM. Furthermore, the fill factor of **16**:PCBM blend was limited by a low parallel resistance, *i.e.* the slope of the IV curve at low voltages. This is often attributed to the morphology of the active layer, for instance to its inhomogeneous formation.

AFM topographies confirm this hypothesis: AFM image of **16**:PCBM spin coated blend reveals the presence of roughly 50 nm big holes in the surface (Figure 18, right), that quite probably plague its charge transport attitude. Conversely, **15**:PCBM generates much more uniform active layers, this reflecting in **15** based device better performances. Further optimization of active layers by means of additives, as well as optimization of device architecture, are expected to further improve device performances.

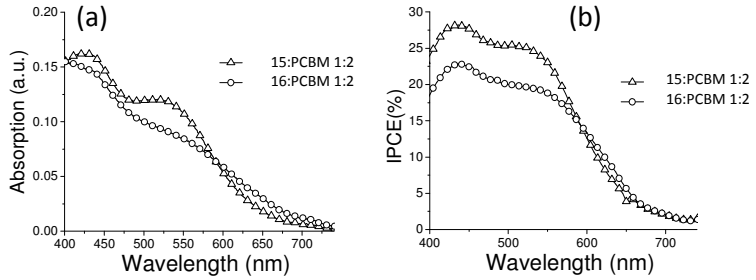


Figure 17. (a) Absorption spectra of polymer:PCBM 1:2 blends; (b) IPCE curves of the corresponding devices. Reprinted with permission from *Sol. Energy Mater. Sol. Cells* **2011**, *95*, 3490. Copyright 2013 Elsevier.

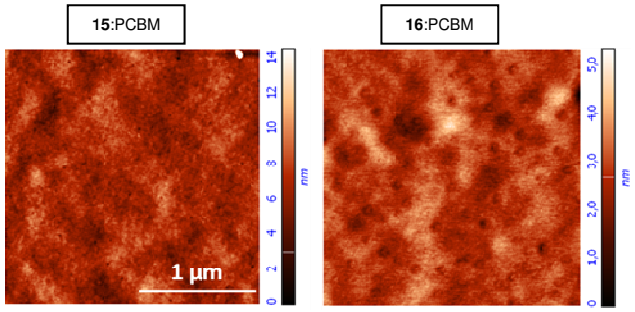


Figure 18. Tapping mode AFM topography images of spin coated blends of polymers:PCBM 1:2 (2 µm x 2 µm). Reprinted with permission from *Sol. Energy Mater. Sol. Cells* **2011**, *95*, 3490. Copyright 2013 Elsevier.

4. Aminoacid- and glucose-substituted phenylenethiophene oligomers for high performance enantio-selective electrical sensors

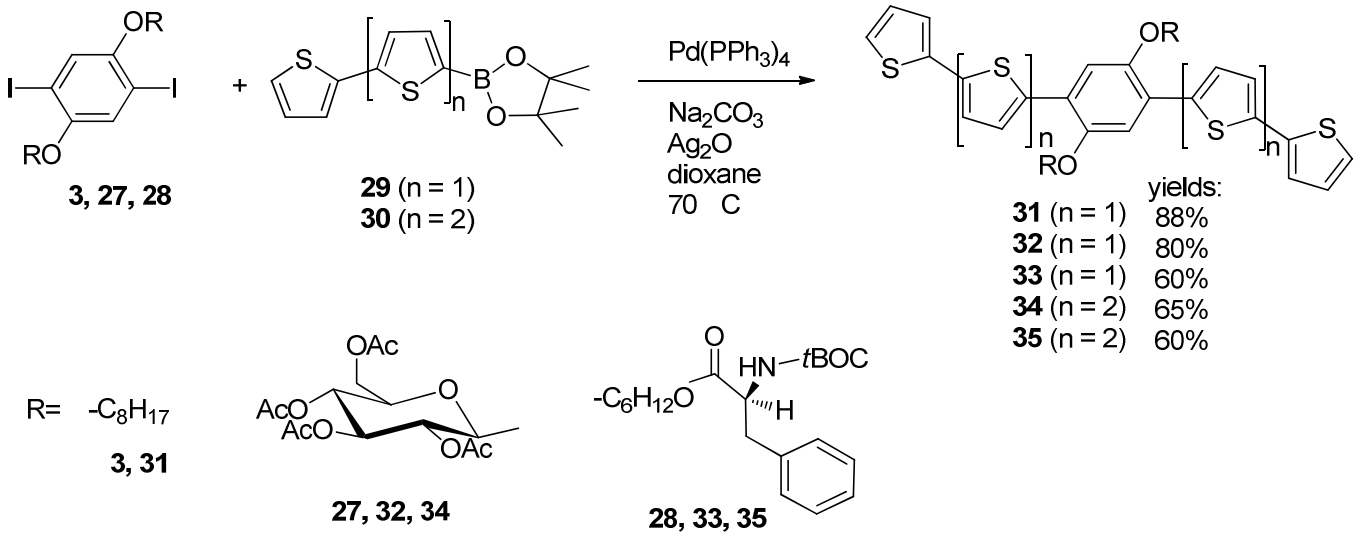
Many applications of semiconducting polymers and oligomers in organic electronics are related to the selective functionalization of their conjugated backbone with tailored substituents. These groups not only enable fine tuning of optoelectronic properties of the resulting materials, but can also confer them specific properties such as the ability to selectively interact with analytes. In particular, the functionalization with chiral enantiopure biomolecules, such as monosaccharides or amino acids, generates polyconjugated materials which can combine the semiconducting properties of the conjugated backbone with the enantioselective recognition ability towards specific chiral molecules, eventually opening the way to the development of highly sensitive enantioselective sensors.[55] Chiral discrimination is in fact a challenging scientific and technological task with huge potential for applications in several areas such as catalysis, pharmacology, food-monitoring and medical diagnostics. The physical-chemical properties of two enantiomers can change exclusively upon interaction with another chiral molecular receptor and biological or physiological effects of such enantio-specific interactions can be dramatically different. Currently, optical isomers detection is mostly carried out using off-line analytical techniques such as chromatography or NMR spectroscopy. On the contrary, chiral solid-state sensors hold the potential to carry out on-line enantiomer

discrimination, with important impact on industrial process monitoring. In this context, chirally functionalized conjugated compounds have been used thus far in fluorescence[56] or electrochemical[57] enantioselective sensing, as well as in enantioselective quartz crystal microbalance gravimetric gas sensors.[58]

With the aim to access a new class of electrical enantioselective sensing devices we focused our attention on the design and synthesis of phenylenethiophene oligomers decorated with small chiral biomolecules, namely peracetylated D-glucose and *N*-*t*-butoxycarbonyl L-phenylalanine which can be bound to the conjugated structure through alkoxy linkages (compounds **32** and **33** in Scheme 9).[59]

4.1. Synthesis of chiral biofunctionalized phenylenethiophene oligomers

The synthesis of **31**, **32** and **33** is based on the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction between the bis(thiophene)pinacol boronic ester **29** and the functionalized diiodobenzenes **3**, **27**[60] and **28**,[61] respectively (Scheme 9). The reaction is catalyzed by $Pd(PPh_3)_4$ and Ag_2O and it is performed in the presence of Na_2CO_3 and dioxane as the base and the solvent, respectively. These conditions well tolerate the presence of the chiral bio-functionalization in **27** and **28**, leading to the coupling products in good yields. Moreover, deboronation of the thiophene derivatives is prevented by the higher reactivity of aryl diodide coupling partners with respect to aryl dibromide counterparts and by the presence of silver oxide which considerably speeds up the reaction, assisting the elimination of iodide from the metal catalyst and favouring the subsequent transmetalation step.[62]



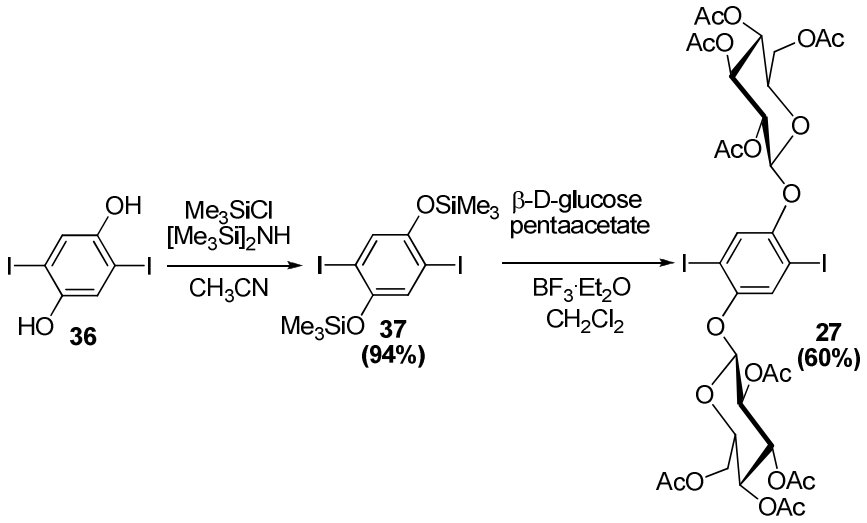
Scheme 9. Synthesis of symmetric oligo(phenylenethiophene)s **31–33** and **34**, **35**.

The D-glucose functionalized diiodide **27** was obtained by converting 2,5-diiodohydroquinone **36** into the corresponding bistrimethylsilyl ether **37** which then reacted with β-D-glucose pentaacetate (Scheme 10), according to a glycosidation protocol reported in the literature for the synthesis of phenyl-*O*-glycosides.[63]

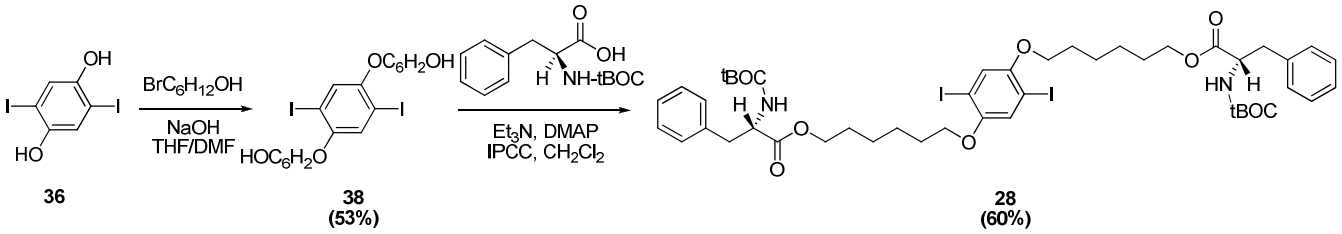
The chiral amino acid substituted aromatic diiodide **28** was obtained in good yield by the nucleophilic substitution of 2,5-diiodo-hydroquinone **36** with 6-bromo-1-hexanol followed by the esterification reaction of the resulting diol **38** with the *N*-protected L-phenylalanine, in the presence of isopropenylchlorocarbonate (IPCC) as the condensing agent (Scheme 11). This process occurs without racemization of the amino acid.

The synthetic approach to **31–33** was extended to the preparation of the homologues **34** and **35** (Scheme 9). A similar procedure was used for the preparation of oligothiophenes **41–44** and **47–50**

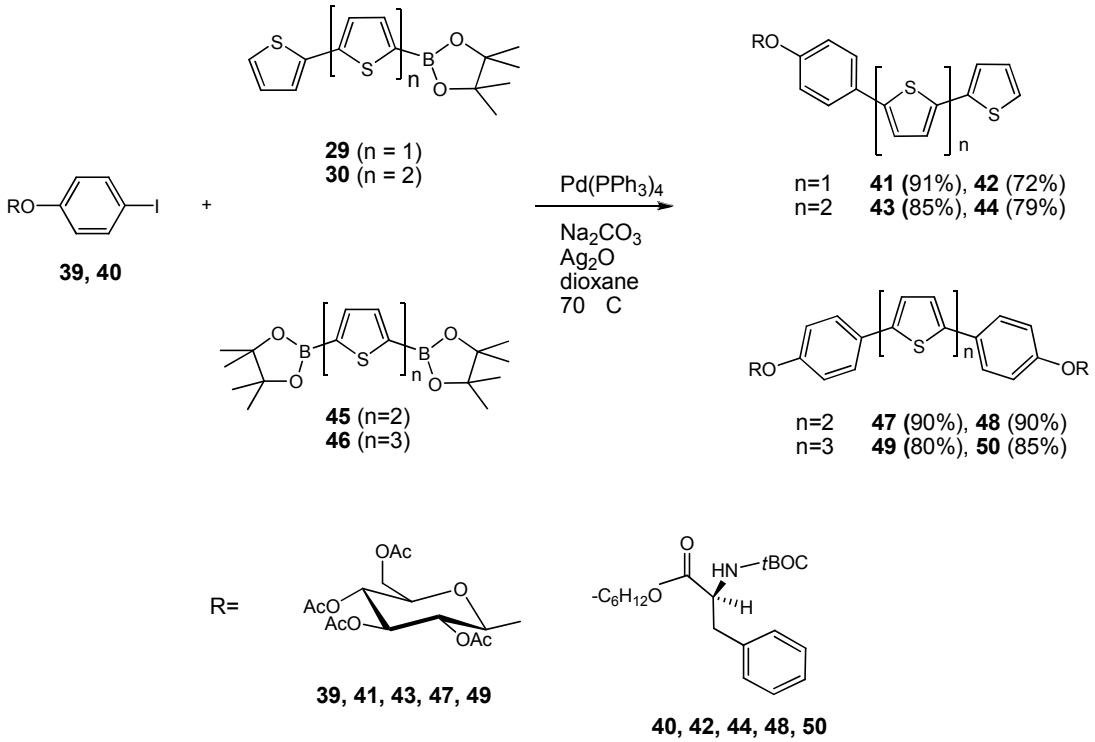
terminating at one or both ends with a D-glucose or L-phenylalanine alkoxy functionalized phenyl ring (Scheme 12). The chiral units **39** and **40** were obtained from 4-iodophenol, according to the method already described for **27** and **28** (Schemes 10 and 11).



Scheme 10. Synthesis of **27**.



Scheme 11. Synthesis of **28**.



Scheme 12. Synthesis of chiral oligomers **41–44** and **47–50**.

4.2. Chiral phenylenethiophene oligomers as active materials in high performance electrical chiral sensors

The D-glucose and L-phenylalanine substituted oligo(phenylenethiophene)s **32** and **33** (Figure 19) were used as the sensing layers in high performance OTFT-based enantioselective sensors for chiral analytes, such as citronellol and carvone, in the vapor phase.[64] A detection threshold three orders of magnitude lower than any other solid state enantioselective sensor reported so far[65] was achieved with these materials. In the enantioselective sensors, an interlayer of the dialkoxy phenylenethiophene **31** was deposited between the gate dielectric SiO_2 and the sensing layer made of **32** or **33**. The bidimensional charge transport typical of transistor behaviour occurs in the **31** film, while **32** and **33** discriminate the enantiomers of chiral analytes in the vapor phase by interaction with the glucose and amino acid side groups. Thin films of **32** or **33** alone did not show field-effect amplified current, most likely due to the bulky bio-substituents preventing effective interchain π–π stacking necessary for effective thin film charge transport. This is a general issue to be faced when developing OTFT-based biosensing devices, especially when receptors are covalently bound to the conjugated main chain and can interfere with the active layer supramolecular organization. The bilayer thin-film architecture developed for **32** and **33** is shown in Figure 19: it comprises an outermost LS layer of the chiral-substituted molecular semiconductors **32** or **33**, deposited on the top of a layer of the achiral **31**.

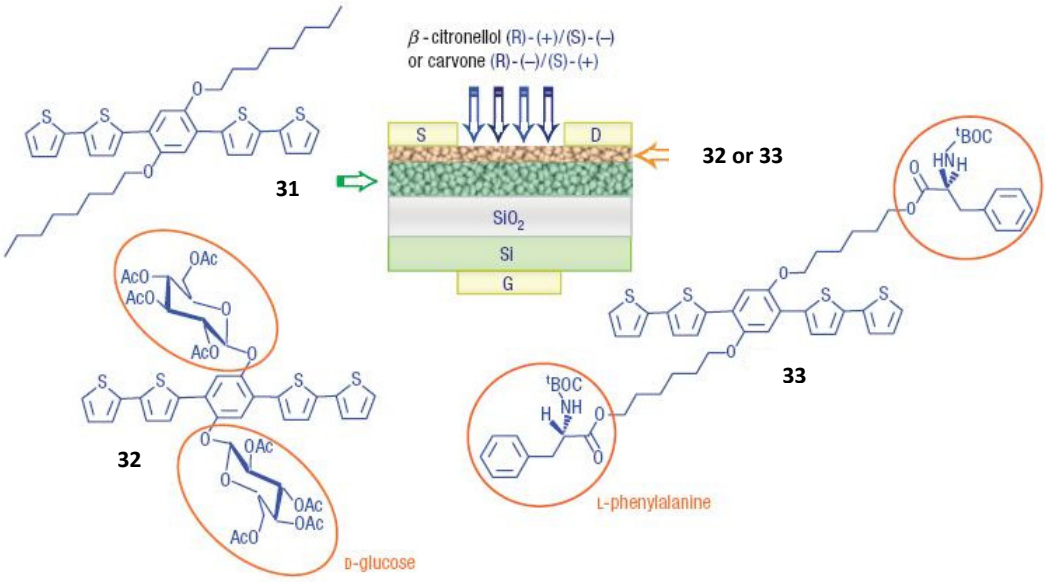


Figure 19. Structures of the phenylenethiophene oligomers **31–33** and OTFT chiral sensor scheme. Reprinted with permission from *Nat. Mater.* **2008**, *7*, 412. Copyright 2013 Nature Publishing Group.

The electrical characteristics measured in nitrogen atmosphere and in the presence of citronellol or carvone analytes were used to derive the sensor response. In particular, the sensor made with the D-glucose functionalized compound **32** discriminated the two enantiomers of carvone (Figure 20a), while the device based on L-phenylalanine functionalized oligo(phenylenethiophene) **33** exhibited different sensitivity to the two citronellol enantiomers (Figure 20b).

Conversely, no chiral differential detection was observed exposing the sensor based on **32** to citronellol and the sensor based on **33** to carvone. This system-dependent selectivity is not surprising since weak intermolecular interactions responsible for chiral discrimination critically depend on structural differences of the molecules involved. A possible working mechanism of the device can be proposed

considering that both the **31** thin film deposited on the gate dielectric and the active **32** or **33** layers are composed of contiguous grains roughly 50–100 nm wide and comparable large voids.

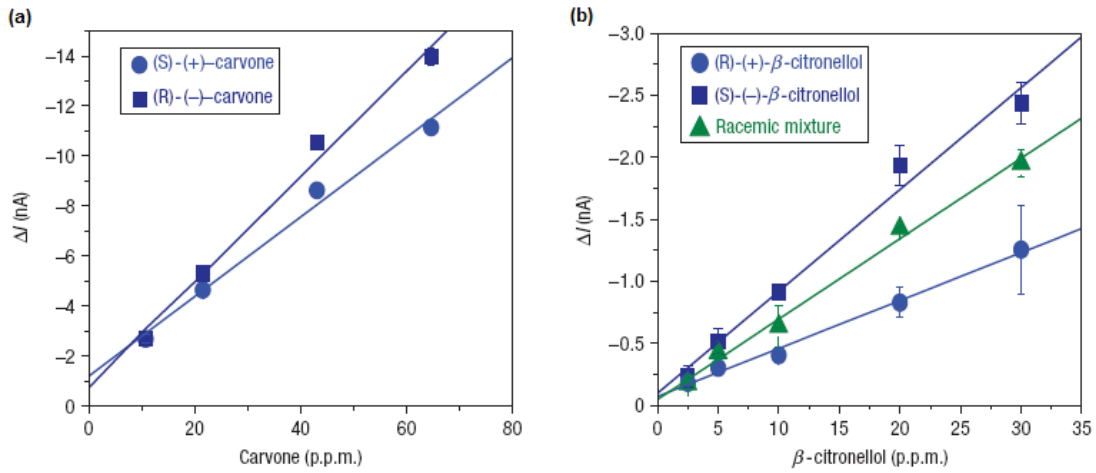


Figure 20. Calibration curves of (a) device made with **32** exposed to carvone enantiomers, (b) device made with **33** exposed to citronellol enantiomers and their racemic mixture. Reprinted with permission from *Nat. Mater.* **2008**, *7*, 412. Copyright 2013 Nature Publishing Group.

When OTFTs are exposed to the vapors, the chiral analyte molecules diffuse into the organic semiconductor solid phase percolating through the voids around the grains. The interaction between specific chiral analyte molecules and chiral side groups in **32** or **33** grains composing the external active layer differentiates the aliquot of the two enantiomers reaching the inner layer of **31** and its interface with the dielectric where the analyte can affect the device transport properties.

5. Conclusions

Our overview has shown wide opportunities offered by tailoring arylene thiophene conjugated structures for different applications in organic optoelectronics. In particular, conjugated polymers and oligomers alternating 2,5-thiophene and 1,4-(2,5-dialkoxyphenylene) units can be easily synthesized by simple chemical routes involving cross-coupling reactions of non-toxic organomagnesium or organoboron derivatives with aryl dihalides. Alkoxy functionalization of the phenyl rings offers easy chemical access to a variety of structures with tailored properties, *e.g.* by introduction of substituents and control of conformation. Here we have discussed two examples of these possibilities: (a) planarization of the structure by non covalent S–O interactions in LS thin fims of **1** with improved electrical properties (applications in transistors and electrical sensors); (b) introduction of chiral biological substituents which confers chiral discrimination ability (high performance electrical chiral sensors). The alkoxy phenylene thiophene structure can be further elaborated into more complex low band gap conjugated materials that can be used as donors in bulk-heterojunction solar cells.

Easy control of properties at the molecular level is a key feature of organic semiconductors: our contributions on functionalized dialkoxyphenylene-thiophene molecules and polymers not only represent well this concept, but also show the key role of synthetic logic in tailoring multifunctional organic semiconductors for advanced applications.

Acknowledgments

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SYNTHESIS AND CHEMISTRY OF THIENOTHIAZOLES AND THIENOFURANS

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Abstract. *Here we review the syntheses of thienothiazoles and thienofurans. The different isomeric forms have been studied for those compounds as well as the syntheses starting either from thiophenes, thiazoles or furans. Some references to benzocondensed systems have also been included.*

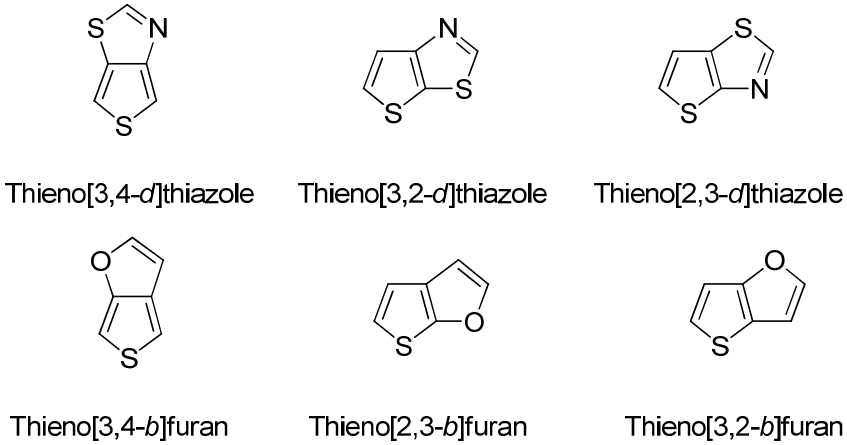
Contents

1. Introduction

Thienothiazoles are condensed heterocyclic systems that exist in three isomeric forms: thieno[3,4-*d*] thiazole, thieno[3,2-*d*]thiazole and thieno[2,3-*d*]thiazole (Scheme 1). They could either be synthesized starting from thiophene or from thiazole. Those heterocyclic scaffolds have found applications in several domains such as electrochromic materials, photovoltaic devices or biological systems.

In this review, we selected the most important literature reports on thienothiazoles and we classified them according to the type of isomer. In each case, we discussed both the synthetic pathways and the developed applications, if any.

We performed the same task on thienofurans, reviewing the three isomeric forms *i.e.* thieno[3,4-*b*] furan, thieno[2,3-*b*]furan and thieno[3,2-*b*]furan (Scheme 1). Synthetic pathways starting from thiophenes or furans were studied.

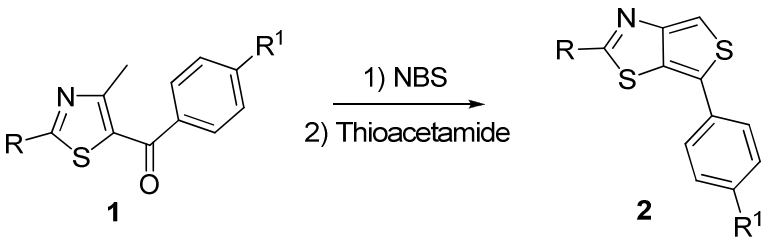


Scheme 1

2. Thienothiazoles

2.1. Thieno[3,4-*d*]thiazoles

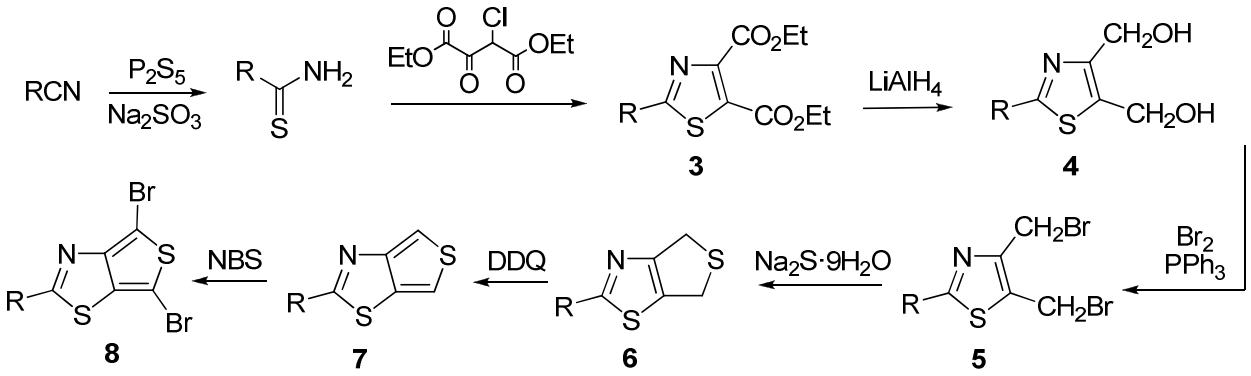
This isomer is the least studied one as a SciFinder's structure search gave only 44 molecules and 14 references (*versus* 559 molecules and 56 references for the preparation of thieno[3,2-*d*]thiazoles; all SciFinder's structure searches were performed in june 2012). Thieno[3,4-*d*]thiazoles are mostly synthesized starting from functionalized thiazoles. Readily available aryl 2-substituted-4-methyl-5-thiazolyl ketones **1** were brominated with *N*-bromosuccinimide (NBS), then reacted with thioacetamide and cyclized to afford 2,6-disubstituted-thieno[3,4-*d*]thiazoles **2** (Scheme 2).[1] The same condensation was also realized on methyl 2-substituted-4-methyl-5-thiazolyl ketones.[2]



Scheme 2

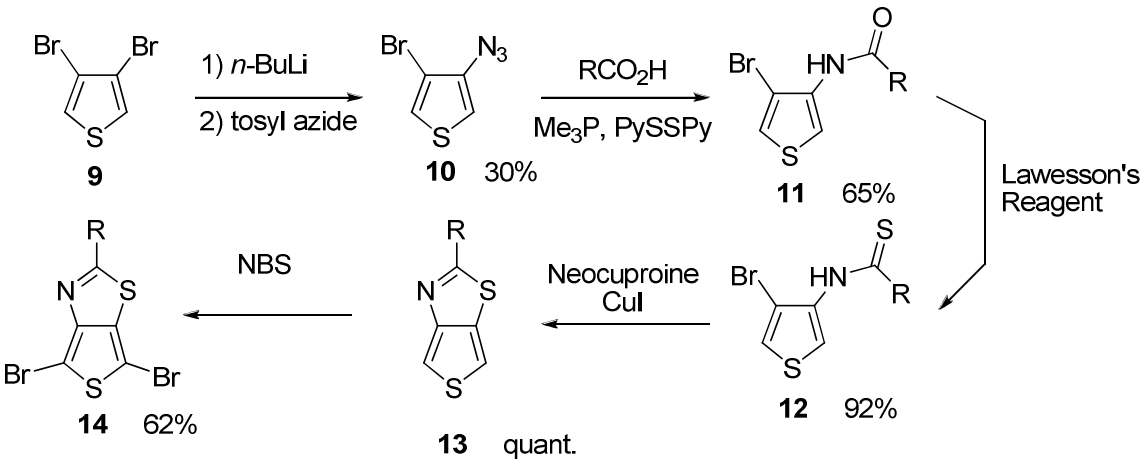
More recently, Kim *et al.* reported the synthesis of novel low band gap conjugated conducting poly (2-nonylthieno[3,4-*d*]thiazole) through cyclovoltammetric polymerization.[3] The monomeric thieno[3,4-*d*] thiazole unit **8** was obtained *via* a seven-step pathway and formation of the intermediate thiazole **3** (Scheme 3). As this polymer showed interesting conductivity values, Allard *et al.* decided to investigate the photovoltaic properties of copolymers using the thieno[3,4-*d*]thiazole unit.[4] They used the same synthetic procedure but introduced an octyl side chain on position 2. The thieno[3,4-*d*]thiazole unit was then brominated at positions 4 and 6 with NBS and engaged in a Stille coupling with 2,6-bis(trimethyltin)-4,8-di-(ethylhexyloxy)benzo[1,2-*b*:4,5-*b'*]dithiophene. The main drawbacks of this synthetic strategy are that this

seven-step synthesis included a low-yielding step (formation of dihydrothiophene **6**; yield=18% for R=C_8H_{17}) and furthermore, the chain length must be decided in the first step so that later structural modification would be difficult.



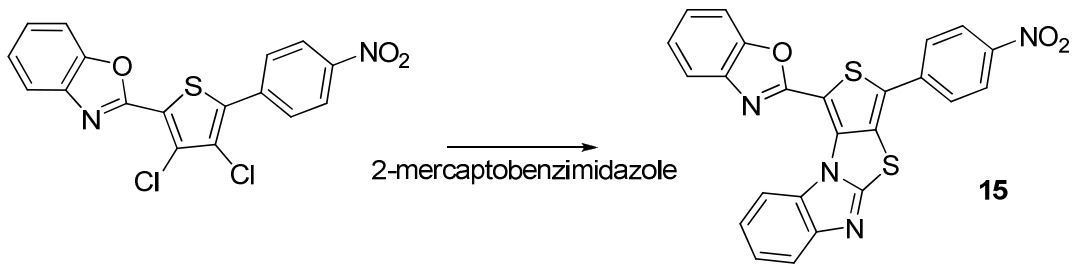
Scheme 3

Uy *et al.* developed an improved synthesis of thieno[3,4-*d*]thiazole unit *via* a four-step high-yielding procedure starting with 3,4-dibromothiophene **9** and using a Cu-catalyzed cyclization of thioamide **12** to form the thieno[3,4-*d*]thiazole core (Scheme 4).[5] The promising results obtained in photovoltaic studies demonstrated the benefits of backbone modification and the great potential of thieno[3,4-*d*]thiazole in the design of new polymers for organic photovoltaics.



Scheme 4

Finally, c-hetero-fused thiophene derivative **15** was obtained starting from a properly substituted 3,4-dichlorothiophene by a condensation with 2-mercaptobenzimidazole in presence of sodium carbonate in refluxing DMF (Scheme 5).[6]

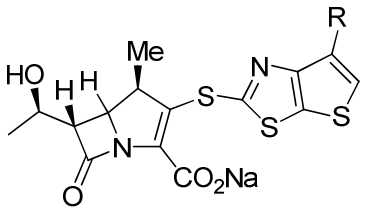


Scheme 5

2.2. Thieno[3,2-*d*]thiazoles

This isomer is much more described than thieno[3,4-*d*]thiazole and its synthesis is usually performed starting from thiophene.

This core has been included in compounds with potent anti-MRSA (methicillin-resistant staphylococcus aureus) activity (Scheme 6).[7] Waddell *et al.* have indeed associated carbapenem moiety with several sulfur-linked aryls and tested their potency on a battery of microorganisms. Compounds **16** with a thieno[3,2-*d*]thiazole as aryl substituent presented a Minimum Inhibitory Concentration of 2 µg/mL on MRSA (*vs*. MIC (Imipenem)=64 µg/mL).

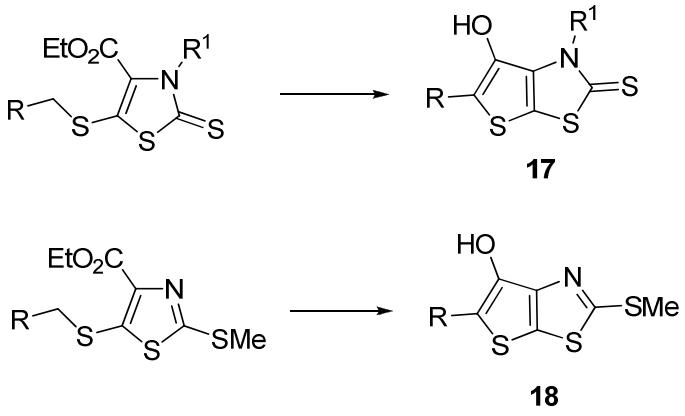


16 R = CO_2Me or CH_2OH

Scheme 6

2.2.1. Synthesis starting from thiazole

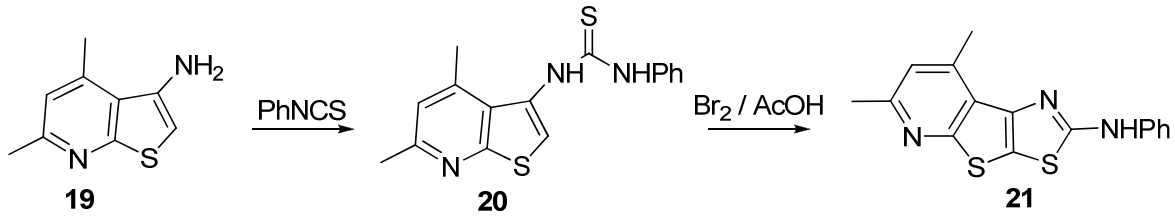
There are only few reports on the synthesis of thieno[3,2-*d*]thiazole starting from thiazole. Thienothiazolinethiones **17** and thienothiazoles **18** have been obtained by cyclocondensation reaction of ethyl (alkylthio)dihydrothioxo- or (methylthio)thiazolecarboxylates, respectively (Scheme 7).[8] In the same way, 5-chloro-2-phenyl-thiazole-4-carboxaldehyde was condensed with thioglycolic acid to lead to 2-phenylthieno[3,2-*d*]thiazole-5-carboxylic acid.[9]



Scheme 7

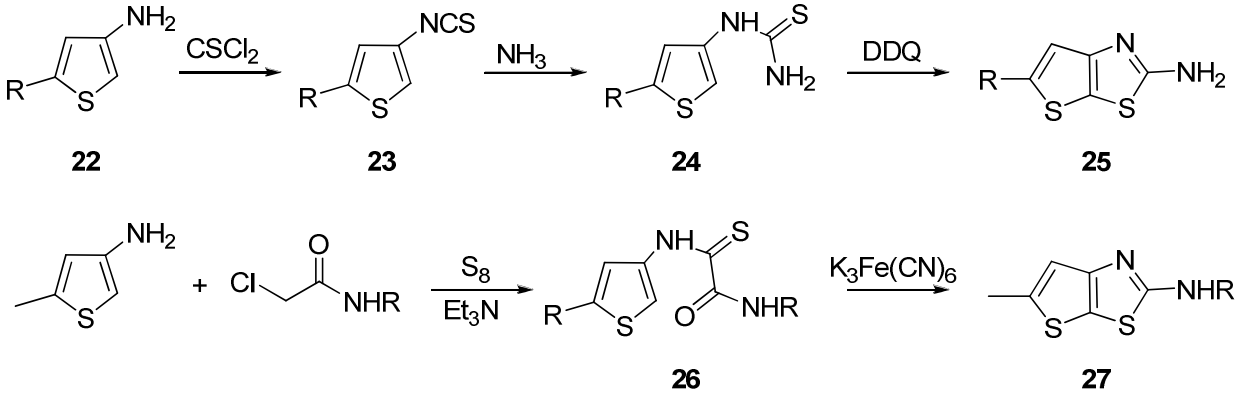
2.2.2. Synthesis starting from thiophene

The main precursors of thieno[3,2-*d*]thiazoles are 3-aminothiophenes. Thiocyanation of 3-amino-thiophene with ammonium thiocyanate and subsequent cyclization allowed the formation of thieno[3,2-*d*] thiazoles.[10,11] 3-Aminothieno[2,3-*b*]pyridine **19** was converted into diarylthiourea **20** by reaction with phenylisothiocyanate. This intermediate was then cyclized in thieno[3,2-*d*]thiazole **21** by Br_2 (Scheme 8).[12] Grehn *et al.* have applied the same methodology using benzoylisothiocyanate giving 2-acylaminothieno [2,3-*d*]thiazole.[13]



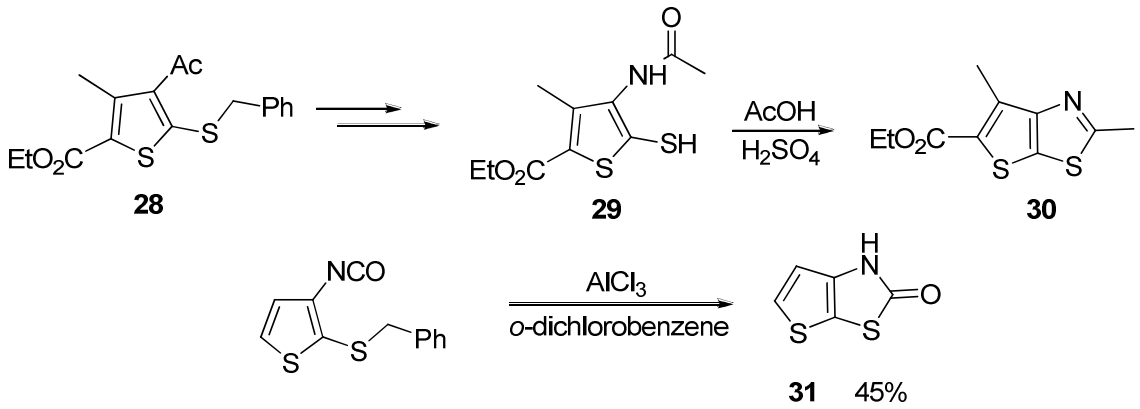
Scheme 8

Revelant *et al.* have transformed 5-substituted-3-aminothiophenes into isothiocyanates **23** and then into primary thioureas **24** which were cyclized in 2-aminothieno[3,2-*d*]thiazoles **25** thanks to DDQ (Scheme 9).[14] Another convenient procedure is the cyclization of monothiooxamides **26** with potassium hexacyanoferrate $K_3Fe(CN)_6$. The monothiooxamides could be easily synthesized by reaction between chloroacetamides and a solution of elemental sulfur and aminothiophenes in amines (Scheme 9).[15,16]



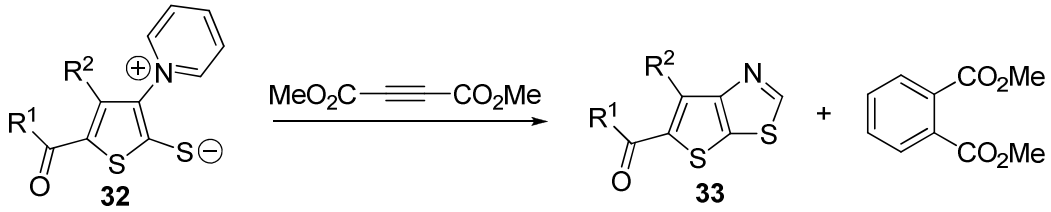
Scheme 9

Beckmann rearrangement of oxime derivative from compound **28**, followed by debenzylation of the resulting acetamido-compound with $AlCl_3$ in benzene gave ethyl 4-acetamido-5-mercapto-3-methyl-thiophen-2-carboxylate **29**. Treatment of this intermediate with AcOH-H_2SO_4 gave thieno[3,2-*d*]thiazole **30** in 87% yield.[17] Ortho-substituted thienyl isocyanates gave thienothiazolinones **31** by thermal rearrangement in presence of $AlCl_3$ (Scheme 10).[18]



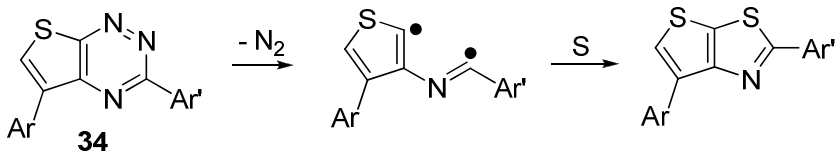
Scheme 10

Reaction of 5-acyl-3-(1-pyridinio)thiophene-2-thiolates **32** with dimethyl acetylenedicarboxylate in refluxing xylene afforded the corresponding 2-unsubstituted 5-acylthieno[3,2-*d*]thiazoles **33** in 25–69% yields together with dimethyl phthalate as another fragmentation product (Scheme 11).[19]



Scheme 11

Finally, thieno[3,2-*d*]thiazole has also been isolated as a product of gas-phase thermolysis of thieno [3,2-*e*][1,2,4]triazine **34** together with benzonitrile, isothiazole, pyrimidine and benzothieno[2,3-*d*] pyrimidine derivatives.[20] A mechanism for the formation of this heterocycle (isolated in 10% yield) was proposed, which included an initial extrusion of N_2 to give a diradical species (Scheme 12).



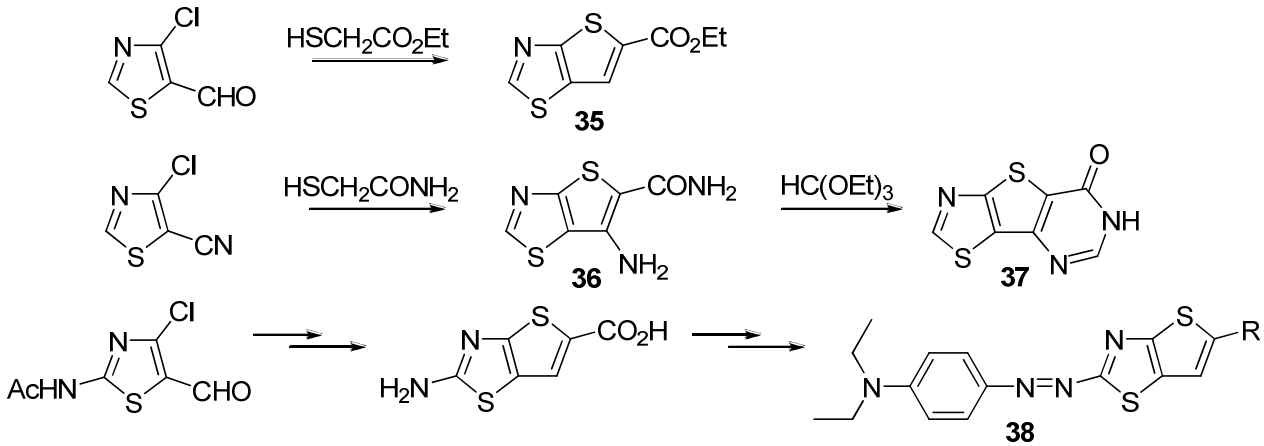
Scheme 12

2.3. Thieno[2,3-*d*]thiazoles

This isomer is much more described than the two others (SciFinder search: 2685 molecules and 87 references for its preparation) and was especially studied by Russian groups in the seventies and eighties due to its applications in dyes. Most of the synthetic pathways correspond to the formation of a thiazole ring on the thiophene scaffold and only few strategies start from thiazole. The thieno[2,3-*d*]thiazole was also reported in one occasion as a product of thermolysis of thieno[2,3-*e*][1,2,4]triazine.[21]

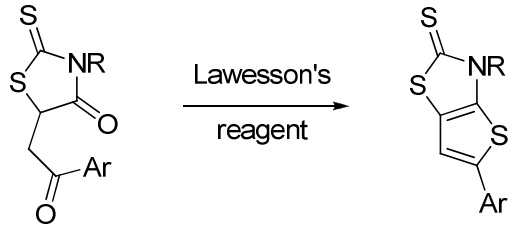
2.3.1. Synthesis starting from thiazole

Ahtmani *et al.* described the synthesis of ethyl thieno[2,3-*d*]thiazole-5-carboxylate **35** in 52% yield by reaction of 4-chlorothiazole-5-carbaldehyde with ethyl-2-mercaptoacetate (Scheme 13).[22] The same year, they reported the formation of thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **37** *via* the 6-aminothieno[2,3-*d*] thiazole-5-carboxamide **36**.[23] Using the same type of pathway, organic dyes **38** of potential interest for non-linear optical applications were prepared by annelation of a thiophene ring to a thiazole core.[24]



Scheme 13

A variety of 3,5-disubstituted-2,3-dihydro-2-thioxothieno[2,3-*d*]thiazoles **39** were synthesized in excellent yields in a one-pot reaction between 3-substituted-5-(2-aryl-2-oxoethyl)-4-oxo-2-thioxo-1,3-thiazolidines and Lawesson's reagent (Scheme 14).[25]



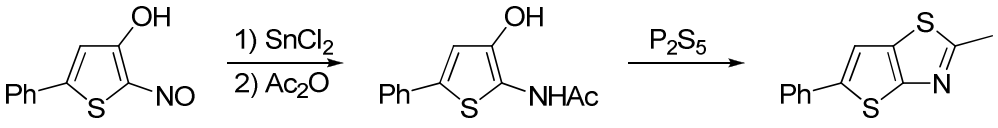
39

Scheme 14

2.3.2. Synthesis starting from thiophene

The main precursors for the synthesis of thieno[2,3-*d*]thiazoles are 2-aminothiophenes, a lot of papers coming from Abramenko's group in different Russian journals.

Reduction of 2-nitrosothiophen-3-ol followed by treatment with acetic anhydride gave 2-acetamido-3-hydroxythiophene **40**. The latter was converted into thieno[2,3-*d*]thiazole **41** with P_2S_5.[26] The same strategy was applied to 2-acetamido-3-hydroxythieno[2,3-*d*]thiophene and allowed access to 2-methylthieno[2,3-*d*] thieno[2,3-*d*]thiazole.[27] In the same way, 2-aminobenzothiophene[28] or 2-amino-5-phenylthiophene[29] were acetylated, converted to thioacetamides and then cyclized by $K_3Fe(CN)_6$.



40 **41**

Scheme 15

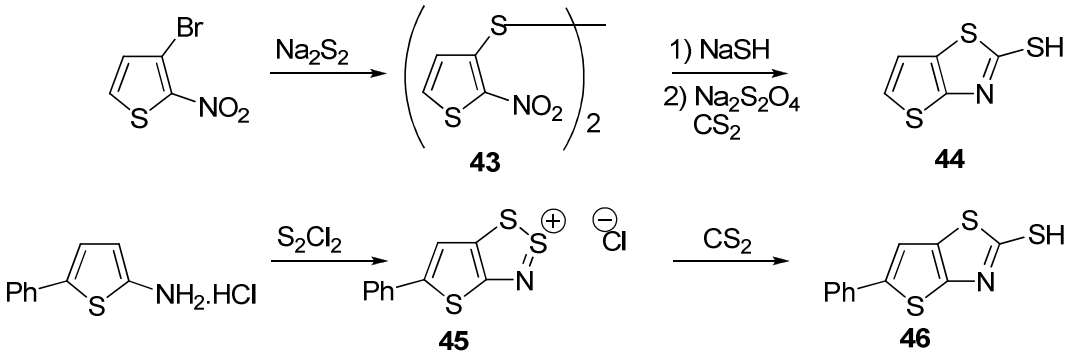
Thiocyanation of thiophenes is also a method of choice to obtain thieno[2,3-*d*]thiazoles. Oxidative thiocyanation of 3-unsubstituted-2-aminothiophenes, followed by ring closure of the resulting 3-thiocyanato-2-aminothiophenes, was described by Gewald and co-workers.[30] Treatment of 3-bromo-2-nitrothiophenes with NH_4SCN or NaSCN, followed by reductive cyclization also allowed the formation of thieno[2,3-*d*]thiazoles **42** in excellent yields: 87% calculated on initial bromo derivative (Scheme 16).[31,32]

42

Scheme 16

3-Bromo-2-nitrothiophene could also be converted into bis(2-nitro-3-thienyl)disulfide **43** by treatment with disodium disulfide Na_2S_2. This intermediate was cleaved with NaSH to give 3-SNa derivatives and then cyclized by sodium hydrosulfite and carbon disulfide (Scheme 17).[33] The same strategy was used successfully on 3-bromo-2-nitrobenzothiophenes.[34] 5-Phenyl-2-aminothiophene was reacted with sulfur

monochloride S_2Cl_2 to give intermediate **45** which was then heated with carbon disulfide in alkaline aqueous alcoholic medium (Scheme 17).[35]



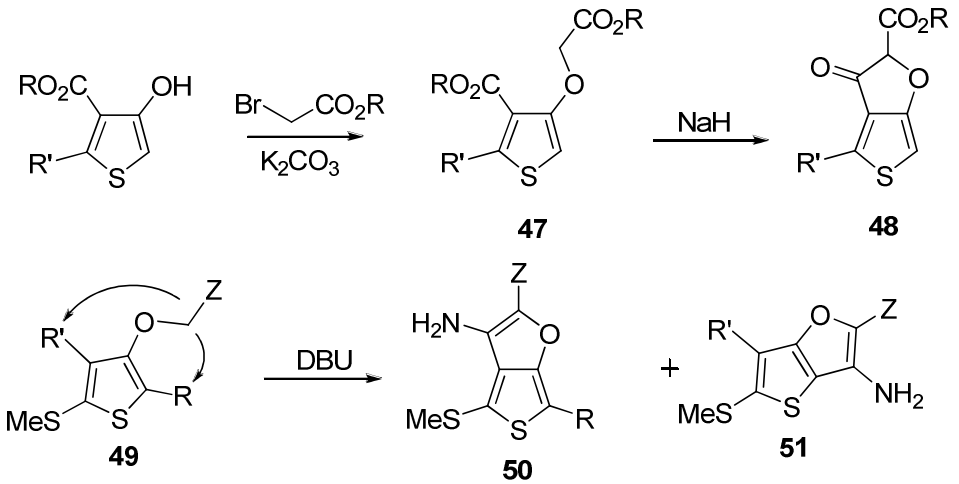
Scheme 17

More recently, Zavarzin developed a method starting from 2-aminothiophenes *via* cyclization of monothiooxamides as he has previously done for thieno[3,2-*d*]thiazoles.[36]

3. Thienofurans

3.1. Thieno[3,4-*b*]furans

As for thieno[3,4-*d*]thiazole, thieno[3,4-*b*]furan is the least described isomer of thienofurans (a SciFinder structure's search gave 64 molecules and 29 references). Moreover, as for thieno[3,4-*d*]thiazoles, the main application of thieno[3,4-*b*]furans takes place in organic semiconductors. In this growing field of organic semiconductors, thiophene-based fused heterocyclic materials play an important role. Indeed, they display promising optical and electrical properties for use in electrochromics, organic light-emitting diodes (OLEDs) and organic photovoltaics (OPVs). Thieno[3,4-*b*]furans are notable monomers as they can be used in the preparation of intrinsically conducting, low band gap polymers.[37] This potential application explains the renewed interest for this moiety, as we will see later.

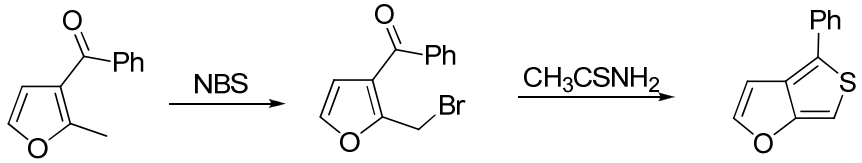


Scheme 18

Thieno[3,4-*b*]furans are mostly synthesized from furans and there are only few reports on synthesis starting from thiophenes. Banks *et al.* treated a variety of 3-hydroxythiophenes with alkyl bromoacetates and they obtained the 3-alkoxy derivatives **47** in good to excellent yields. Thieno[3,4-*b*]furans **48** were then

synthesized by a Dieckmann condensation (Scheme 18) and existed predominantly in either keto or enol form dependent upon the nature of substitution on the thiophene ring.[38] Gadais *et al.* have shown that Thorpe-Ziegler condensation on polysubstituted 3-*O*-alkylated thiophenes **49** could lead either to 3-amino-thieno[3,4-*b*]furans **50** or to 3-aminothieno[3,2-*b*]furans **51** depending on the position of the nitrile group (Scheme 18).[39]

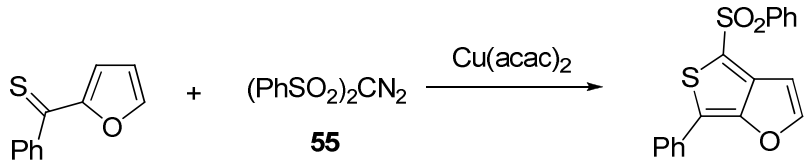
2-Methyl-3-benzoylfuran was brominated with NBS and the resulting bromo derivative **52** was reacted with thioacetamide to give 1-phenylthieno[3,4-*b*]furan **53** (Scheme 19).[40,41] The same methodology was also used on aryl 3-methyl-2-benzo[*b*]furyl ketones[42] and aryl 2-methyl-3-benzo[*b*]furyl ketones[43] and allowed formation of thieno[3,4-*b*]benzofurans.



52 **53**

Scheme 19

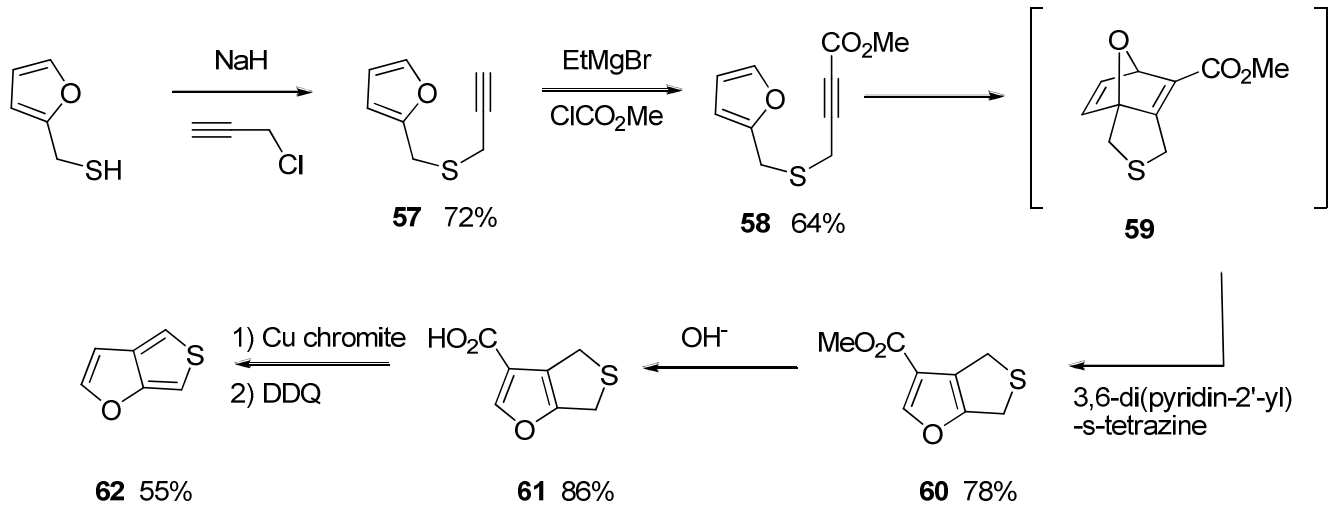
A new method for the synthesis of thieno[3,4-*b*]furans was described in 1995 by Saito and co-workers.[44] Aryl heteroaryl thioketones **54** were reacted with carbene precursor bis(arylsulfonyl) diazomethane **55** (Scheme 20).



54 **55** **56**

Scheme 20

Unsubstituted thieno[3,4-*b*]furan **62** has been prepared by a route involving as the key step the intramolecular Diels-Alder addition between a furan and a pendant acetylenic ester **58** and the subsequent retro-Diels-Alder fragmentation of the adduct **59**, induced by 3,6-di(pyridin-2'-yl)-s-tetrazine (Scheme 21).[45]

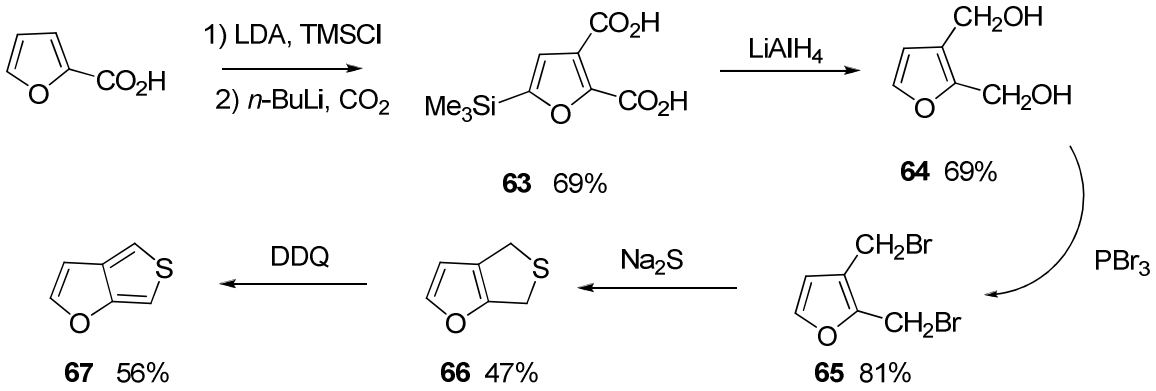


57 72% **58** 64% **59**

62 55% **61** 86% **60** 78%

Scheme 21

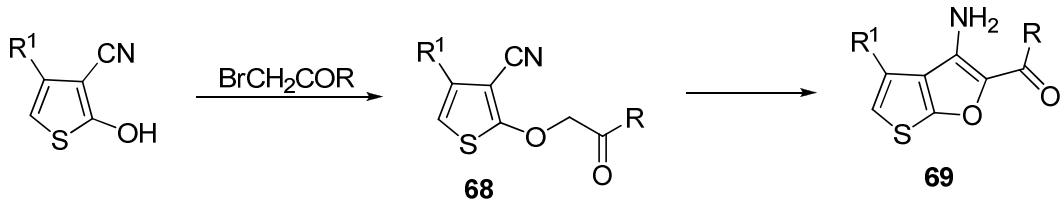
Kumar *et al.* used the same synthetic pathway with very little modifications to gain access to unsubstituted thieno[3,4-*b*]furan monomer and then prepared electrochemically poly(thieno[3,4-*b*]furan).[46] This new optically transparent, near-infrared-absorbing low energy gap conjugated polymer showed promising attributes for photovoltaics. However, its reported synthesis used some expensive chemicals such as 3,6-di(pyridine-2'-yl)-s-tetrazine which makes the polymer thereof more costly. In 2010, Dey *et al.* developed a new multi-step synthesis of unsubstituted thieno[3,4-*b*]furan starting from inexpensive furan-2-carboxylic acid (Scheme 22).[37]



Scheme 22

3.2. Thieno[2,3-*b*]furans

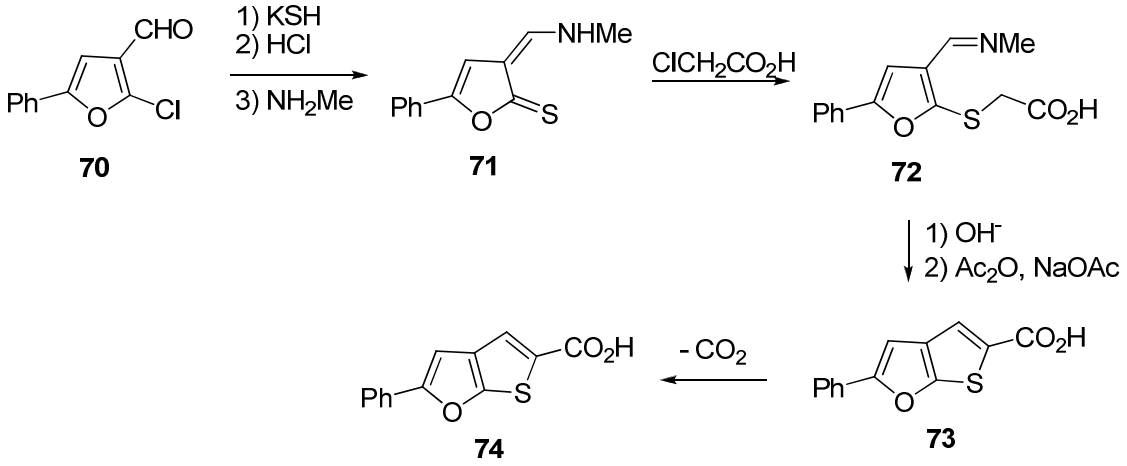
Thieno[2,3-*b*]furans are more described (SciFinder search returned 103 molecules and 28 references) and they have been mostly synthesized starting from furans; there's only one report starting from thiophenes. 2-Hydroxythiophene-3-carbonitriles were alkylated with bromoacetates and the *O*-alkylated intermediates **68** underwent a Thorpe-Ziegler cyclization to give thieno[2,3-*b*]furan **69** in low yields (Scheme 23).[47]



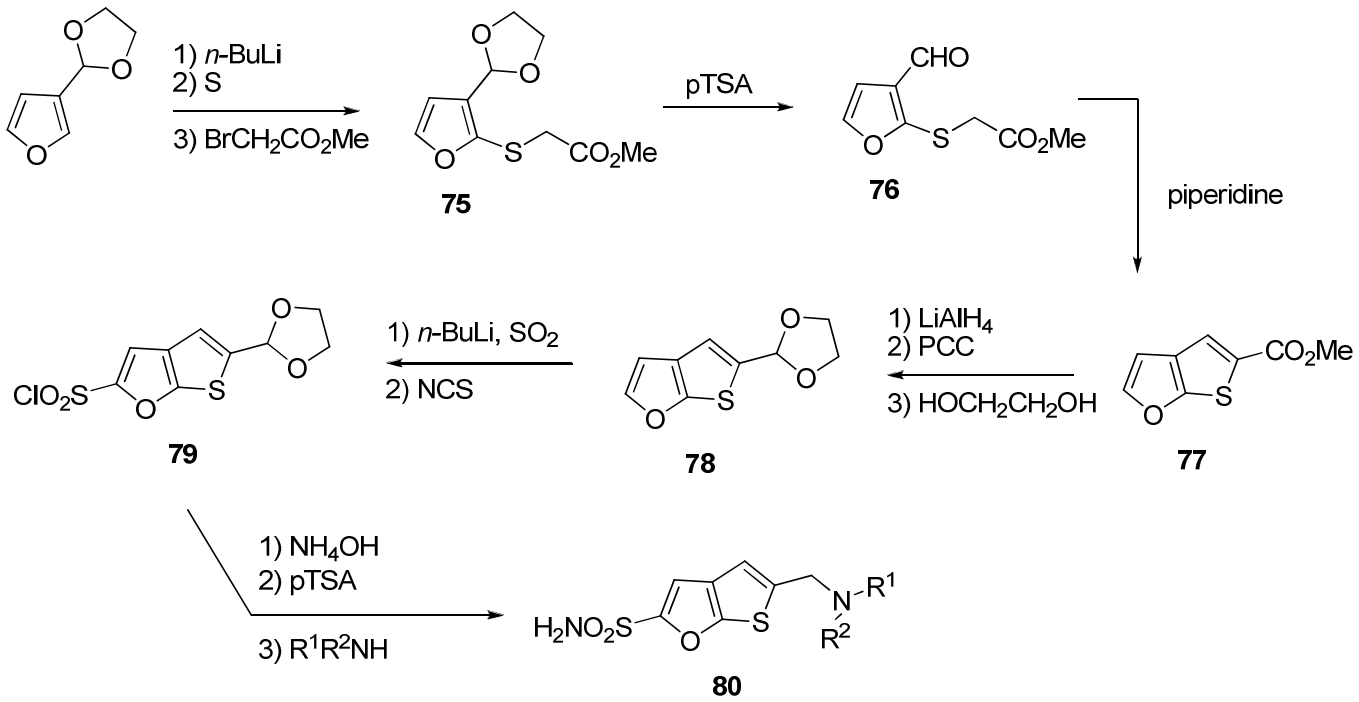
Scheme 23

2-Phenylthieno[2,3-*b*]furan **74** was synthesized in 20% yield in five steps from 2-chloro-5-phenyl-3-furancarbaldehyde **70**. The latter compound was treated with KSH, HCl and methylamine to give amino derivative **71** which was then reacted with chloroacetic acid. Cyclization of **72** in thienofuran **73** was realized using Ac_2O-NaOAc (Scheme 24).[48]

Hartman *et al.* reported the preparation of 5-substituted thieno[2,3-*b*]furan-2-sulfonamides **80** starting from 3-furancarbaldehyde in several steps. The key step was the cyclization of furan **76** under Knoevenagel conditions to give the bicyclic moiety **77** in 61% yield (Scheme 25).[49] Further functional transformations on ester group and introduction of the sulfonamide group on 2-position allowed the formation of the desired compounds which were then evaluated as Carbonic Anhydrase II inhibitors.[50] In particular, compound **80** with R^1=H and R^2=Me displayed nanomolar potency *in vitro* for CA II inhibition, high water solubility in pH 5.2 buffer and extensive binding to ocular pigment.



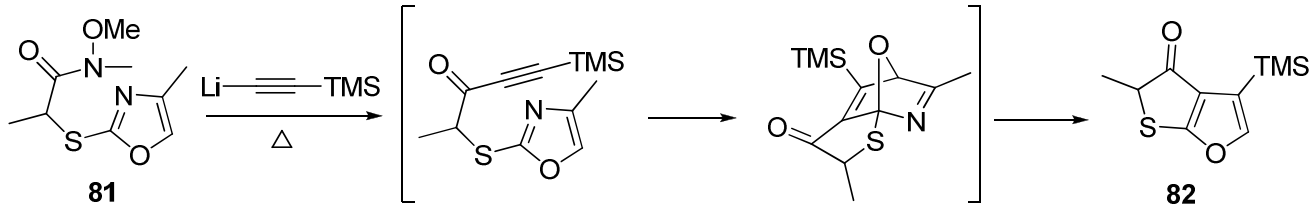
Scheme 24



Scheme 25

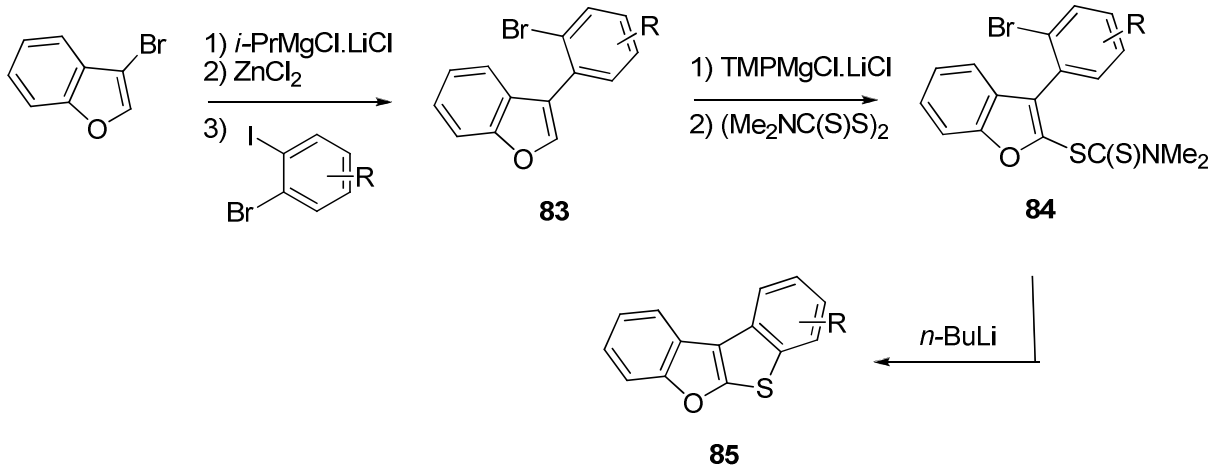
The same kind of methodology was performed in the benzofuran series by Litvinov and co-workers. 2-Bromo-3-benzo[*b*]furaldehyde was successively treated with sodium hydrosulfide, ethyl chloroacetate and sodium ethoxide to allow the formation of thienobenzofuran.[51]

Selnick and Brookes used a Diels-Alder/retro-Diels-Alder sequence on oxazoles to gain access to fused furan derivatives. In particular, compound **82** was obtained in 81% yield starting from oxazole **81** (Scheme 26).[52]



Scheme 26

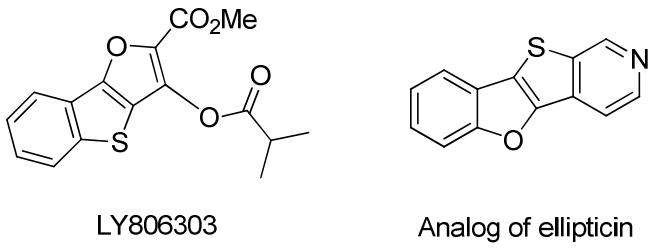
Recently, benzo[4,5]thieno[2,3-*b*]benzofurans **85** were obtained starting from readily available halosubstituted dithiocarbamates **84**. The biaryls **83** were synthesized *via* a Br/Mg exchange carried out with *i*-PrMgCl.LiCl, followed by a transmetallation with $ZnCl_2$ and finally a Negishi cross-coupling (Scheme 27).[53]



Scheme 27

3.3. Thieno[3,2-*b*]furans

Thieno[3,2-*b*]furans have been synthesized starting either from thiophenes or from furans but also by total construction of the two heterocyclic moieties (it's the most reported isomer with 708 molecules and 72 references in SciFinder). Some of those derivatives have been reported for their biological activities such as methyl 3-(2-methyl-1-oxopropoxy)[1]benzothieno[3,2-*b*]furan-2-carboxylate LY806303, described as a selective inhibitor of thrombin.[54] This thieno[3,2-*b*]furan scaffold was also introduced in biheterocyclic analogs of ellipticine (Scheme 28).[55]

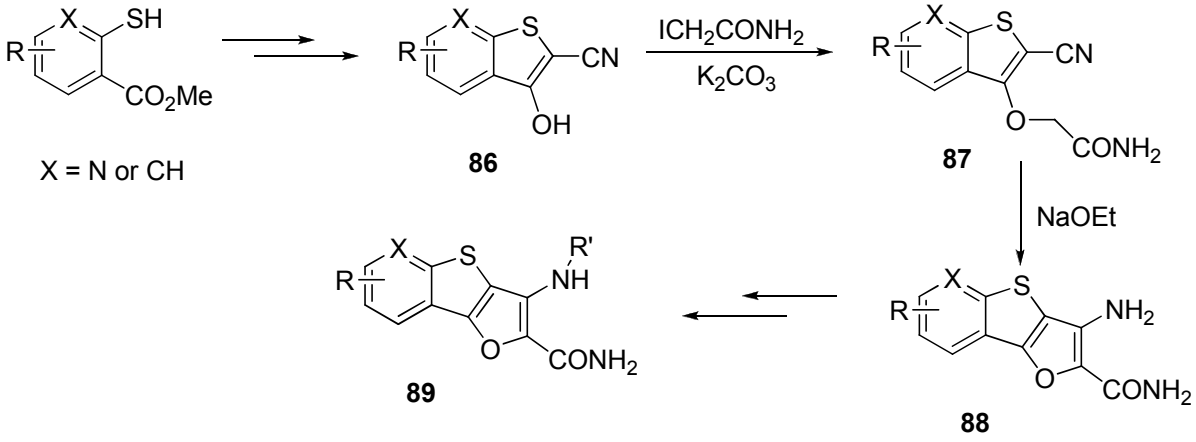


Scheme 28

3.3.1. Synthesis starting from hydroxythiophenes

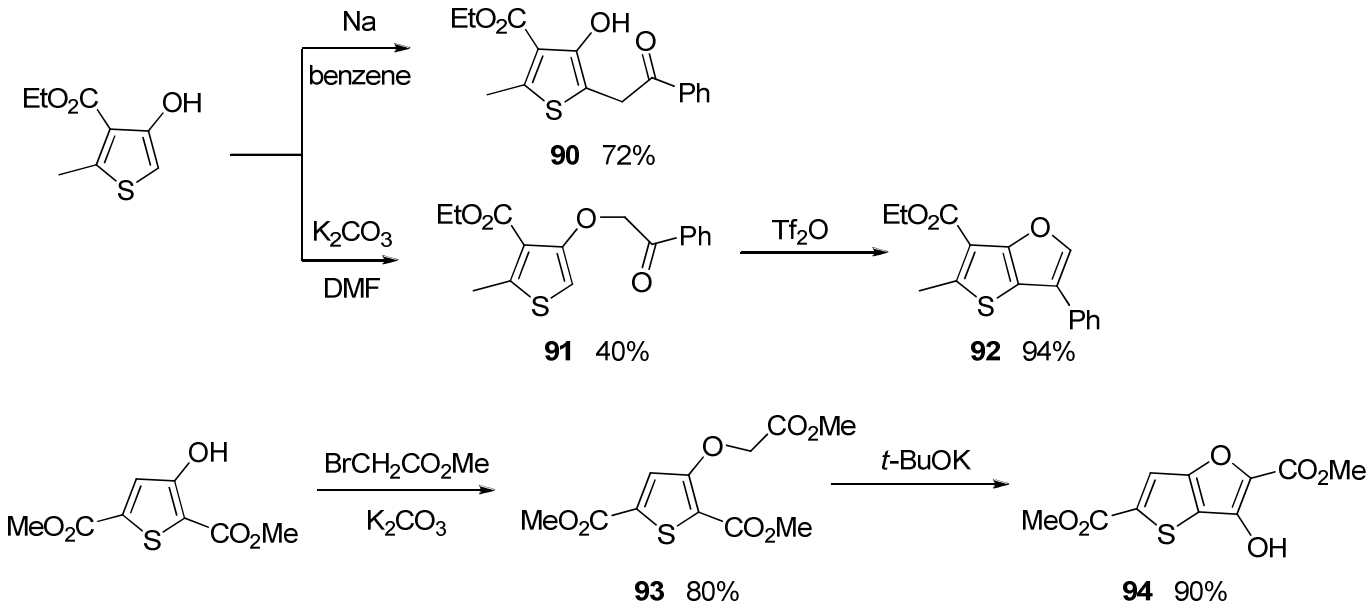
Thieno[3,2-*b*]furans could be prepared by a Thorpe-Ziegler cyclization of 3-hydroxy-2-thiophene-carbonitriles with high yields, as described by Gewald *et al.*[47] This methodology was also used recently on polysubstituted 3-hydroxythiophenes to lead to trisubstituted 3-aminothieno[3,2-*b*]furans; cyclization was this time performed in the presence of 1,8-diazabicycloundec-7-ene (DBU).[39] Benzothieno[3,2-*b*]furan and furo[2',3':4,5]thieno[2,3-*b*]pyridine derivatives **89** were also synthesized using a similar method from 3-hydroxybenzo[*b*]thiophene-2-carbonitriles **86** (X=CH_2) and 3-hydroxythieno[2,3-*b*]pyridines **86** (X=N), respectively (Scheme 29). Those compounds were successively alkylated with halogenoacetamide and cyclized in presence of sodium ethoxide to give derivatives **88**. The final compounds were evaluated for

their inhibition potential on IKKβ kinases and benzothieno[3,2-*b*]furancarboxamide **89** (X=CH_2, R=H and R'=$CONH_2$) displayed potent inhibitory activity (IC_{50}=45 nM).[56]



Scheme 29

Access to hydroxythieno[3,2-*b*]furans starting from 3-hydroxythiophene-2-carboxylates required harder conditions to perform the Dieckmann condensation. Moreover, it has been shown that a competition may exist between *O*- and *C*-alkylation during the synthesis of 3-*O*-alkylated thiophenes.[57] Krayushkin *et al.* have demonstrated that the direction of the reaction depends on the structure of the starting hydroxylthiophene, the nature of the alkylating agent and the base employed but also on the polarity of the solvent. In benzene and ethanol, *C*-alkylation products were exclusively obtained while *O*-alkylated derivatives were isolated using DMF or acetonitrile (Scheme 30).[58] Cyclization of 3-*O*-alkylated thiophenes can occur on the ester group in presence of sodium ethoxide or potassium *tert*-butoxide to give 3-hydroxythieno[3,2-*b*]furan **94**[59] or trifluoromethanesulfonic anhydride may be used to obtain thieno[3,2-*b*]furan **92**.[60,38]

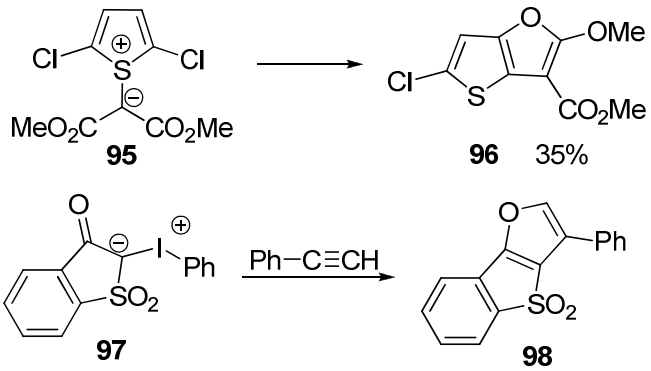


Scheme 30

Similar reaction was conducted on 3-[(methoxycarbonyl)methoxy]benzo[*b*]thiophen-2-carboxylate to give [1]benzothieno[3,2-*b*]furan *via* cyclization with alkoxide.[61,62]

3.3.2. Synthesis starting from thiophenes

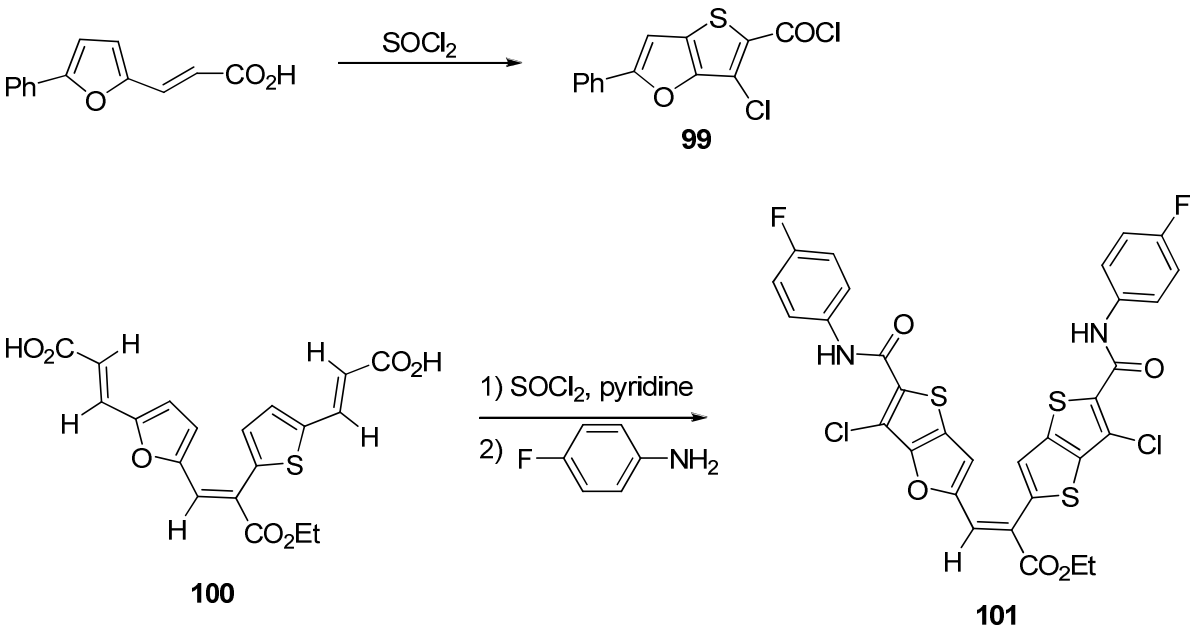
Some other less common ways of synthesis were also described. For example, thermolysis of 2,5-dichlorothiophenium bismethoxycarbonylmethylide **95** in the absence of transition metal catalysts led to a novel eliminative rearrangement resulting in the formation of methyl 5-chloro-2-methoxythieno[3,2-*b*] furan-3-carboxylate **96** (Scheme 31).[63] 2,3-Dihydro-2-phenyliodonium-3-oxobenzo[*b*]thiolenide-1,1-dioxide **97** was reacted with phenylacetylene to give **98** in 34% yield (Scheme 31).[64]



Scheme 31

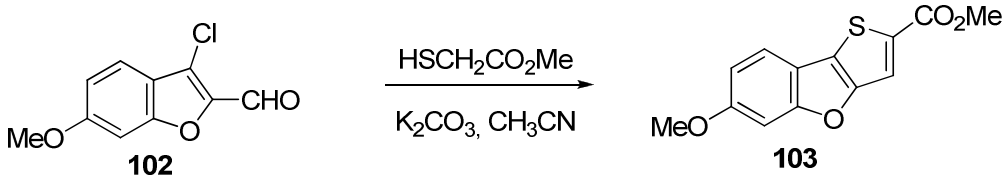
3.3.3. Synthesis starting from furans

Many syntheses involved the cyclization of acrylic acid derivatives as a key step. Thus, reaction of furylpropenoic acids with thionyl chloride in presence of triethylbenzylammonium chloride was first described in 1986 by Kralovicova *et al.* and allowed the formation of 2-arylthieno[3,2-*b*]furan-5-carboxylic acid chloride **99** (Scheme 32).[65] 3,5-Dichloro-*N*,*N'*(*p*-chlorophenyl)dithieno[3,2-*b*;2',3'-*d*]furan-2,6-carboxamide was synthesized along the same pathway.[66] A double cyclization of *(Z)*-3-[5-(2-carboxy) ethenyl-2-furyl)]-2-[5-(2-carboxy-ethenyl)-(2-thienyl)]acrylate **100** with $SOCl_2$ in the presence of a catalytic amount of pyridine afforded 3-chloro-5-{2-ethoxycarbonyl-2-[3'-chlorocarbonyl-5'-thieno[3,2-*b*]thienyl] ethenyl}-thieno[3,2-*b*]furancarbonyl chloride in 35% yield, which was successfully converted into the corresponding dianilide **101**.[67]



Scheme 32

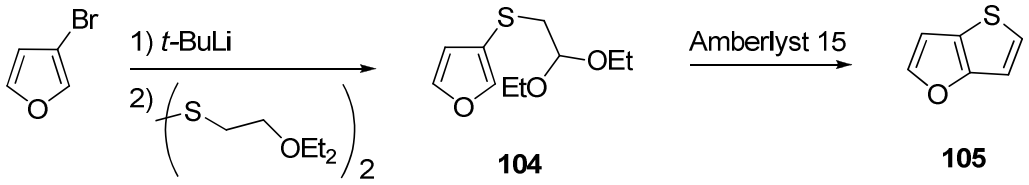
Sekhar *et al.* described the condensation of methyl thioglycolate on 3-chlorobenzo[*b*]furan-2-carbaldehyde **102** in presence of potassium carbonate and subsequent cyclization to give condensed thienofuran derivative **103** (Scheme 33).[68] The same reaction was conducted on 3-chloro-naphtho[2,3-*b*] furan-2-carbaldehyde and allowed the formation of naphtho[2,3-*b*]thieno[2,3-*d*]furan.[69]



Scheme 33

Thieno[3,2-*b*]benzofuran derivatives were synthesized starting from benzo[*b*]furan-3(2*H*)-one or benzo[*b*]furan-2-carbaldehyde.[70] Their mesomorphic properties were investigated and those derivatives could constitute ferroelectric liquid crystals.[71,72]

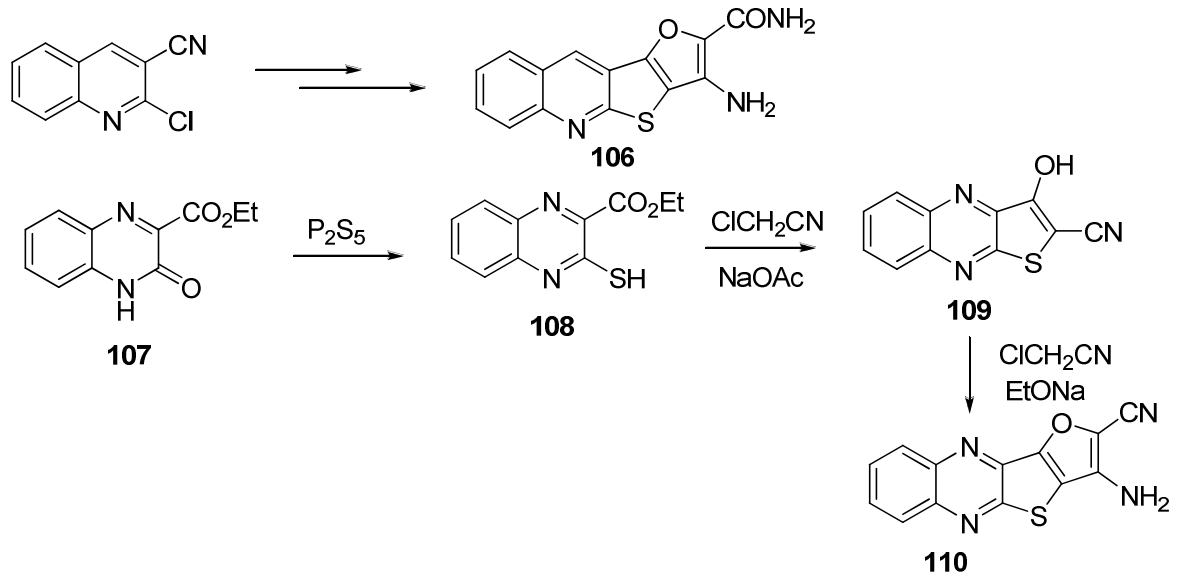
Recently, an optimized synthetic methodology which allowed efficient and scalable access to the important fused-ring heterocycle thieno[3,2-*b*]thiophene and the first reported isolation of unsubstituted thieno[3,2-*b*]furan **105** was presented by Henssler *et al.* (Scheme 34).[73] 3-Bromofuran was converted into **104** by action of *tert*-butyl lithium followed by quenching with 1,2-bis(2,2-diethoxyethyl)disulfide. Cyclization to **105** was performed using Amberlyst 15 in THF in 35% yield.



Scheme 34

3.3.4. Synthesis with construction of the two heterocycles

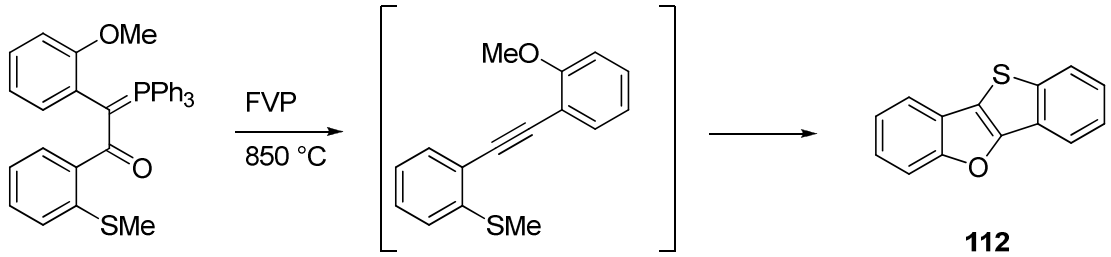
Furothienoquinoline **106** was obtained from 2-chloroquinoline-3-carbonitrile by thiation, followed by two cyclocondensation reactions with chloroacetonitrile (Scheme 35).[74]



Scheme 35

The thiation of ethyl (quinoxalin-2(1*H*)-one)-3-carboxylate **107** using P_2S_5 in dry pyridine resulted in the formation of thioxo derivative **108** which was then condensed with chloroacetonitrile in refluxing ethanol and in presence of sodium acetate to give 2-cyano-3-hydroxythieno[2,3-*b*]quinoxaline **109**. Condensation of the latter compound with chloroacetonitrile in presence of sodium ethoxide allowed a Thorpe-Ziegler cyclization and the formation of 3-amino-2-cyanofuro[2',3':4,5]thieno[2,3-*b*]quinoxaline **110** (Scheme 35).[75]

Benzothieno[3,2-*b*]benzofuran **112** was prepared for the first time by a tandem radical cyclization in the flash vacuum pyrolysis of (benzoyl)benzylidenetriphenylphosphorane **111**. In a first time, flash vacuum pyrolysis resulted in extrusion of Ph_3PO to give substituted diphenylacetylene and then produced a mixture of **112** (20%) and 2-phenylbenzo[*b*]thiophene (20%) (Scheme 36).[76] The same reaction was realized later on methylthiopyridinyl (triphenylphosphoranylidene)aryl ketones to give benzofuro[2',3':4,5]thieno[2,3-*b*] pyridine.[77]



111 **112**

Scheme 36

4. Conclusion

Thienothiazoles and thienofurans are always under current interest both in syntheses and applications as there are still new papers about those scaffolds. In this review, we have summarized and classified the main access to the different isomers of those two scaffolds.

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DITHIOCARBOXYLATES AND RELATED COMPOUNDS IN THE SYNTHESIS OF HETEROCYCLES

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Abstract. *Dithiocarboxylates are versatile multifunctional synthons in organic synthesis. This overview attempts to present the general reactivity patterns of dithiocarboxylates with a particular emphasis on the synthesis of heterocycles. A broad range of three- to six-membered and several fused heterocycles have been synthesized using dithioesters.*

Contents

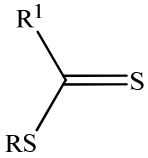
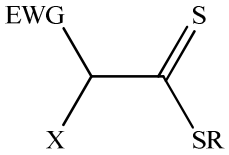
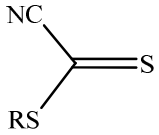
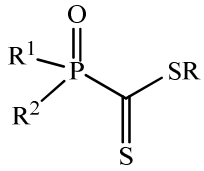
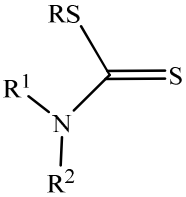
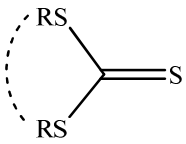
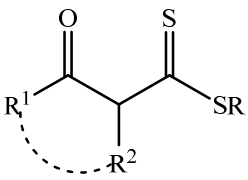
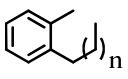
1. Introduction

The chemistry of dithiocarboxylic esters has attracted the increasing attention of synthetic chemists owing to their varied intrinsic chemical properties, which can be exploited easily in various functional group transformations and in their wide applications in organic synthesis and industry.[1] Thioketones in general are known to be unstable compounds and therefore have limited use for preparative applications. On the other

hand, dithioesters are relatively stable and can be obtained by a variety of convenient synthetic procedures.[2] They are considered as promising starting materials for the synthesis of heterocycles.

Comprehensive reviews of the chemistry of this class of compounds have been published,[3] with most of them discussing their synthesis and functional group transformations.

Table 1. Structures of the most commonly used dithioesters.

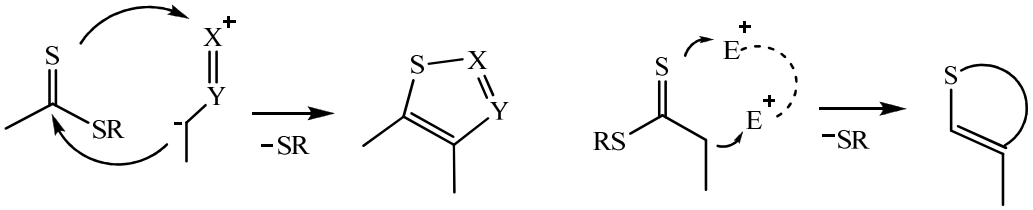
A. Dithioesters		**1a**, R = R^1 = CH_3 **1b,** R = CH_3; R^1 = alkyl, aryl, heteroaryl **1c**, R = CH_3; R^1 = acetyl, aroyl **1d**, R = CH_3; R^1 = EWG
B. Dithioesters with electron-withdrawing groups (EWG) at the a-position		**2a**, R = CH_3; X = H; EWG = CN **2b,** R = CH_3; X = $CO_2C_2H_5$; EWG = CN **2c**, R = CH_3; X = CN; EWG = CN **2d**, R = CH_3; X = aryl; EWG = CN
C. Cyanodithioformates		**3a**, R = CH_3 **3b,** R = C_2H_5 **3c**, R = C_6H_5
D. Phosphonodithioformates		**4a,** R = CH_3; R^1 = R^2 = OC_2H_5 **4b,** R = C_2H_5; R^1 = R^2 = OiPr
E. Dithiocarbamates		**5a**, R = R^1 = CH_3; R^2 = H **5b,** R = CH_3; R^1 = C_2H_5; R^2 = H **5c**, R = C_2H_5; R^1 = C_6H_5; R^2 = H **5d**, R = CH_3; R^1 = aryl, heteroaryl; R^2 = H **5e**, R = CH_3; R^1 = aryl, heteroaryl; R^2 = alkyl, aryl
F. Trithiocarbonates		**6a**, R = CH_3 **6b,** R = C_2H_5 **6c**, R = C_6H_5 **6d**, R = long chain alkyl,  n = 0, 1, 2
G. b-Oxodithioesters		**7a**, R = R^1 = CH_3; R^2 = H **7b,** R = C_2H_5; R^1 = C_6H_5; R^2 = H **7c**, R = CH_3; R^1 = aryl, heteroaryl; R^2 = H **7d**, R = CH_3; R^1 = aryl, heteroaryl; R^2 = alkyl, aryl **7e**, R = CH_3; R^1 = R^2 =  **7f**, R = CH_3; R^1 = R^2 =  n = 0, 1, 2, 3

The present review is based on the synthetic applications of dithioesters to heterocyclic systems in order to show the potential of these building blocks in heterocycle synthesis.

2. Applications of dithiocarboxylates in the synthesis of heterocycles

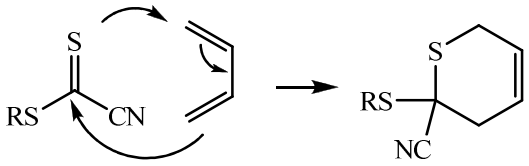
Several structural types of dithioesters are described in the literature. Some are reported as being unstable and are generated *in situ*; however, the dithioesters shown in Table 1 are found to be stable and are used in the synthesis of heterocycles.

Dithioesters of type **1** and **2** are well documented in earlier reviews.[3] Due to their simple methods of preparation and flexible substitution patterns, they have been used to generate libraries of heterocycles. The presence of the thioalkyl group, which behaves as a good leaving group in such systems, may enhance the binding activity during nucleophilic attack. Some heterocyclization reactions of this type of dithioester with dielectrophiles, particularly when there is an acidic α-hydrogen, may lead to sulfur-containing heterocycles as shown in Scheme 1. However α-ketodithioesters are less explored in heterocyclic chemistry due to their unstable nature and limited availability.[4]



Scheme 1

Methyl cyanodithioformates and phosphonodithioformates **3** and **4**[5,6] are used as dienophiles in many hetero-Diels-Alder and photochemical addition reactions (Scheme 2).



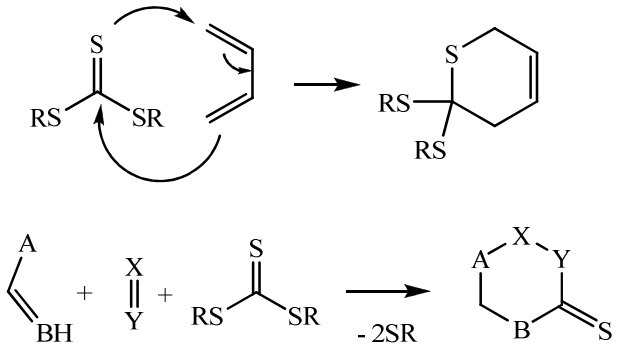
Scheme 2

Dithiocarbamates **5**[7] are useful synthetic intermediates with two nucleophilic centres localized on the heteroatoms (sulfur and nitrogen). They are used widely in heterocycle synthesis due to their ambident properties, having an electrophilic thiocarbonyl centre and nucleophilic nitrogen atoms. As with other dithioesters, they can undergo cycloadditions, addition-elimination reactions and ring-cyclization processes to yield various heterocyclic systems (Scheme 3).

Scheme 3

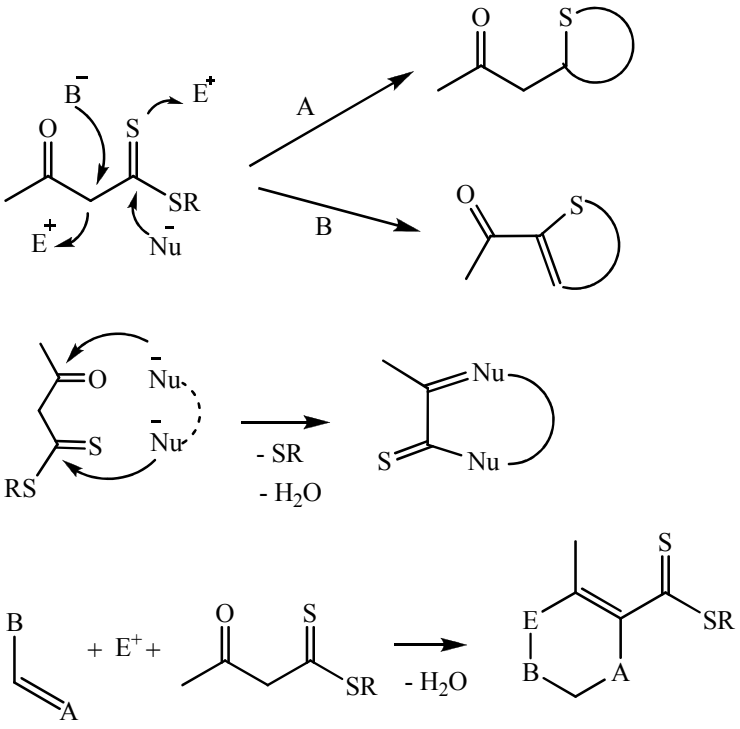
Trithiocarbonates **6**[8] are also useful dipolarophiles in many heterocyclization reactions, and are also used as one-carbon synthons in multicomponent reactions (MCR) for introducing a thiocarbonyl

functionality into heterocyclic frameworks (Scheme 4). They also act as precursors for the synthesis of β-oxodithioesters which have greater scope in the synthesis of heterocycles.



Scheme 4

β-Oxodithioesters **7**[3a,9] exhibit intriguing nucleophilic reactivities as shown in Scheme 5. Possessing ambident electrophilicity at the 1,3-carbon centres due to the presence of carbonyl and thiocarbonyl functionalities, they can react with various dinucleophiles to afford a number of five- and six-membered heterocycles. In addition to this, they undergo cycloadditions, addition-elimination reactions, intramolecular ring cyclizations and multicomponent reactions to generate libraries of bioactive heterocycles. Among the dithioesters, functionalized β-oxodithioesters have been recognized as potential C_3 fragments for the synthesis of diverse heterocyclic systems.[10]



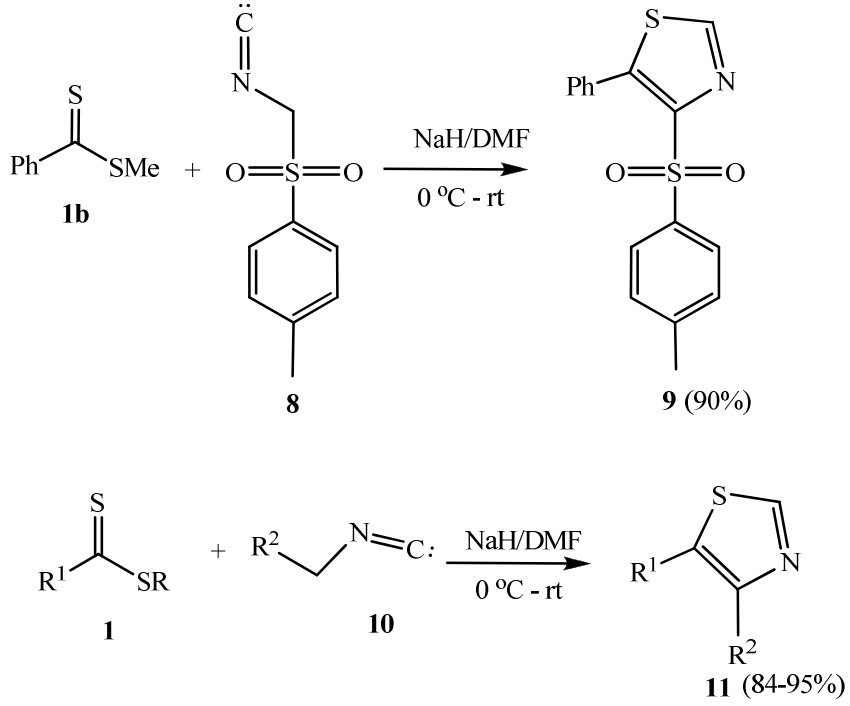
Scheme 5

2.1. Reactions of dithioesters (type 1)

2.1.1. Synthesis of thiazoles

As thiazole rings are present in the structures of many biologically active compounds, methods for their synthesis still hold the interest of chemists. The reaction of active methylene isocyanides with methyl dithiocarboxylates has been reported[11] as a convenient route for the synthesis of 4,5-disubstituted thiazoles.

When methyl dithioester **1b** was treated with tosylmethyl isocyanide **8** in the presence of sodium hydride, 4,5-disubstituted thiazole **9** was obtained in 90% yield (Scheme 6). This procedure was extended to various aryl and heteroaryl substituted methyl dithioesters **1** and substituted isocyanides **10** to afford a library of thiazoles **11** with yields of 84–95%.



R^1 = 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-thienyl;
R^2 = Ts, CO_2Et, Ph, 4-FC_6H_4

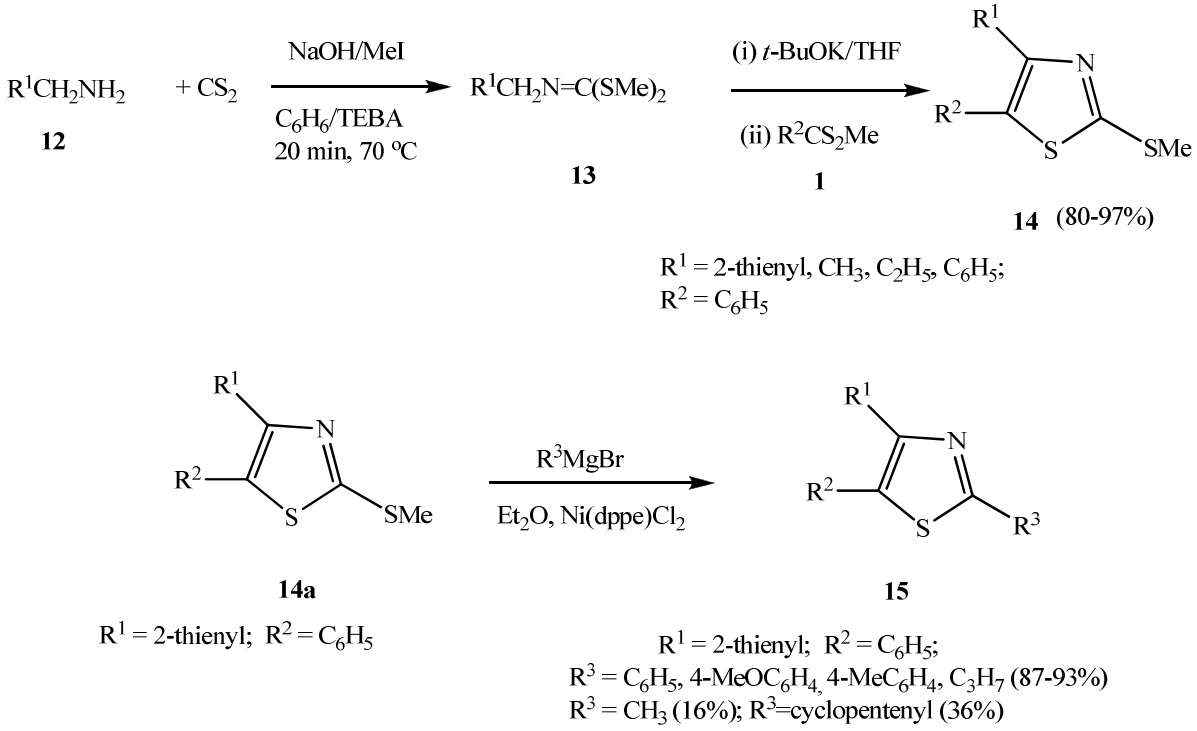
Scheme 6

Quiroga *et al.*[12,13] reported another method for the synthesis of thiazoles from methyl dithioesters involving addition-cyclization (Scheme 7). Their specific aim was the selective preparation of 2-methylthiothiazoles **14** with substituents at positions C4 and C5. Thus, thiazoles **14** were obtained from readily available precursors such as alkylamines **12** by initial conversion into dimethyl *N*-(alkylimino) dithiocarbonates **13** and subsequent reaction with dithioesters **1** as shown in Scheme 7. This route represents a useful approach to the synthesis of thiazoles **15** because the 2-methylthio group can be replaced by carbon-nucleophiles.[13] The cross-coupling reactions of methylthio-substituted thiazole **14a** with aryl and alkyl Grignard reagents in ether in the presence of a catalytic amount (2.5% mol) of $Ni(dppe)Cl_2$ was carried out to give excellent yields of 2-alkyl/aryl substituted thiazoles **15**. With aryl and propyl Grignard reagents the yields were excellent (87–93%), however, with methyl and cyclopentenyl Grignard reagents the yields of products were poor (16–36%).

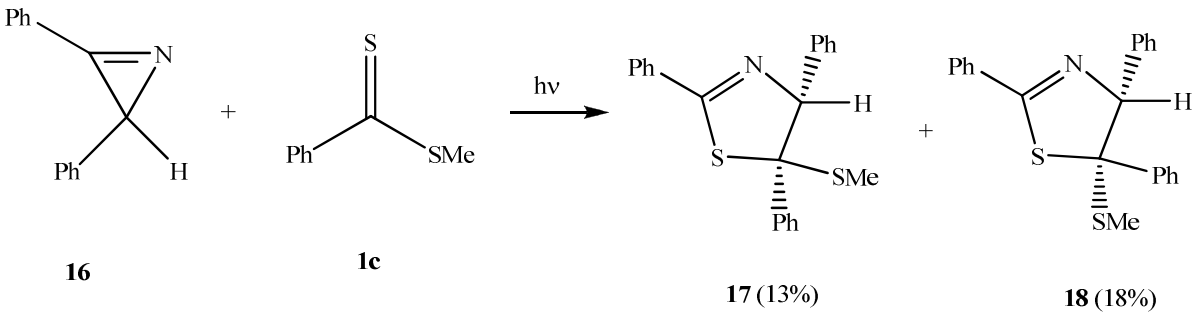
2.1.2. Cycloaddition reactions of methyl dithioesters

Dithioesters have been utilized in photochemical reactions to yield thiazolines.[14] The results outlined below (Scheme 8) demonstrate that the photoaddition of 2*H*-azirines **16** proceeds with methyl dithioester **1c** to provide thiazoline regioisomers **17** and **18**. Irradiation of 2,3-diphenylazirine **16** in benzene using an internal water-cooled mercury arc lamp in the presence of an equimolar amount of methyl dithiobenzoate **1c**

produced a mixture of two epimeric thiazolines, **17** and **18**. The methyl dithioester acts as a dipolarophile and the ^{1}H NMR analysis of the crude photolysate indicated that **17** was the major adduct. However, the final isolated yields were low (**17**=13%, **18**=18%).



Scheme 7

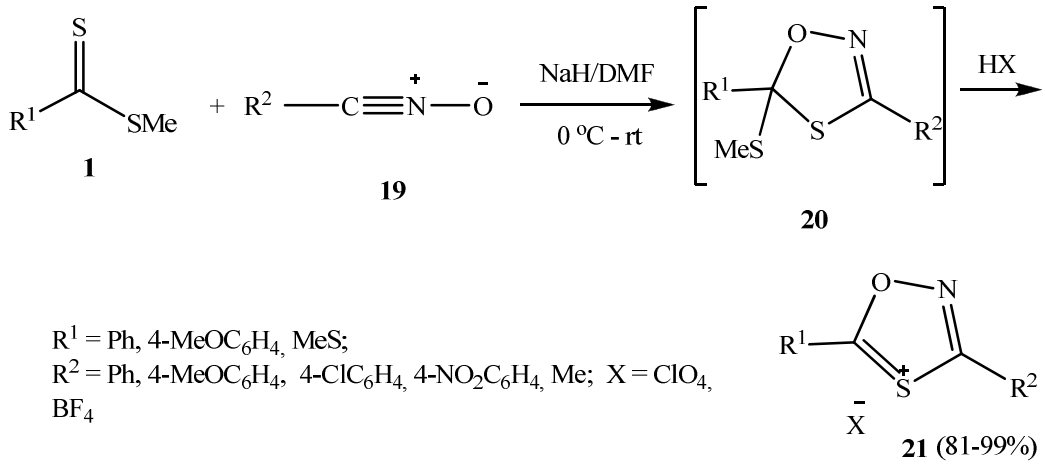


Scheme 8

Methyl dithioesters **1** exhibit extremely rich 1,3-dipolar cycloaddition chemistry. Such cycloaddition and dipolar cycloaddition reactions of methyl dithioesters lead to heterocycles of various ring sizes. Thus 1,3-dipolar cycloaddition of nitrile oxides **19** with methyl dithioesters **1** yielded 1,4,2-oxathiazolium salts **21**, after thiomethyl (a methyl sulfide anion) elimination from the intermediate **20** (Scheme 9).[15] Similar types of cycloaddition reactions with imines, nitrones and nitronates, nitrylimines and azomethine ylides led to heterocycles, which have been used for further transformations into carbonyl compounds and other derivatives.[3h]

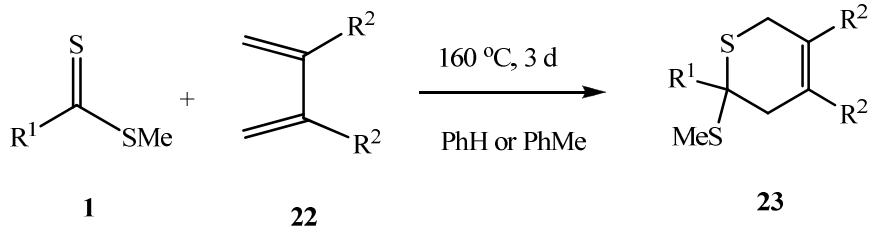
[2+4] Cycloaddition reactions of dithioesters with various dienes can afford six-membered heterocycles. Metzner *et al.*[16] reported a Diels-Alder reaction of methyl alkanedithiocarboxylates with various dienes at 160 °C which afforded 6-alkylthio-5,6-dihydro-2*H*-thiopyrans **23**. The regioselectivity and the scope of this reaction were examined. Diels-Alder addition of dithioesters **1**, which do not possess an

electron-withdrawing substituent at the thiocarbonyl site, with dienes **22** furnished reasonable yields of 6-alkylthio-5,6-dihydro-2*H*-thiopyrans **23** (Scheme 10).



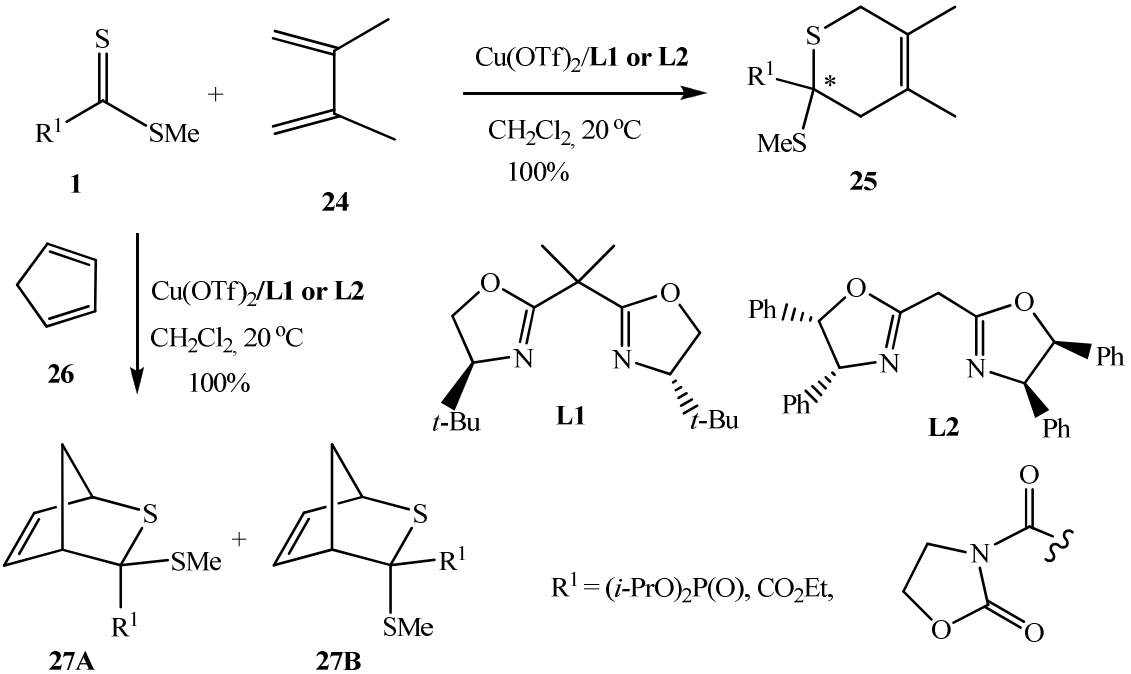
R^1 = Ph, 4-$MeOC_6H_4$, MeS;
R^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, Me; X = ClO_4, BF_4

Scheme 9



R^1 = CH_3, C_2H_5, *i*-C_3H_7, C_6H_5; R^2= H, CH_3 (50-70%)

Scheme 10



R^1 = $(i\text{-PrO})_2P(O)$, CO_2Et,

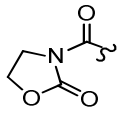
Scheme 11

The asymmetric hetero-Diels-Alder (HDA) reaction represents a powerful and atom economical method to obtain optically active six-membered heterocycles.[17] Gulea *et al.*[18a,b] reported a catalytic

asymmetric thia-Diels-Alder reaction of methyl dithioesters **1** with various dienes, in which a dithioester dienophile was activated by a chiral Lewis acid (Scheme 11). Two types of chiral ligands, **L1** and **L2**, were examined for their catalytic activities actions to afford 6-methylthio-5,6-dihydro-2*H*-thiopyrans. The cycloadduct is a cyclic dithioacetal, containing a quaternary thio-substituted stereocentre. In the presence of $Cu(OTf)_2$**/L1** catalyst no significant changes in the enantioselectivity was obtained. The use of a stoichiometric amount of $Cu(OTf)_2$**/L2** as the catalyst increased considerably the ee in the cycloaddition with **1** as shown in Table 2.

Further, the same authors extended their work with cyclopentadiene and observed similar enantioselectivities (Scheme 11). The use of the $Cu(OTf)_2$**/L2** catalytic system improved the *endo*/*exo* selectivities for the respective substituents as shown in Table 2.

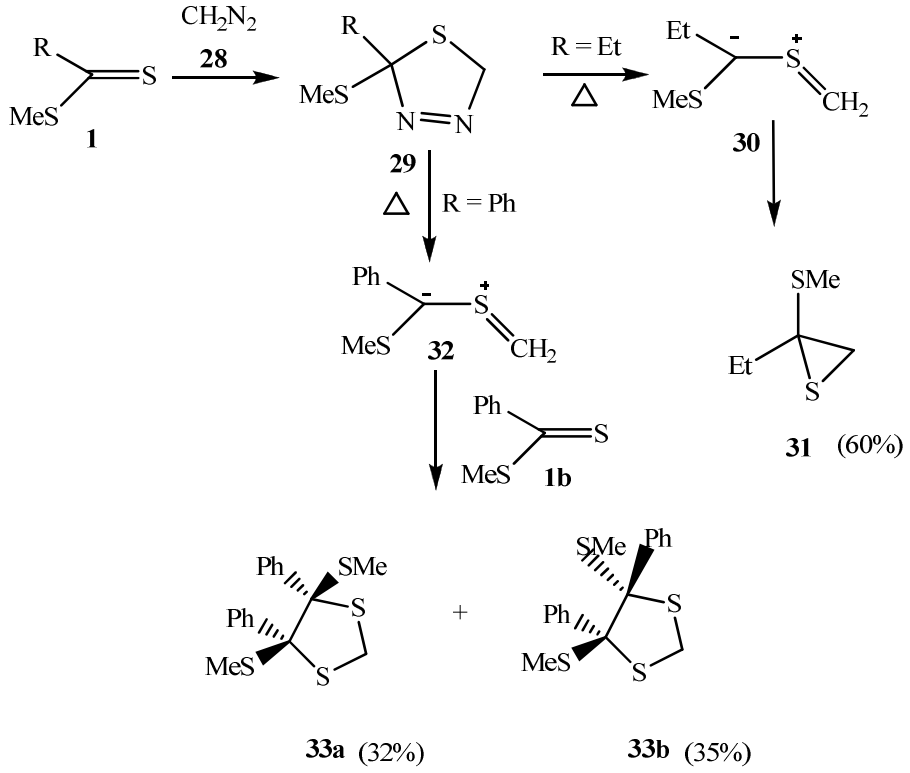
Table 2.

Entry	R^1	Time	**25** Er [ee (%)]	**27** (*endo*/*exo*)	**27** ee (%) *endo*; *exo*
1	(*i*-PrO)$_2$P(O)	12 h	81/19 (62)	76/24	6; 4
2	C(O)OEt	10 min	90/10 (80)	93/7	–; 32
3		24 min	71/29 (42)	92/8	–; 32

Timoshenko and co-workers[18c] also reported similar synthetic strategies (thia-Diels-Alder) for the synthesis of a series of fluorine substituted dihydrothiopyrans. Fluoroalkyl *S*-alkyl(aryl)thiocarboxylates were treated with symmetrical conjugated dienes, such as 1,3-butadiene, 2,3-dimethyl-1,3-butadiene or cyclopentadiene to give the corresponding cycloadducts in good yields. The reaction of the thionoesters with symmetrical 1,3-dienes proceeded with diastereoselectivity up to 60%. The structures of the cycloaddition products and corresponding transition states were studied using DFT.

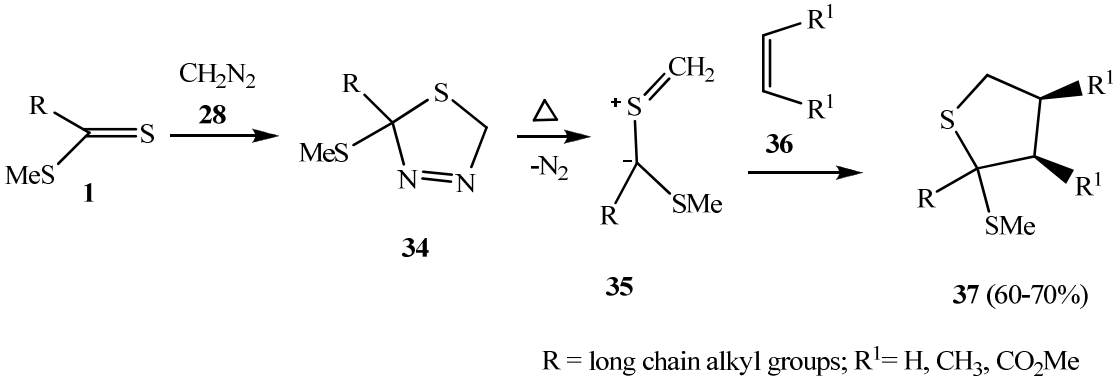
Jorgensen *et al.*[18d] reported the formation of highly enantio-enriched thiopyrans *via* an asymmetric catalytic thio-Diels-Alder reaction. By employing a strategy which explored the use of *in situ* generated catalyst-bound dienes, dihydrothiopyrans as well as other bi- and tricyclic sulfur-containing heterocycles were synthesized in high yields and high to excellent selectivities. DFT calculations were performed to examine the mechanism of the described reaction.

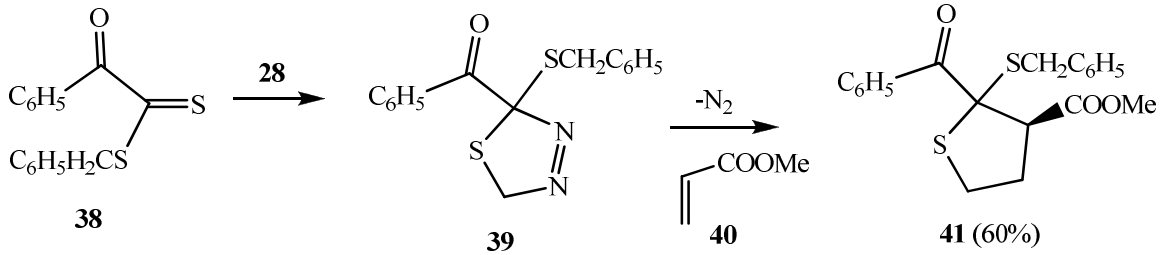
Among the few methods for the generation of sulfur-containing dipolar intermediates, the reaction of diazomethane **28** with C=S dipolarophiles and subsequent elimination of N_2 is applied most frequently (Scheme 12).[19] The reactive 1,3-dipoles (thiocarbonyl ylides) formed *in situ* can be trapped by different electron-deficient dipolarophiles, but aromatic thioketones proved to be the most reactive. In contrast to thioketones, dithioesters have been used less often as precursors of sulfo-methanides (thiocarbonyl ylides). However, reports[19,20] on the formation of thiiranes of type **31** have described starting with methyl propanedithioate (Scheme 12). The intermediate **29** was subjected to thermal cleavage to give thiocarbonyl *S*-methanides **30**, which underwent intramolecular rearrangement to give thiirane **31**. In addition, the intermediate thiocarbonyl *S*-methanides could be trapped with methyl dithioesters such as **1b**, in a regioselective manner, to afford the sterically more hindered 1,3-dithiolane isomers **33a** and **33b**. In these reactions, thiocarbonyl *S*-methanide **32** was proposed as the reactive intermediate (Scheme 12).



Scheme 12

On the other hand, the intermediate thiocarbonyl *S*-methanides could be trapped and utilized in electrocyclic ring closure reactions with other dipolarophiles such as maleic anhydride and acrolein in a regioselective manner, to afford the tetrahydrothiophenes **37** as the cycloadducts (Scheme 13).[21]

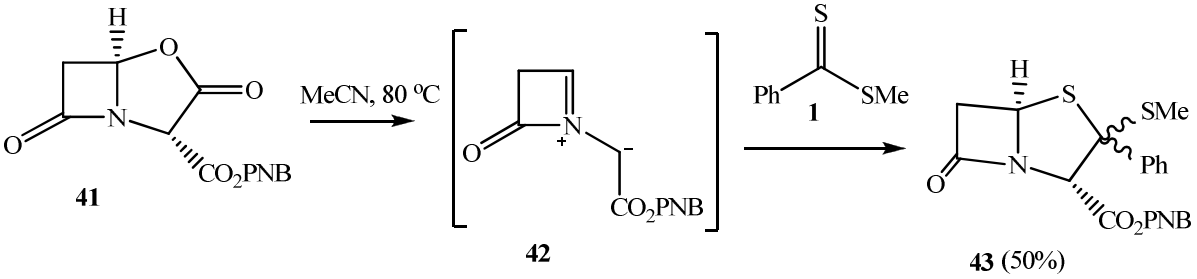




Scheme 13

Dithioesters are used in the synthesis of natural products such as the penam and penems.[22] An example is the bicyclic sulfur-based β-lactam **44** (Scheme 14). The central feature of the chemistry described revolves around application of a versatile range of thiocarbonyl derivatives as 1,3-dipolarophiles toward β-lactam-

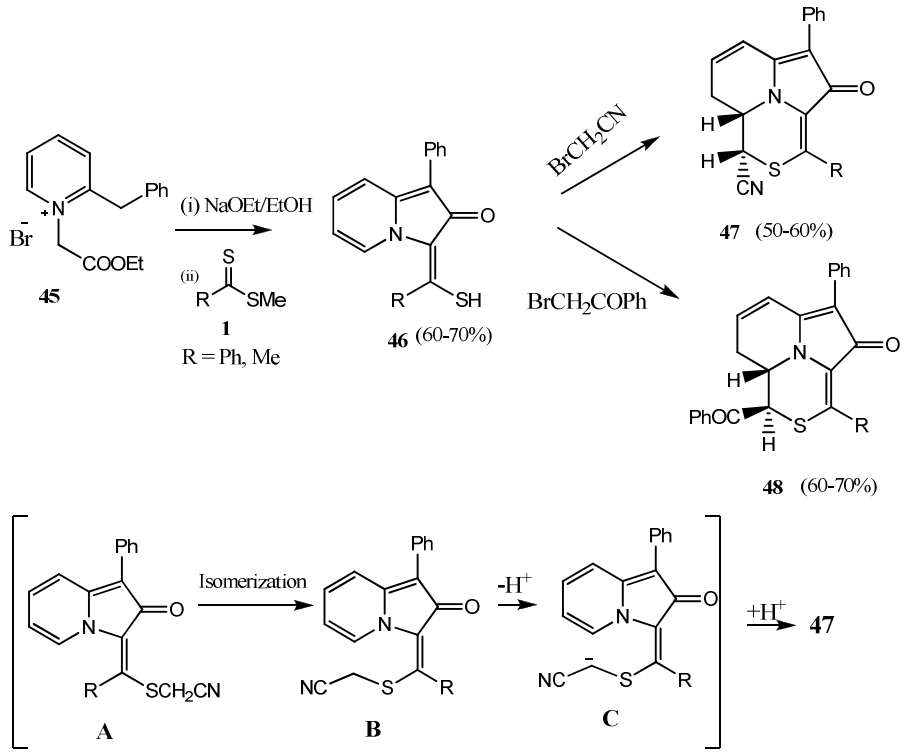
based azomethine ylides, which allows the penam/penem skeleton to be assembled in a single step. The readily available oxazolidinone **42** provides a convenient source of reactivity that is, in essence, equivalent to the stabilized azomethine ylide **43**. Thermolysis of **42** (MeCN, 80 °C, 80 h) in the presence of the dithiocarboxylate **1** provided the adduct **44** directly in 50% yield.



Scheme 14

2.1.3. Synthesis of condensed heterocycles with methyl dithioesters

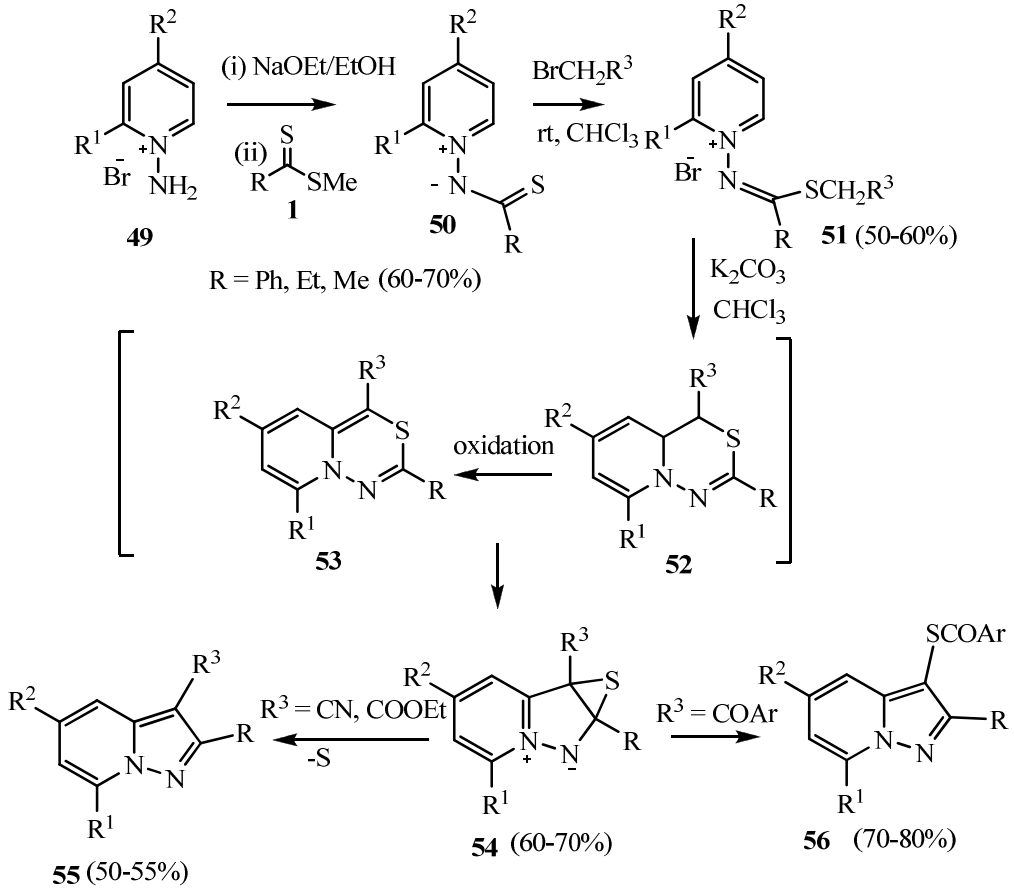
Kakehi and co-workers[23] reported a method for the preparation of indolizines using methyl dithioesters (Scheme 15). When an ethanolic solution of 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide **45** and methyl dithiobenzoate **1** was treated with sodium ethoxide at room temperature, the corresponding 3-(mercaptomethylene)-1-phenyl-2(3*H*)-indolizinones **46** were obtained in 60–70% yield. Indolizinones **46** were further converted into tricyclic heterocycles **47** and **48** by treatment with bromoacetonitrile and phenacylbromide, respectively, in the presence of DBU. A plausible mechanism for the formation of tricycles **47** from indolizinones **46** is shown in Scheme 15.



Scheme 15

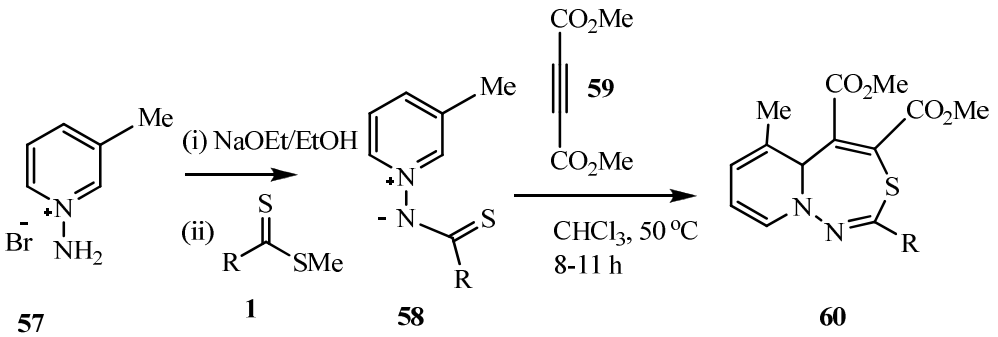
The same authors also reported[24] the formation of pyrazolo[1,5-*a*]pyridine derivatives **55** and **56**, possessing various substituents at the 2- and 4-positions, by the desulfurization and rearrangement of

pyrido[1,2-*d*]-1,3,4-thiadiazine **52**, which was prepared by cyclization of **51**. When methyl dithioesters **1** were treated with pyridinium hydrazides **49**, the corresponding derivatives **50** were obtained, which in a further reaction with bromoalkanes, generated the intermediates **51** in good yields. The wide applicability of this approach toward the syntheses of pyrazolo[1,5-*a*]pyridines was established (Scheme 16).



Scheme 16

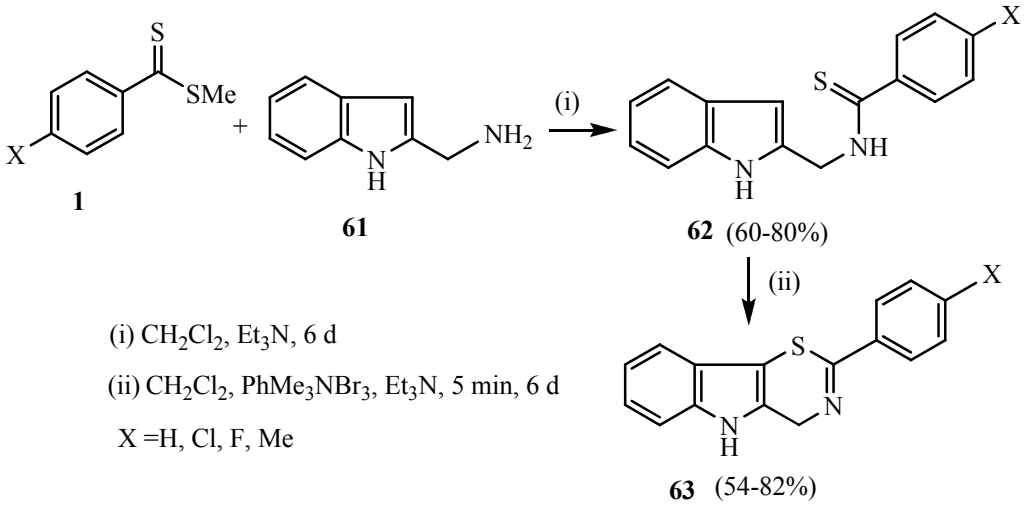
Similarly, pyridine hydrazide **57** was converted into nitrogen-containing heterocycles **60** (Scheme 17).[25] 1-Pyridinio- and 1-(4-methylpyridinio)(arenethiocarbonyl)amidates **58** (which were prepared by reacting methyl dithioesters **1** with pyridine hydrazides **57**) were reacted with dimethyl acetylene-dicarboxylate **59** in chloroform to afford dimethyl 2-aryl-6-methyl-5a*H*-pyrido[1,2-*d*][1,3,4]-thia-diazepine-4,5-dicarboxylates **60** in low yields.



R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$Me_2NC_6H_4$ (20-47%)

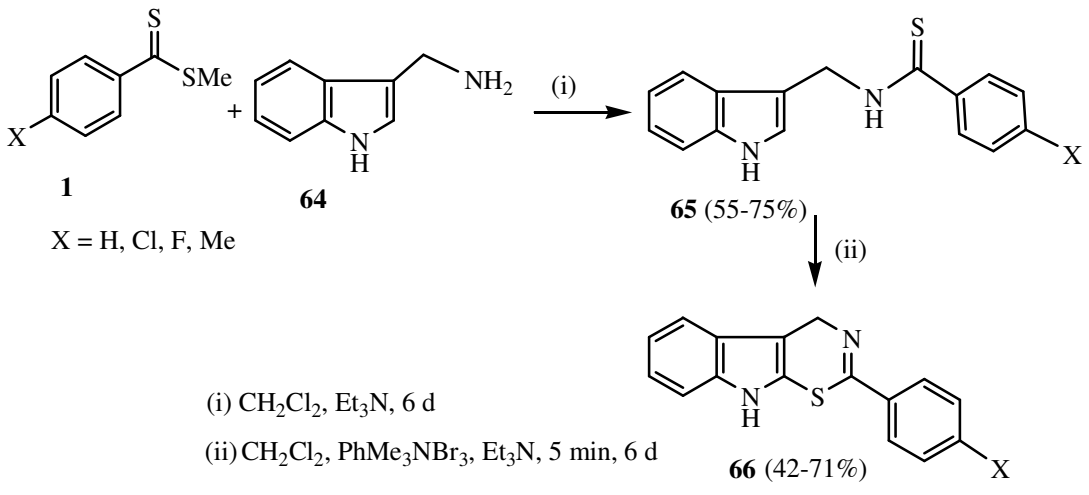
Scheme 17

Condensed heterocycles containing indole moieties are well known biologically active alkaloids.[26] The first cruciferous phytoalexin, cyclobrassinin (2-methylthiothiazino[6,5-*b*]indole), was isolated from Chinese cabbage.[27] Increasing attention has been paid to 1,3-thiazino[6,5-*b*]indole derivatives and many novel synthetic methods for this class of heterocycles have been reported.[28] An efficient route for the synthesis of substituted 2-thiobenzamidomethylindole derivatives was reportedby Bernath *et al.*,[29] which involved the reaction of 2-aminomethylindole **61** with substituted benzoyl chlorides, followed by sulfurization using Lawesson's reagent. Alternatively, these thioamides were obtained from the amine in one step, in an efficient manner, by using substituted benzaldehydes in the presence of sulfur or at room temperature with the aid of substituted methyl dithiobenzoates **1** (Scheme 18). The Hugerschoff reactions of thiobenzamides **62** with phenyltrimethylammonium tribromide provided 2-arylthiazino[5,6-*b*]indoles **63** in moderate to good yields.



Scheme 18

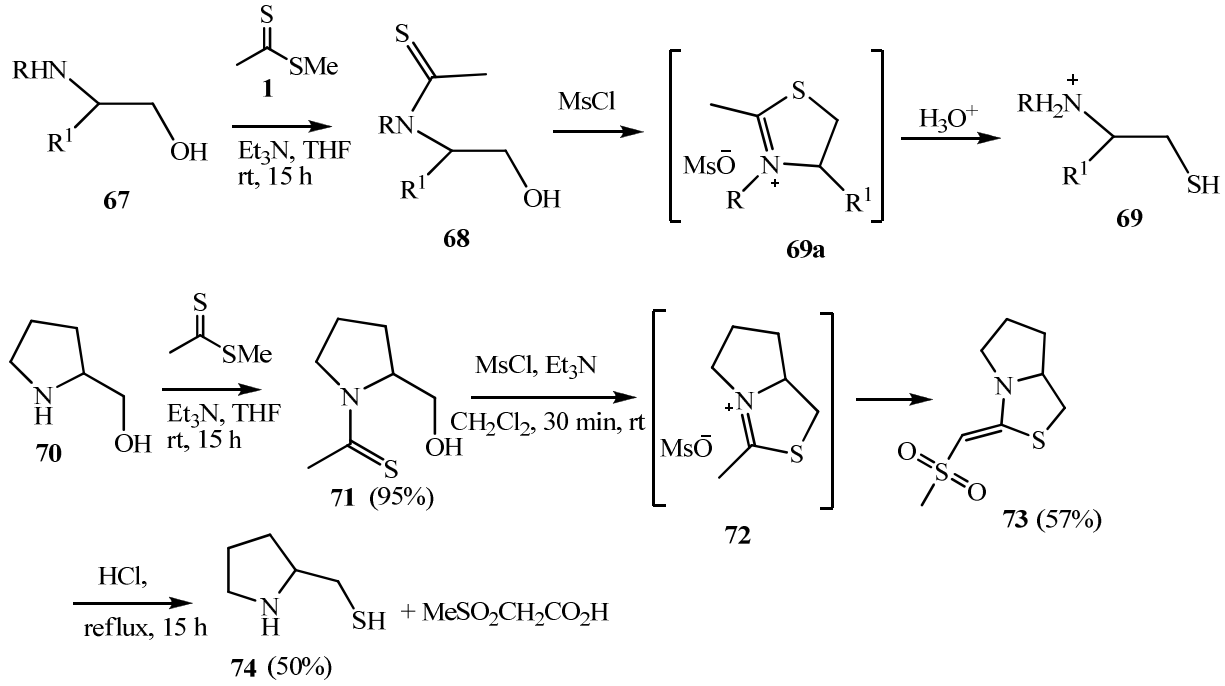
Bernath and co-workers[30] reported another route for similar indole moieties as analogues of the phytoalexin cyclobrassinin. The reactions of indole **64** with substituted methyl dithiobenzoates **1** gave 3-(arylthiocarbonylaminomethyl)indoles **65**. The Hugerschoff ring closure reactions of these thiobenzamide intermediates **65** with phenyltrimethylammonium tribromide and subsequent basic treatment furnished 2-arylthiazino[6,5-*b*]indole derivatives **66** (Scheme 19).



Scheme 19

2.1.4. Synthesis of miscellaneous heterocyclic systems using methyl dithioesters

Gulea and co-workers have reviewed various transformations of commercially available β-amino alcohols into 2-thiazolines,which use methyl dithioacetate as the source of sulfur.[31a]One such example[31b] described a procedure which involved thioacylation of secondary 2-amino alcohols **67** with methyl dithioacetate **1** and subsequent intramolecular cyclization of the resulting *N*-(β-hydroxy)thioamides **68** to give the intermediate thiazolinium salts **69a**. Acid hydrolysis of these salts gave the corresponding secondary 2-amino thiols **69** (Scheme 20). The reactions of a primary 2-amino alcohol and methyl dithioacetates were reported to give quantitative yields and the conversions of the dithioester derivatives into thiazolidines and their corresponding thiazolinium salts were reported in 49–81% and 60–88% yields, respectively. With a substrate where the *N*-alkylating agent was $EtMeCHCH_2Br$, low yields of 22% of the salt and 47% of the thiazolidine were reported. Further, Gulea and co-workers extended their work by transforming the thiazolinium salts **72** or thiazoles **73** into secondary β-amino thiols **74** by acid hydrolysis.

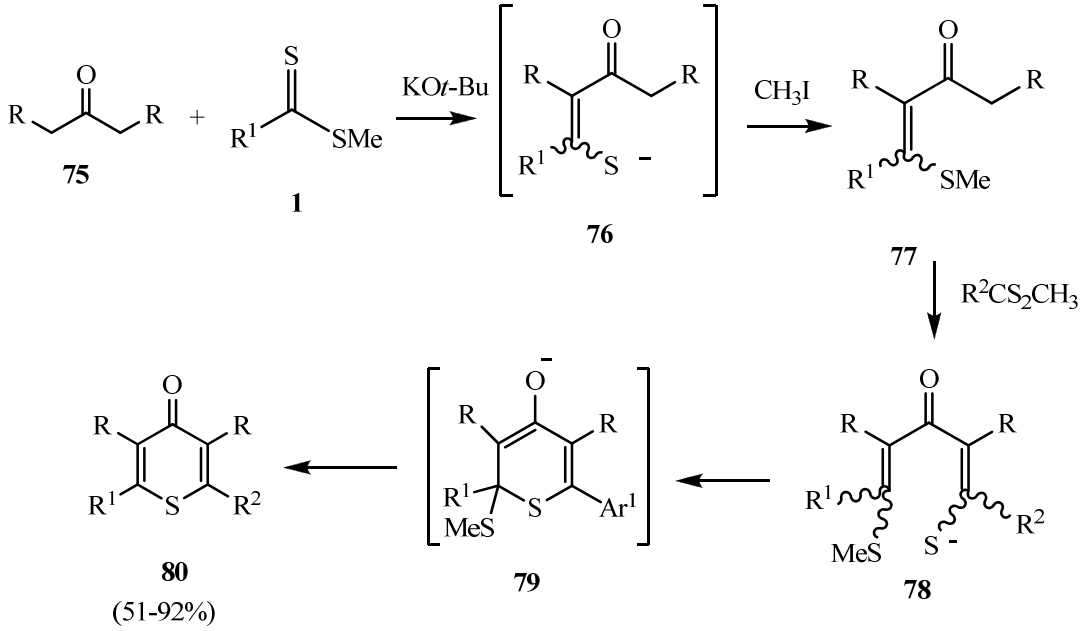


Scheme 20

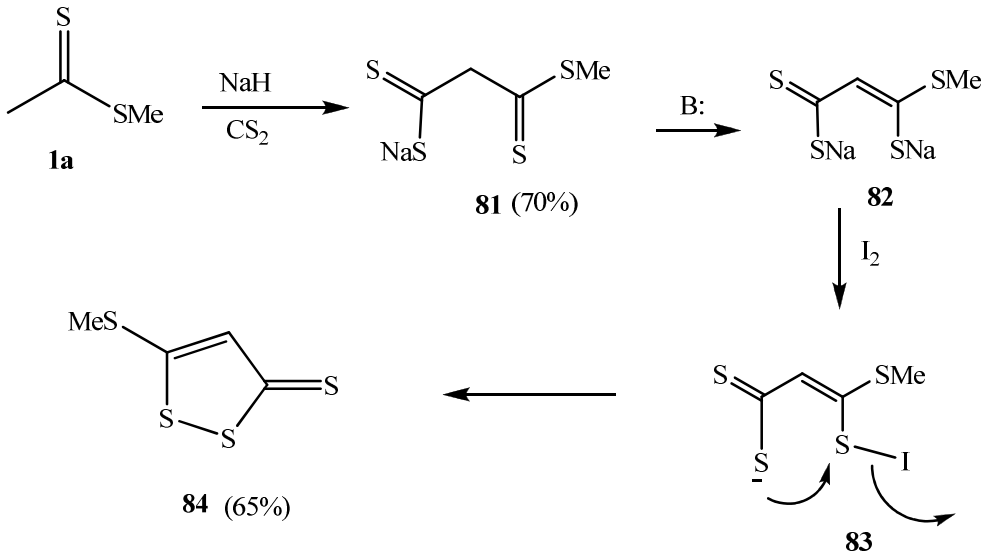
2,6-Diaryl-4*H*-thiopyran-4-ones are key building blocks for the synthesis of numerous electron-donors,[32] sensitizers[33] and dyes[34] used for research on organic conductors and photoconductors. A novel synthesis of 2,6-diaryl-4*H*-thiopyran-4-ones **80** was developed by Boaz and Fox which involved the use of dithioesters.[35] These were prepared by two sequential thio-Claisen condensations of a dialkyl ketone **75** and two dithioesters **1** (Scheme 21). The intermediate **76** from the first condensation was converted into the corresponding (methylthio)enone **77** for both protection and reactivity purposes. Addition-elimination of the methylthio moiety of **78** generated in the second thio-Claisen condensation afforded the desired heterocycle **80**.

The preparation of 5-(alkylthio)-1,2-dithiole-3-thiones **84** using dithioester **1a** is highlighted in Scheme 22.[36] When methyl dithioester **1a** was treated with CS_2 in presence of NaH, intermediate **81** was generated, which on further reaction with a base and iodine afforded 5-(methylthio)-1,2-dithiole-3-thione **84** in 65% yield. The formation of **84** as the final product was explained by the existence of intermediates **82** and **83**.

One interesting observation in this reaction was that the sulfur atom acted as a nucleophile as well as an electrophile in the intramolecular cyclization reaction to yield the product.



Scheme 21

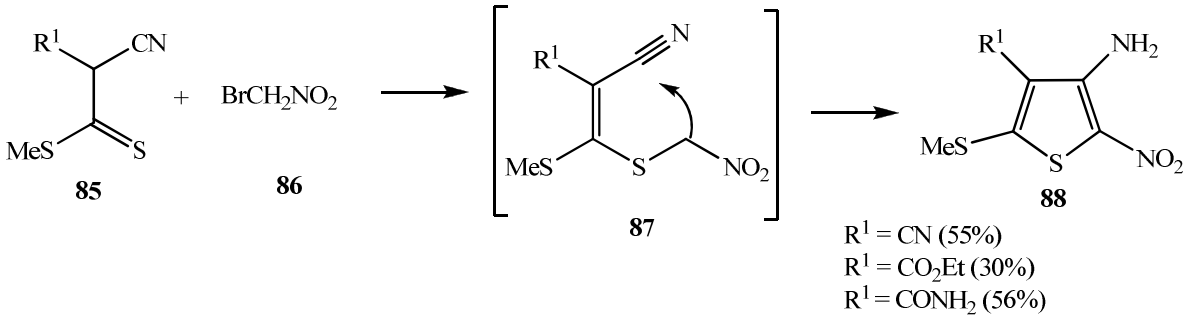


Scheme 22

2.2. Reactions of methyl dithioesters containing an electron-withdrawing group (EWG) at the α-position

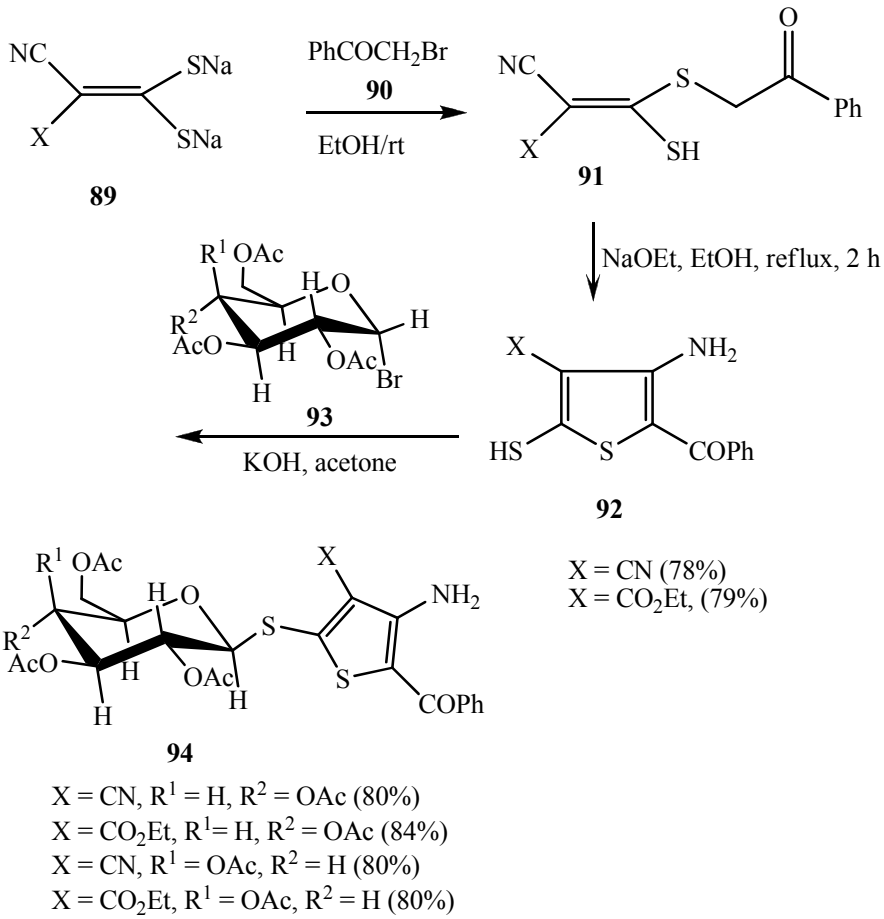
During investigations of various pathways in reactions of bromonitromethane **86** with various nucleophiles, specific methyl cyanodithioesters were reported as starting materials (thiolates) for the synthesis of nitro-substituted thiophenes **88** (Scheme 23).[37] When the thiolate ion itself carried an electrophilic centre such as a carbonyl or cyano group α to the sulfur (*cf.* **85**), the product was a nitrothiophene **88** derived from reaction of the initially formed sulfide anion **87**. A series of

nitroaminothiophenes obtained by variation of this procedure was reported,[37] starting from bromonitromethane **86**. The common feature of all of these thiophene-forming reactions was cyclization as a consequence of nucleophilic attack of a thiolate on bromonitromethane.



Scheme 23

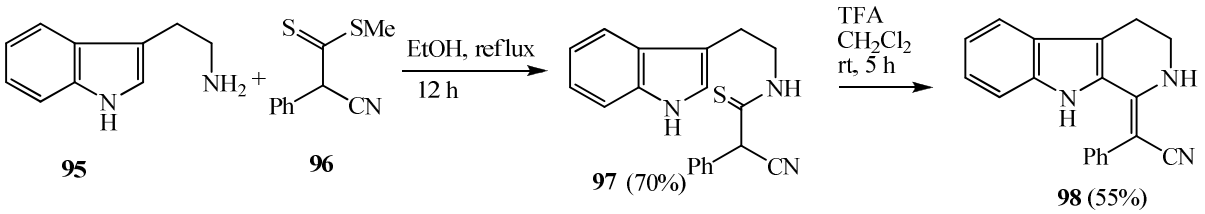
Elgemie *et al.*[38] reported a new method for the preparation of thiophene thioglycosides **94** *via* a one-pot reaction of the sodium salts of **92** with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides **92** (Scheme 24).



Scheme 24

Substrates **89** were readily monoalkylated with one equivalent of phenacyl bromide **90** to give the corresponding products **91** in good yields, which underwent intramolecular cyclization in the presence of sodium ethoxide and ethanol to give the thiophenes **92**. Upon alkylation of thiophenes **92** with halogeno-sugars **93**, the corresponding 2-(glycopyranosylthio)-thiophene derivatives **94** were obtained.

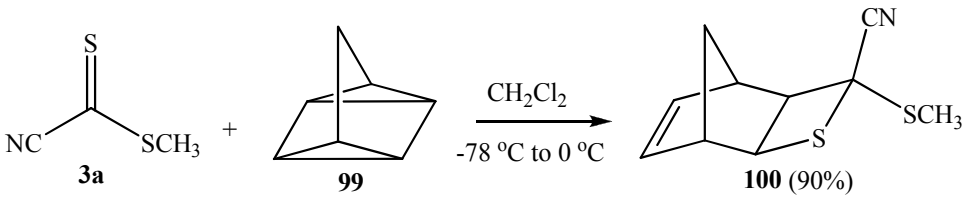
Junjappa and co-workers[39] also utilized ethyl cyanodithioesters during their investigation of the synthesis of functionalized 1,2,3,4-tetrahydro-β-carbolines. When tryptamine **95** was treated with cyanodithioester **96** in refluxing ethanol, an interesting thioamide **97** was generated. This thioamide was subjected to cyclization at room temperature in TFA-CH_2Cl_2 to afford 1,2,3,4-tetrahydro-β-carboline **98** in 55% yield (Scheme 25). However, the authors prepared only one β-carboline compound using dithioester **96**, and most of the other similar compounds were prepared from ketene *N*,*S*-acetals derived from tryptamine and ketene dithioacetals.[39]



Scheme 25

2.3. Reactions of cyanodithioformates

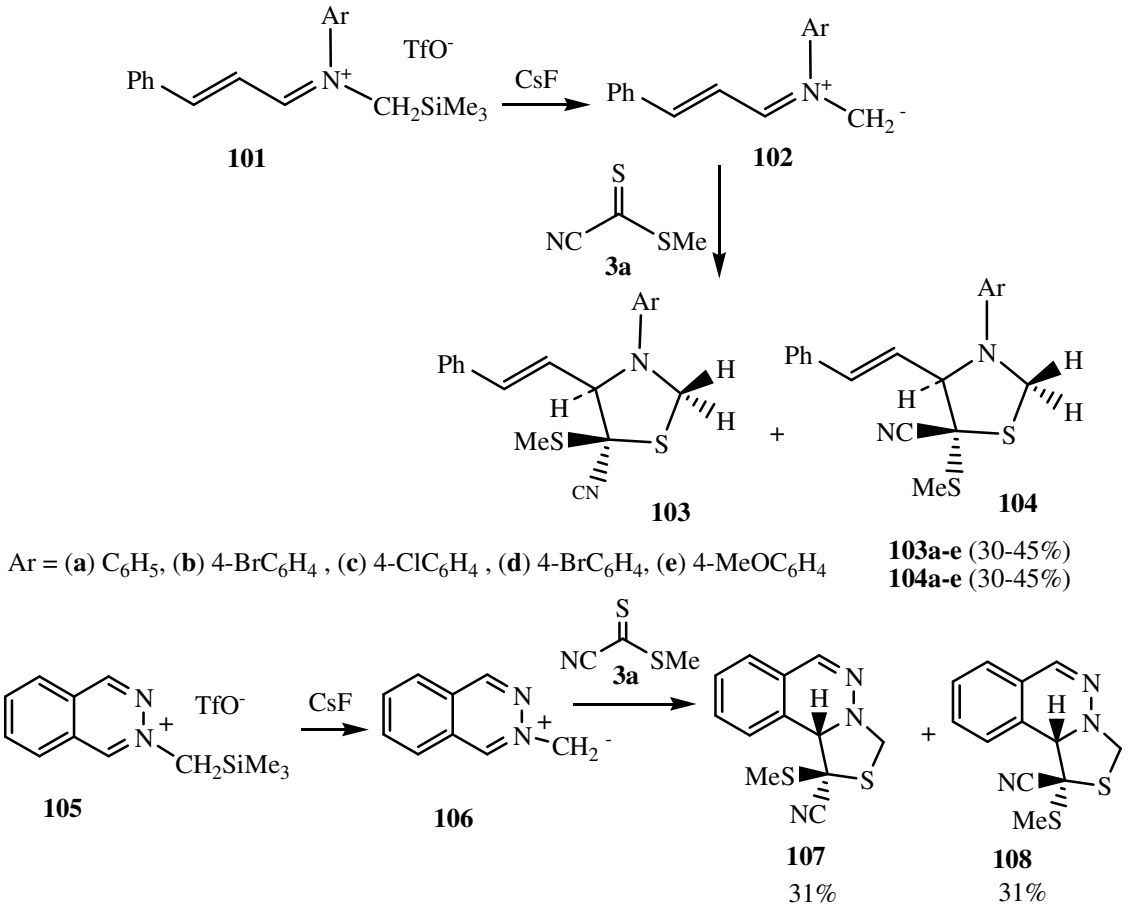
The cycloaddition reaction of dithioester **3a** with quadricyclane **99** afforded annelated thietane **100** in good yield (Scheme 26).[40]



Scheme 26

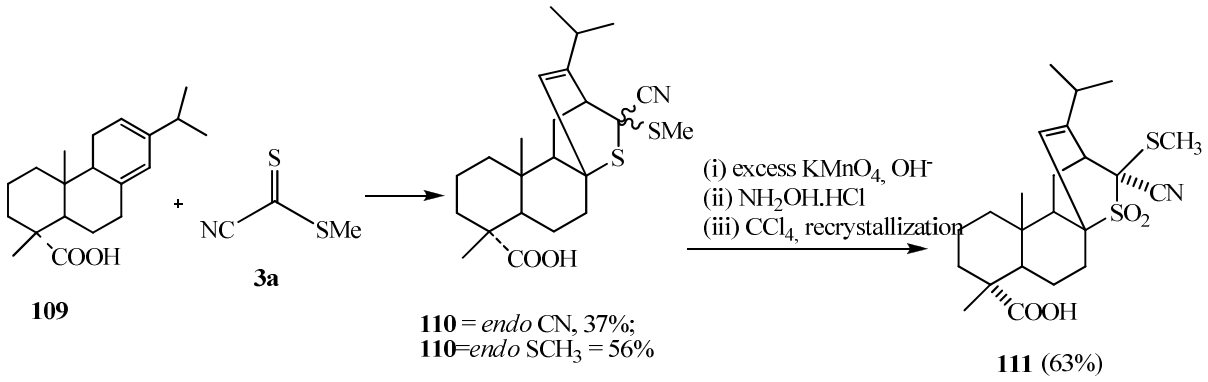
As with the other dithioesters shown in the previous schemes, the thiocarbonyl group of methyl cyanodithioesters can participate in cycloaddition reactions as a dienophile to give thiazoles (Scheme 27).[41] In cycloaddition reactions of aryl(3-phenylprop-2-en-1-ylidene)ammoniomethanide **102** and phthalazinium-2-methanide **105**, 1,3-dipoles with thiobenzophenone, phenyl dithioacetate and methyl cyanodithioformate, the regiochemistry was such that the nucleophilic methanide terminus of the dipole formed a bond to the sulfur atom, thus giving stereoisomeric 4-styryl substituted tetrahydrothiazoles **103** and **104** and thiazolo [4,3-*a*]phthalazines **107** and **108**. With dicyclopropyl thioketone and thioadamantanone, steric effects caused a gradual reversal of this regiochemistry. The solvent polarity did not alter the distribution of the regioisomers. X-Ray crystal structures have been reported for 1,1-diphenyl[1,3]thiazolo[4,3-*a*]phthalazine **107** and 3-(*p*-bromophenyl)-4-[(*E*)-styryl]-5-*trans*-cyano-5-*cis*-methylthio-2,3,4,5-tetrahydro-thiazole **103b**.

The dipoles **102** and **106** were generated at ambient temperatures in dichloromethane by desilylation of the trimethylsilylmethyl trifluoromethanesulfonate (triflate) salts **101** and **105** with CsF following a literature procedure. With imine systems, these types of salts were generally not isolated prior to desilylation and the influence, if any, of their *E*,*E* or *E*,*Z* stereochemistry was not been commented on previously in the literature. The reactions of the dipoles **102** and **106** (Scheme 27) with methyl cyanodithioformate **3a** gave mixtures (1:1) of stereoisomeric pairs. The methanide carbon atom in these thiazolo[4,3-*a*]phthalazine products forms a bond to the thione sulfur atom.



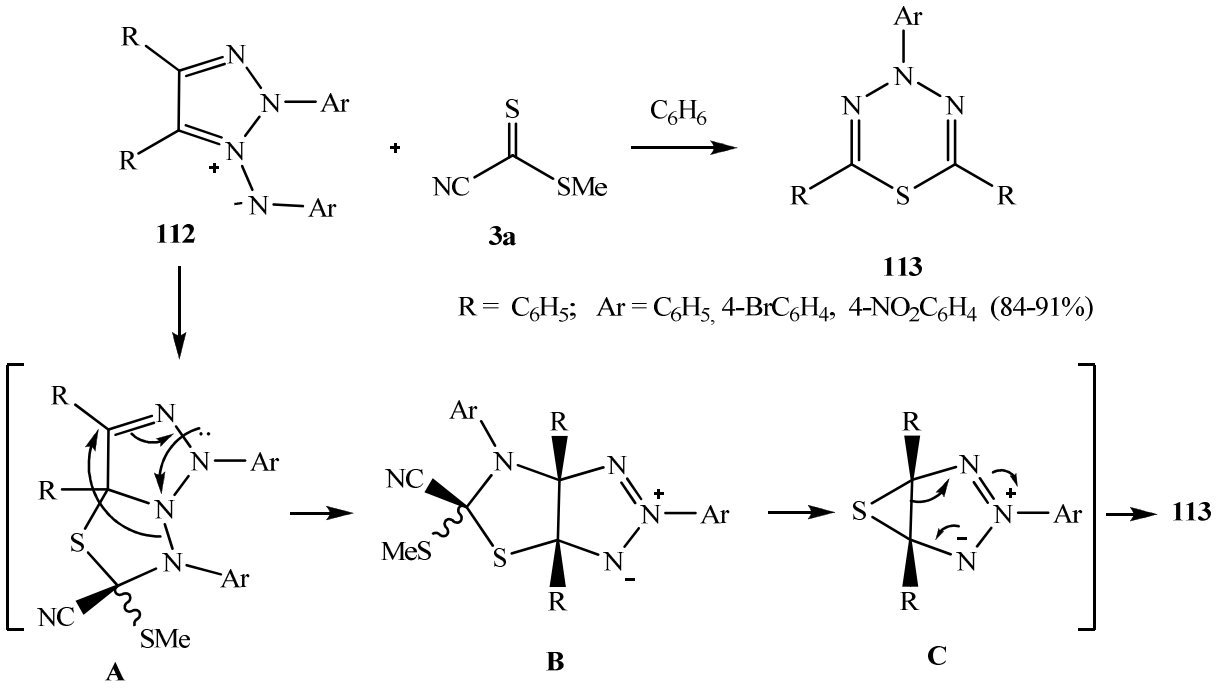
Scheme 27

The use of cyanomethyl dithioformates in the Diels-Alder reaction with levopimaric acid to yield a thiopyran-fused derivative of the acid was reported by Friedrich.[42] The reaction of levopimaric acid (**109**) with the activated dienophile, methyl cyanodithioformate **3a** initially generated **110** (*endo*) (Scheme 28). The alternative Diels-Alder adduct, **110** (*endo* SCH_3), was subjected to permanganate oxidation, to give sulfone derivative **111** in 63% yield.



Scheme 28

Methyl cyanodithioformate has also been used in cycloaddition reactions with triazolium imide 1,3-dipolar compounds to afford 1,3,4,5-thiatriazines.[43] Treatment of the triazolium imide 1,3-dipoles **112** with methylcyanodithioformate **3a** in benzene at ambient temperature gave the new products **113** (Scheme 29). A total of three products derived from methyl cyanodithioformate were reported, but the yields were very high (84–91%) and the structures were established from X-ray structural data.



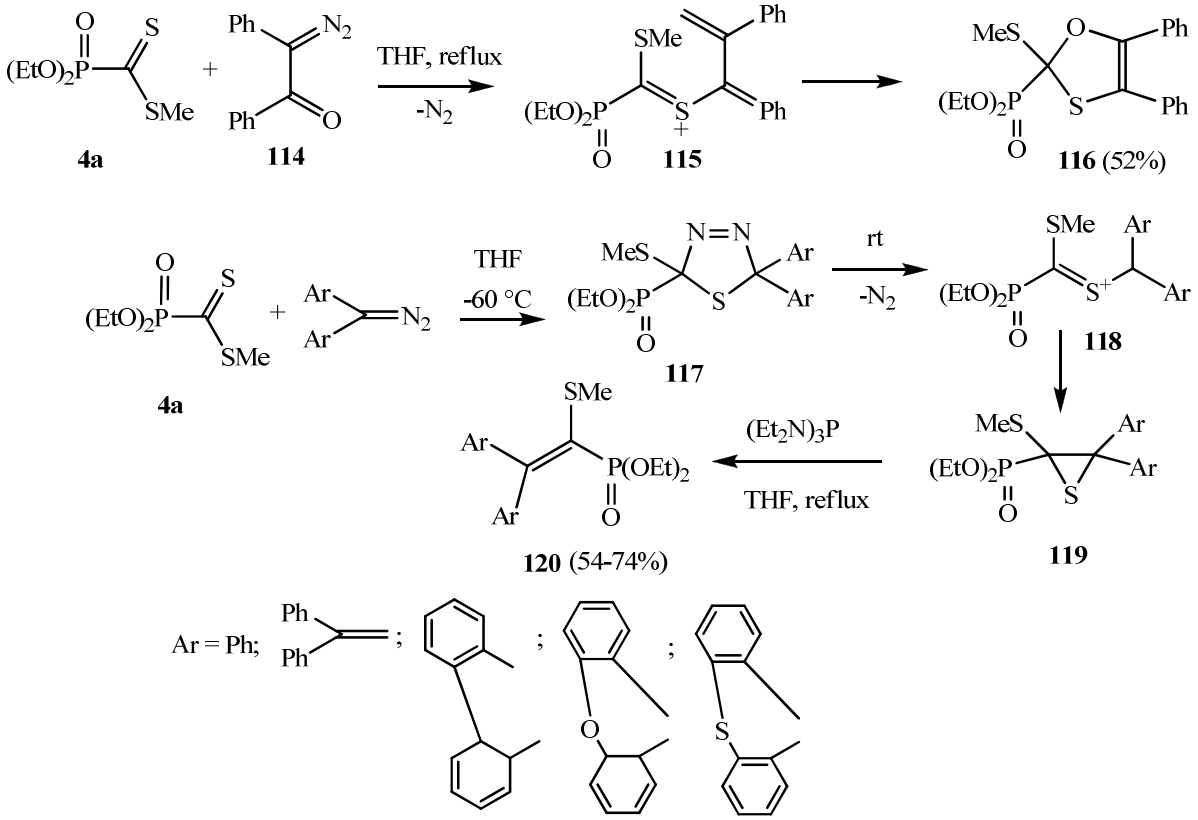
Scheme29

2.4. Reactions of phosphonodithioformates

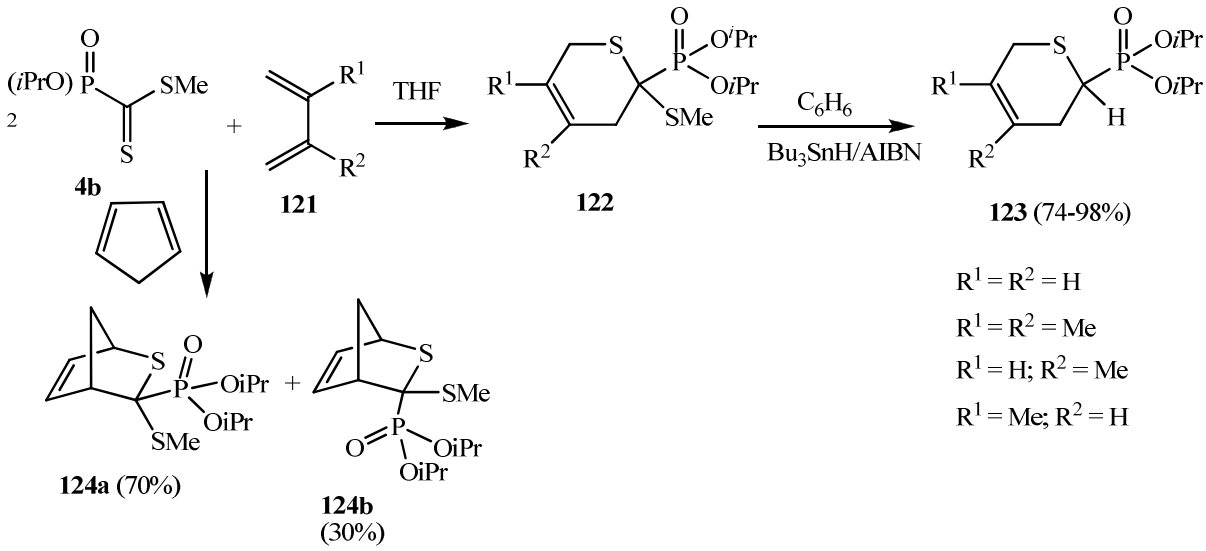
Phosphonodithioformates and dithioacetates are shown to be versatile building blocks through their use in various reactions such as thiophilic addition of nucleophiles, thioacylation of amines and hetero-Diels-Alder reactions.[44] Among other applications, these dithioesters can be used as precursors of novel phosphorylated thia-substituted heterocycles and phosphonate analogues of glycoside or nucleoside monophosphates. The reaction of methyl (diethylphosphoryl)dithioformate **4a** and 2-diazo-1,2-diphenyl-ethanone **114** in boiling THF gave 1,3-oxathiole **116**. The reaction occurred *via* an intermediate thiocarbonyl ylide **115**, followed by 1,3-dipolar electrocyclization and sulfur extrusion or 1,5-dipolar electrocyclization (Scheme 30).[44c]

The reactions of diaryldiazomethanes with **4a** yielded crude products which were identified as a mixture of thiirane **118** and the vinyl phosphonate **120**, formed after spontaneous desulfurization (Scheme 30). Phosphonodithioformates undergo hetero-Diels-Alder cycloadditions with a variety of dienes. In some cases, Lewis acid catalysts were used to control the rate and selectivity of the reactions. Selective radical desulfanylation and subsequent dihydroxylation of the cycloadducts allowed the syntheses of new thiapyran derivatives and, in particular, a phosphono and thio analogue of shikimic acid.

Phosphonodithioformates are shown to be good heterodienophiles in [4+2] cycloadditions with open chain and cyclic dienes.[45] Lewis acids catalyze efficiently this hetero-Diels-Alder reaction and a selective radical desulfanylation of the cycloadducts using Bu_3SnH leads to new (3,6-dihydro-2*H*-thiopyran-2-yl)phosphonates (Scheme 31). Methyl diisopropylphosphono dithioformate **4b** reacts with excess (5 equiv) of butadienes **121**, in methylene chloride to give the corresponding (3,6-dihydro-2-methylsulfanyl-2*H*-thiopyran-2-yl)phosphonates **122** (Scheme 31). When **4b** was treated with excess (10 equiv) freshly dedimerized cyclopentadiene, a 70:30 mixture of two isomeric thia-norbornene derivatives **124a** (SMe-*endo*) and **124b** (SMe-*exo*) was obtained. When the reaction was extended for at least 30 minutes, the ratio of the two isomers changed into 40:60 indicating that **124a** was the kinetic product and that **124b** was the thermodynamic product.



Scheme30



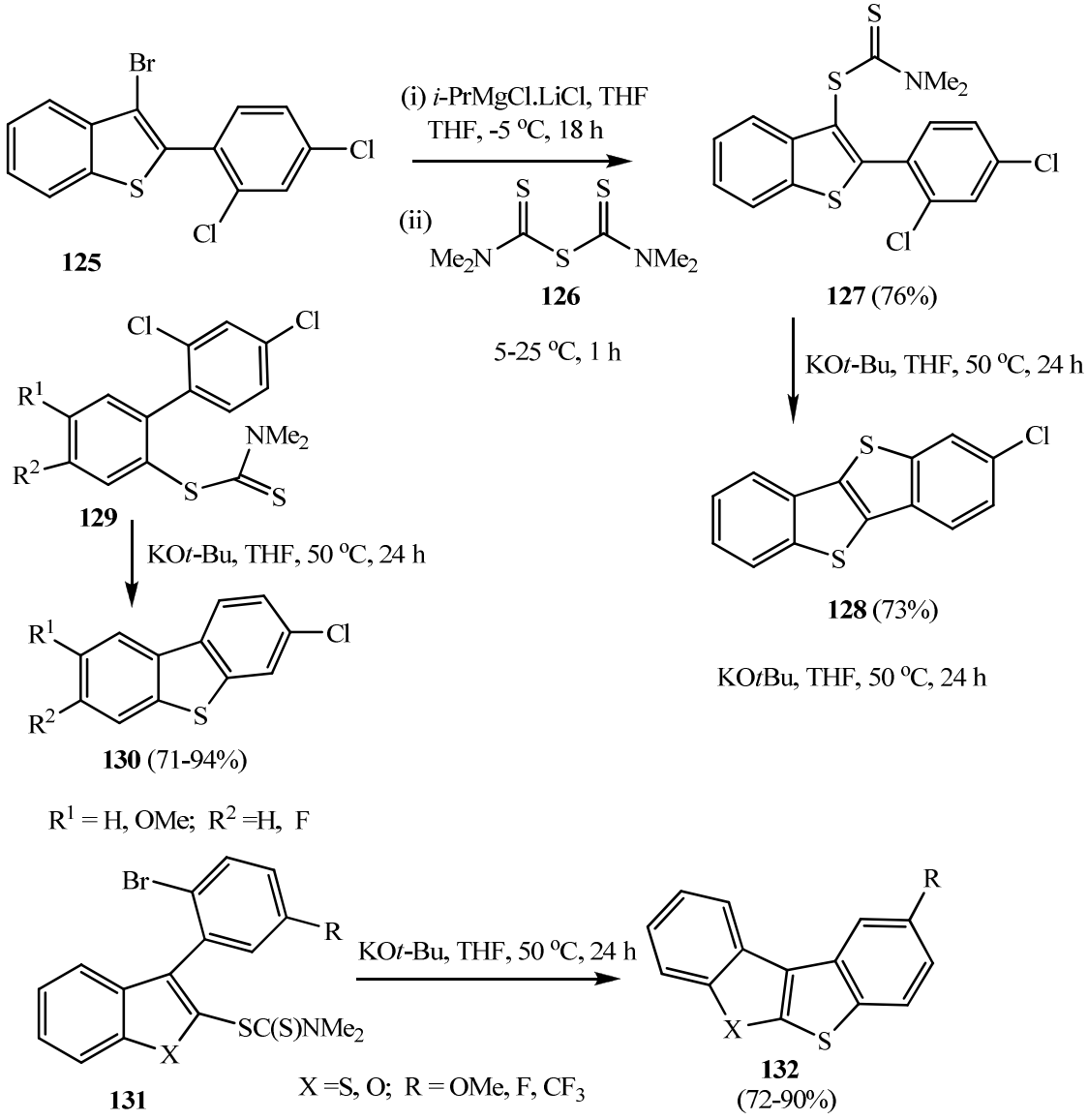
Scheme31

2.5. Reactions of dithiocarbamates

Dithiocarbamic acids are analogues of carbamic acids in which both oxygen atoms are replaced by sulfur. Although dithiocarbamic acids are not unstable, their esters and complexes with metals are stable, and have found wide applications as fungicides and pesticides in agriculture,[46] as sulfur vulcanization agents in rubber manufacturing,[47] as radical chain-transfer agents in reversible addition-fragmentation chain-transfer (RAFT) polymerizations,[48] as organic intermediates[49] and in medicinal chemistry.[50]

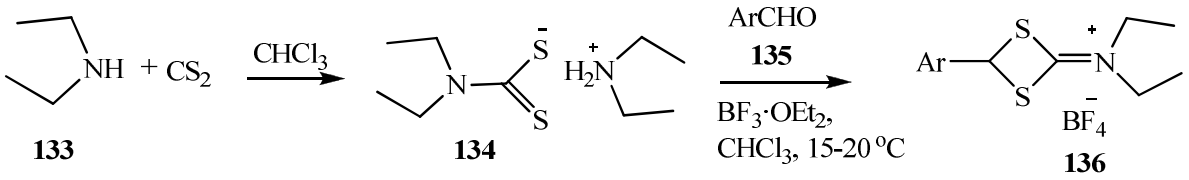
Knochel *et al.*[51] used dithiocarbamates for the synthesis of dibenzothiophene-fused heterocycles. The halo-substituted dithiocarbamates **127**, **129** and **131** were converted, by treatment with *t*-BuOK (3.0 equiv,

THF, 50 °C), into the corresponding potassium thiolates, which underwent an addition/elimination ring-closure to provide the corresponding functionalized dibenzothiophenes **128**, **130** and **132** in 71–96% yields within 0.75–24 hours (Scheme 32). Dibenzothiophenes, benzo[*b*]thiophenes and benzo[*c*]thiophenes have found numerous applications as dyes, pharmaceuticals, agrochemicals and as building blocks for the synthesis of conducting polymers.[52]



Scheme 32

Notash *et al.*[53] reported a synthetic method for the generation of libraries of 2-iminium-1,3-dithietanes from dithiocarbamic salts (Scheme 33). The reaction of dithiocarbamic acid salts with carbonyl compounds in the presence of $BF_3 \cdot OEt_2$ gave the corresponding four-membered ring compounds. The reaction was found to be temperature-dependent and gave *gem*-bis(dithiocarbamates) at 35–45 °C with excess dithiocarbamate. At lower temperatures (15–20 °C), the 2-iminium-1,3-dithietane was obtained as the only product. The structures of the 2-iminium-1,3-dithietanes (Figure 1) were established by X-ray crystallographic analysis. The dithiocarbamic acid salt **134** was prepared separately and was added to a solution of benzaldehyde and $BF_3 \cdot OEt_2$ in $CHCl_3$ at room temperature to afford the 2-iminium-1,3-dithietanes **136**.



Scheme 33

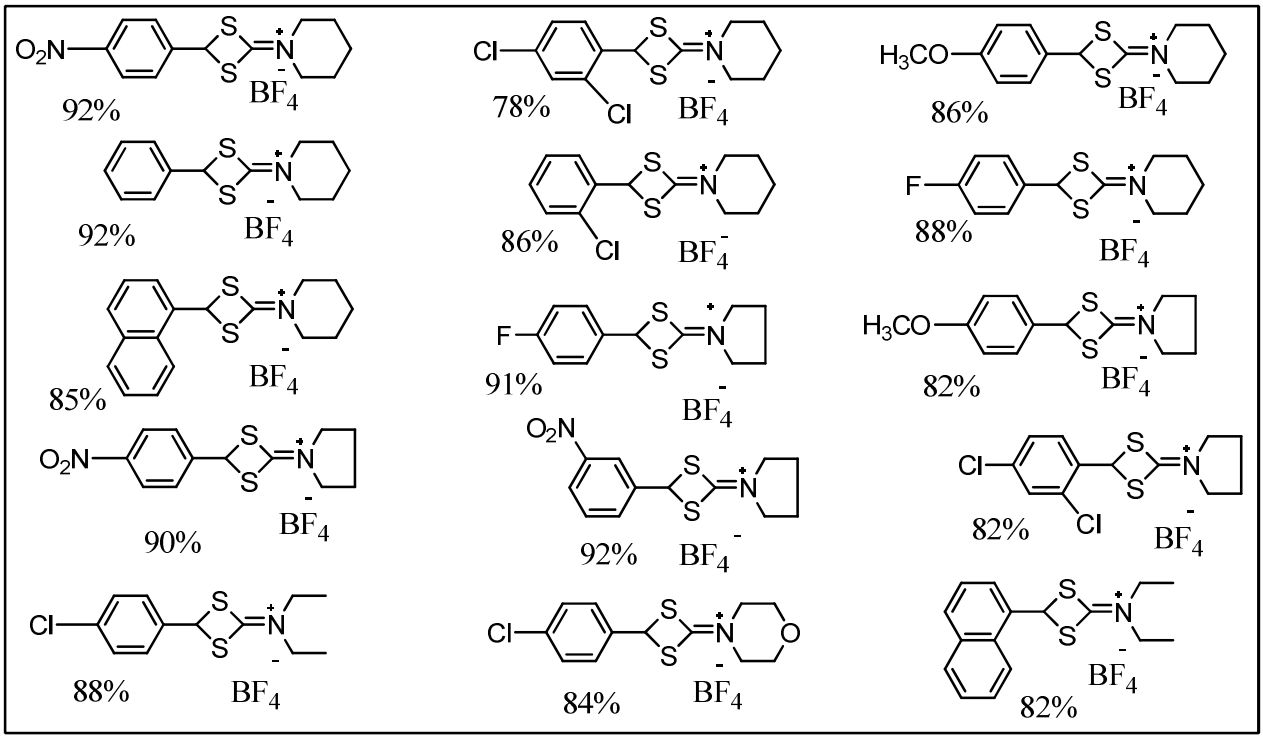
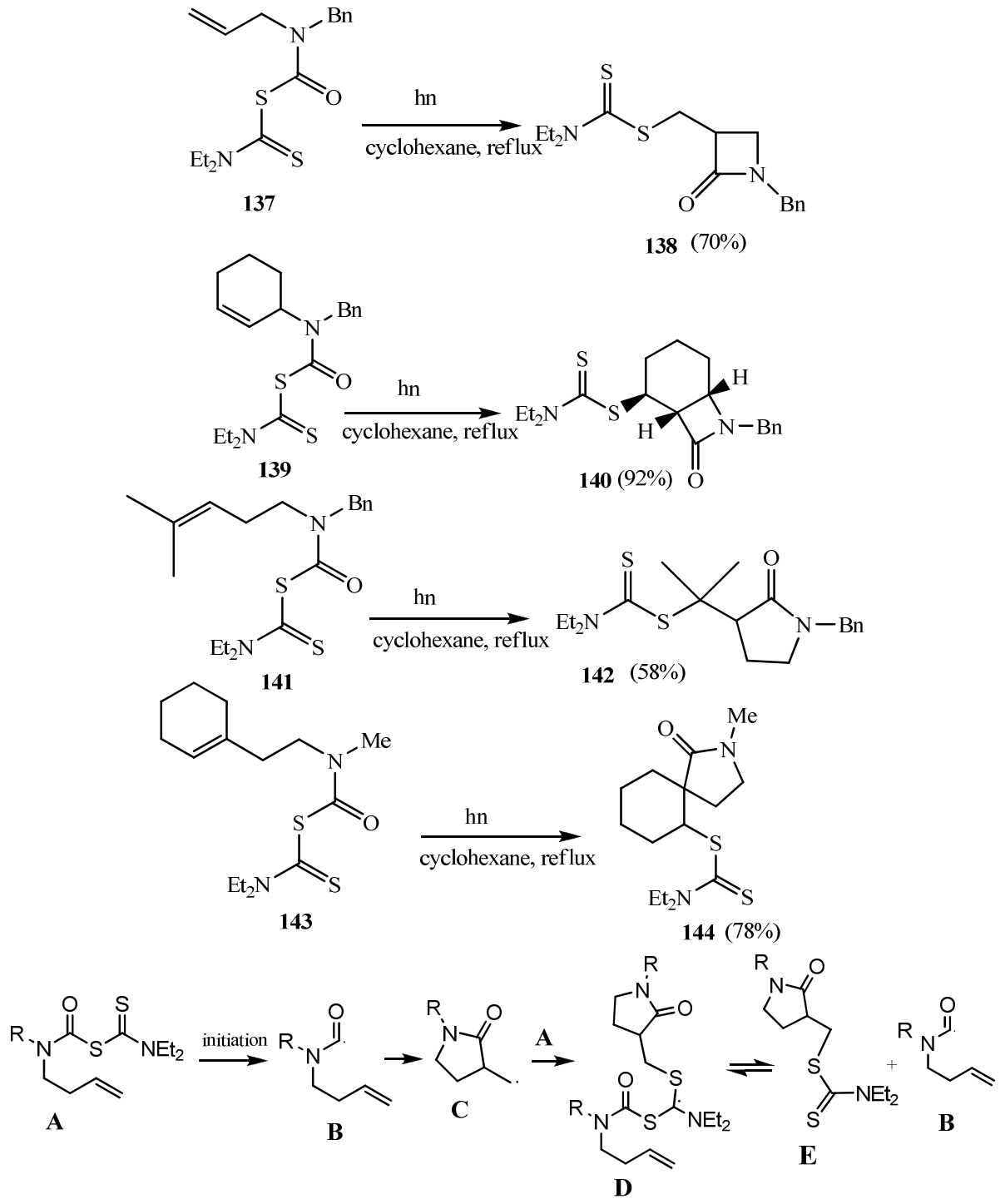


Figure 1. Library of 2-iminium-1,3-dithietane products.

The application of dithiocarbamates in group transfer radical cyclization reactions has been described by Grainger and Innocenti (Scheme 34).[54] Carbamoyl diethyldithiocarbamate **137** was synthesized in two high-yielding steps from a secondary amine and acts as a source of carbamoyl radicals through chemical or photochemical initiation. A group transfer radical cyclization reaction led to dithiocarbamate-functionalized lactam **138**. Other cyclizations of similarly prepared dithiocarbamates gave various lactams of different ring sizes, products **140**, **142** and **144**, in moderate to good yields.

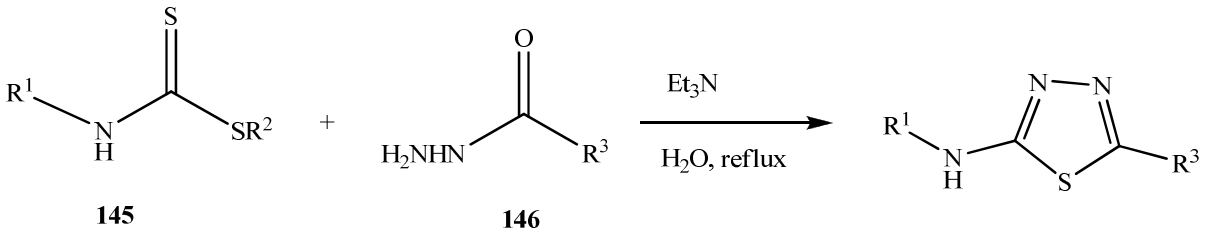
A plausible mechanism for this transformation was proposed involving carbamoyl group transfer radical cyclization. Carbamoyl xanthate **A** is expected to act as the source of carbamoyl radical **B**, which can cyclize to form alkyl radical **C**. Xanthate group transfer *via* addition of the thiocarbonyl group of **A** gives **D** and subsequent fragmentation leads to the desired product **E** along with carbamoyl radical **B**, which allows the chain process to continue (Scheme 34).

Saidi and co-workers[55] have reported a new and facile protocol for the synthesis of 2-amino-1,3,4-thiadiazoles in water. Reactions of acid hydrazides with readily accessible dithiocarbamates gave the corresponding thiadiazoles in moderate to excellent yields. As shown in Scheme 35, dithiocarbamates **145** derived from primary aliphatic and aromatic amines underwent the condensation reaction with hydrazide **146** in water to afford thiadiazoles **147**,in moderate to excellent yields, without using any cyclization promoters.



Carbamoyl radical cyclization (group transfer)

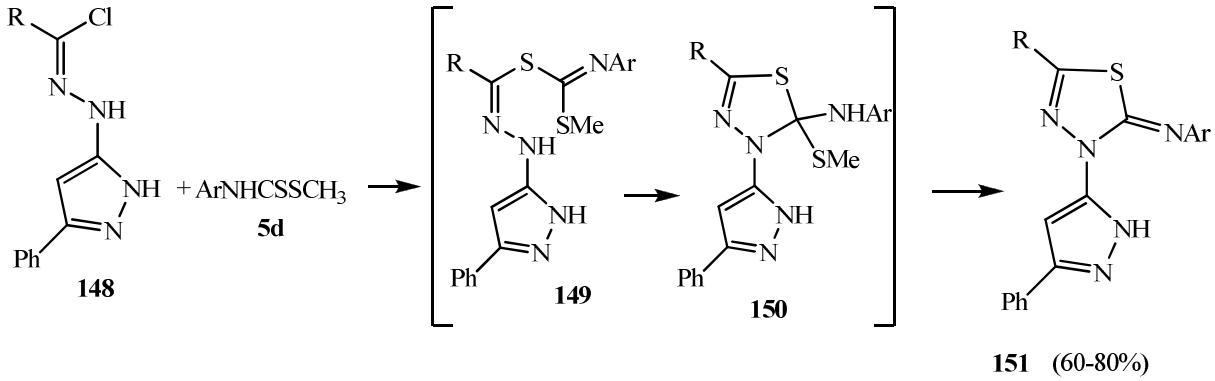
Scheme 34



R^1 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 3,4-$Cl_2C_6H_3$, $C_{10}H_7$
R^2 = CH_2CH_2CN, CH_2CH_3, $CH_2CH{=}CH_2$
R^3 = Ph, $PhCH_2$, 4-MeC_6H_4, 2-HOC_6H_4, 4-pyridine

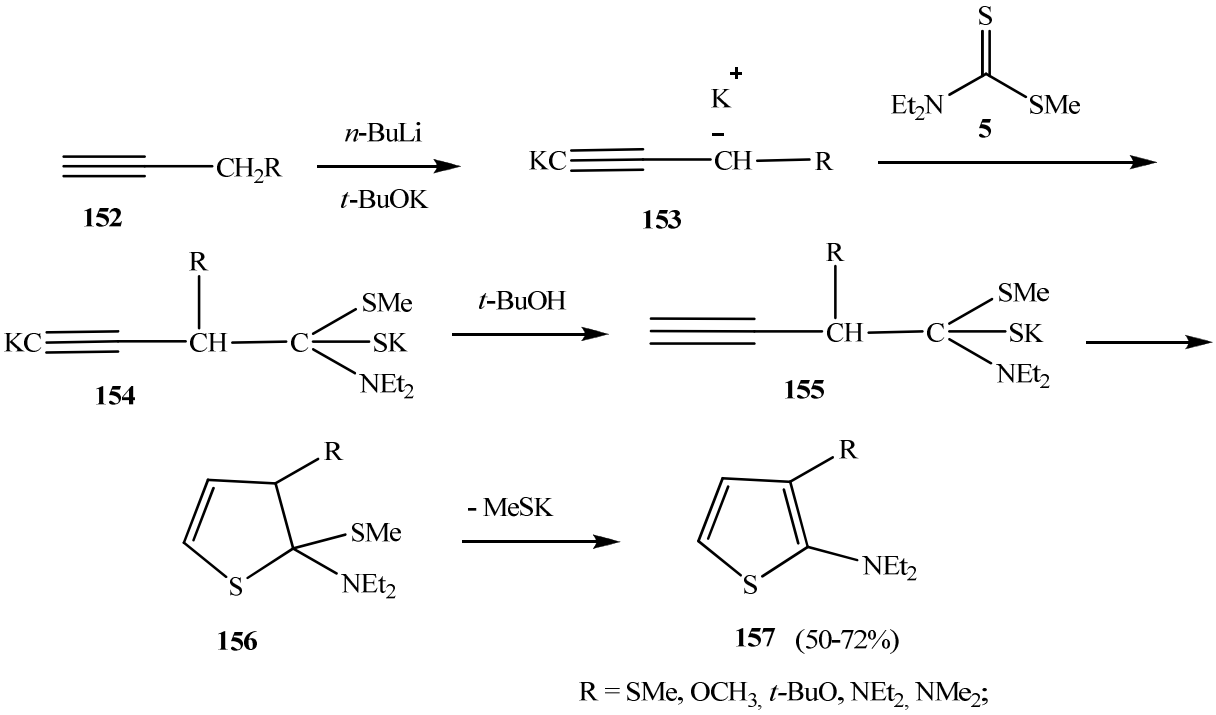
Scheme 35

Dithiocarbamates can also be utilized in the synthesis of 2,3-dihydro-1,3,4-thiadiazoles.[56] Scheme 36 highlights a synthetic route to 2,3-dihydro-1,3,4-thiadiazoles **151**. On treatment of 1-[5-hydrazono-4-(5-phenyl-2*H*-pyrazol-3-yl)-4,5-dihydro[1,3,4]thiadazol-2-yl]ethanone **148**, with the appropriate carbodithioates **5d**, an intermediate **149** was formed, which underwent cyclization followed by dethiomethylation leading to the corresponding 2,3-dihydro-1,3,4-thiadiazoles **151**.



Scheme 36

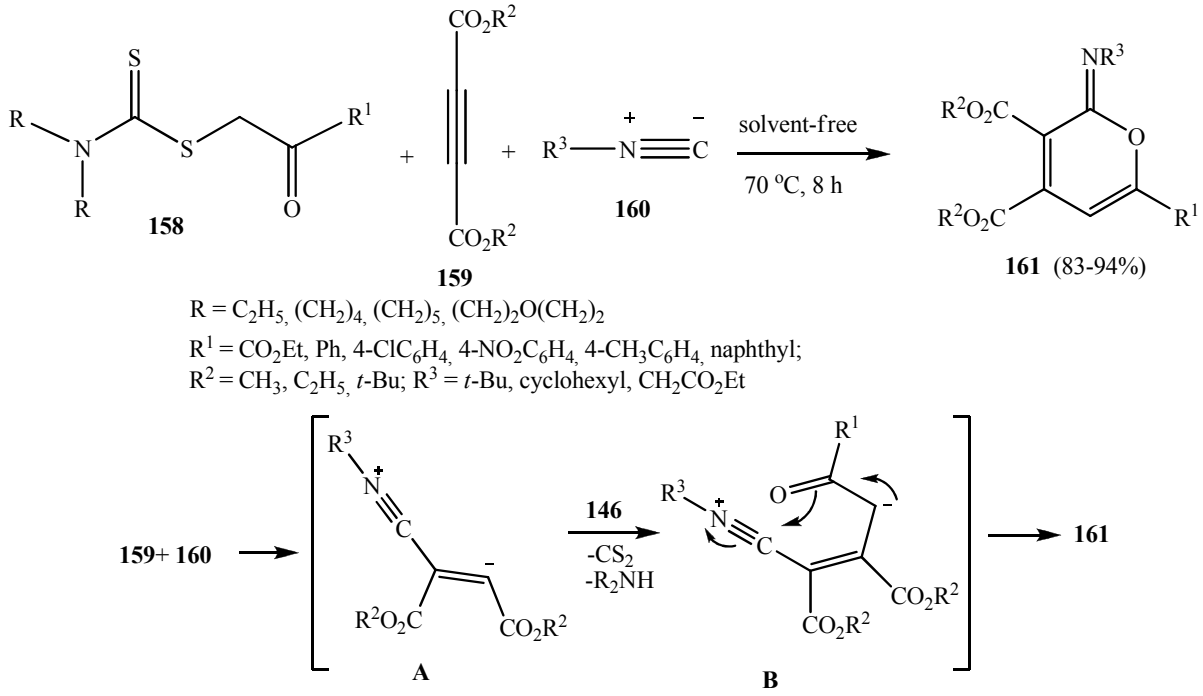
Thiophenes can be synthesized conveniently from dithiocarbamates. Scheme 37 highlights one such synthetic route to 2,3-disubstituted thiophenes **157**.[57] The reaction of 1,3-dimetallated acetylenes with dithiocarbamate **5** gives the corresponding 2,3-disubstituted thiophenes.



Scheme 37

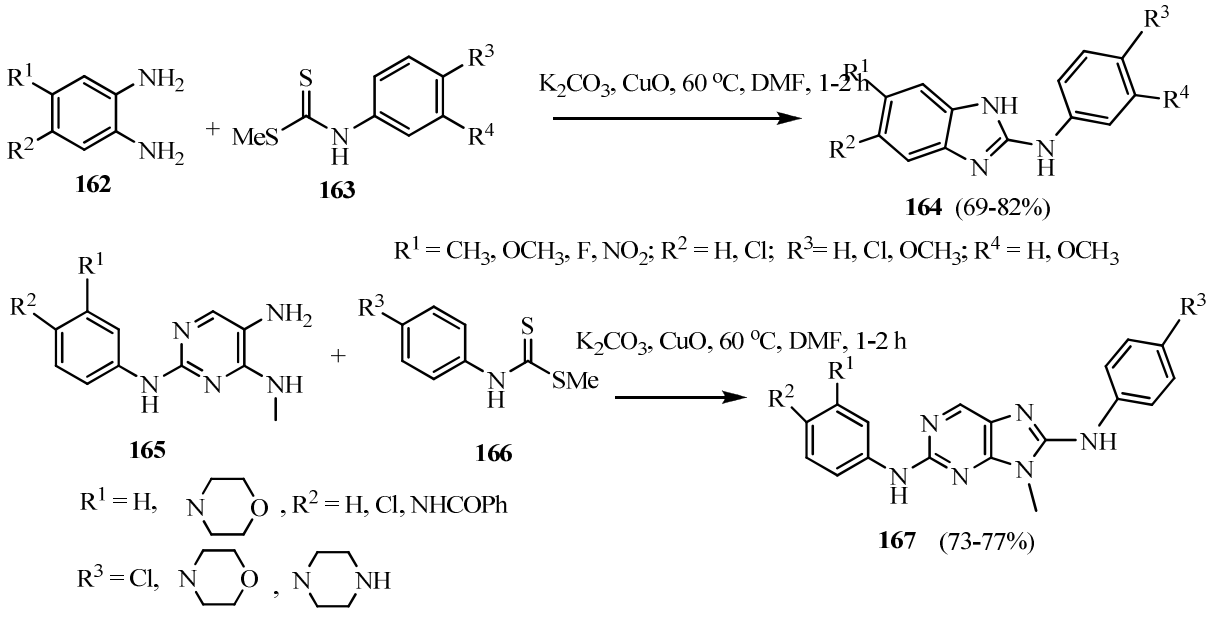
An efficient method for the synthesis of 2*H*-pyran-3,4-dicarboxylates **161** *via* the three-component reaction of dithiocarbamates, dialkyl acetylenedicarboxylates and isocyanides under solvent-free conditions has been described (Scheme 38).[58] As shown, dithiocarbamates **158**, activated acetylenes **159**, and isocyanides **160** underwent a smooth 1:1:1 addition reaction at 70 °C (the activated acetylenes and dithio-

carbamates were mixed together and then the isocyanide was added) to produce 2*H*-pyran-3,4-dicarboxylate derivatives **161** in 83–94% yields. Probably, the adduct **A** formed by the addition of **159** and **160** reacts with dithiocarbamate **158** to generate the intermediate **B**, which undergoes intramolecular cyclization to yield the product **161**.



Scheme 38

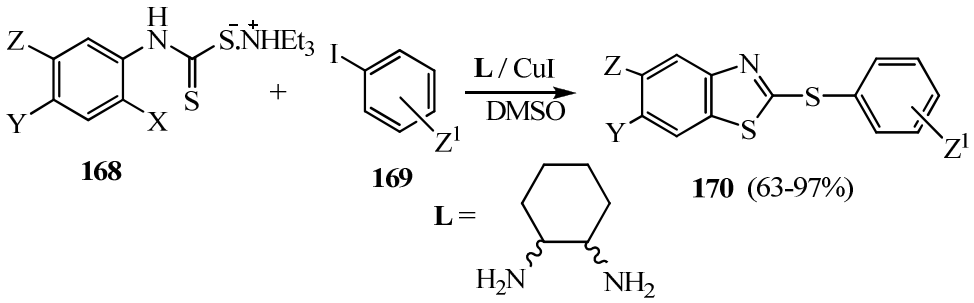
A rapid and efficient one-pot method for the synthesis of 2-(*N*-substituted) aminobenzimidazoles was reported using dithiocarbamates.[59]The reaction was promoted by the dithiocarbamate and catalytic CuO. The initial experiments were performed with commercially available *o*-phenylenediamines **162** and methyl *N*-aryldithiocarbamate **163** using CuO (0.2 equiv) and K_2CO_3 in DMF at 60 °C for 1–2 hours. The desired 2-aminobenzimidazole **164** was isolated in good yield (Scheme 39).



Scheme 39

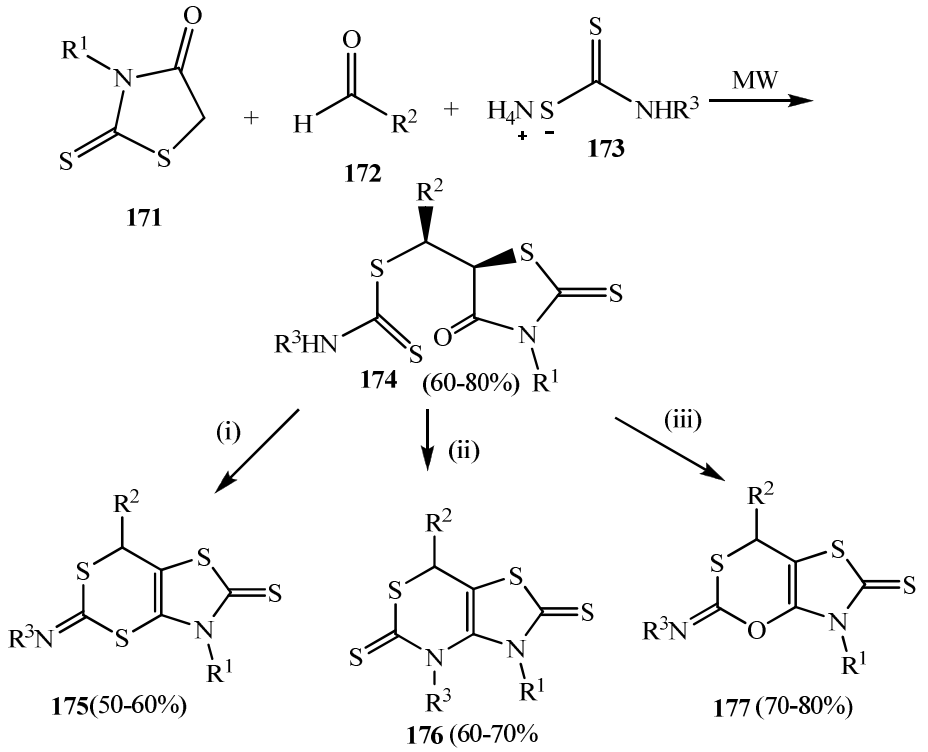
The authors also investigated this methodology with respect to different diamines **165** and dithiocarbamates **166**, and several functionalized 2-aminobenzimidazoles **167** were obtained from structurally diverse diamines.

Patel and co-workers[60] reported a facile synthesis of benzthioimidazoles **170** (Scheme 40). The method consists of ligand-assisted Cu(I)-catalyzed sequential intra- and intermolecular *S*-arylations of functionalized dithiocarbamates **168** leading to the direct synthesis of arylthiobenzothiazoles **169**, in one pot, without an inert atmosphere. Low catalyst loading, an inexpensive metal catalyst and ligand, a lower reaction temperature and shorter reaction times make this method superior to those reported for the synthesis of arylthiobenzothiazoles. The cyclohexyl-1,2-diamine ligand (**L**) (as a mixture of *cis*- and *trans*- isomers) was found to be an efficient catalyst leading to yields of 63–97% of the desired products in a short reaction time (4 h).



X = I, Br; Z = H, Me; Y = H, Me; Z^1= *p*-Me, *p*-OMe, *p*-NO_2, *p*-NHAc, *m*-Cl, *o*-COOMe

Scheme 40



(i) Montmorillonite K-10, MW; (ii) Montmorillonite, MW, Li; (iii) MW, I_2
MW = microwave irradiation
R^1= Ph, 2-$CH_3C_6H_4$; R^2 = Ph, 4-$CH_3OC_6H_4$, 4-ClC_6H_4;
R^3= Ph, 2-$CH_3C_6H_4$

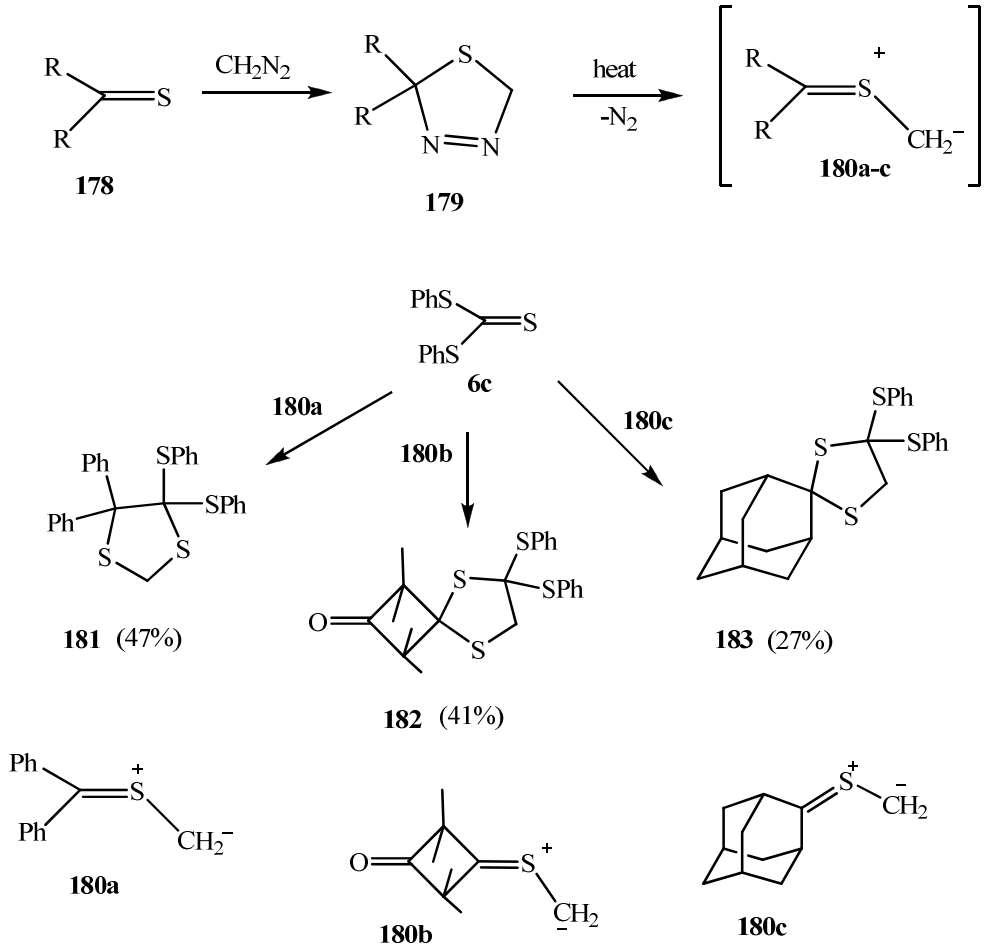
Scheme 41

Yadav *et al.*[61] have reported a solvent-free, microwave (MW)-activated, synthesis of thiazolo-1,3-dithiins **175**, -thiazines **176** and -oxathiins **177** *via* one-pot Knoevenagel and Michael reactions (Scheme 41). MW irradiation of mixtures of 3-arylrhodanines **171**, aromatic aldehydes **172** and ammonium *N*-aryldithiocarbamates **173** under solvent-free conditions, followed by heterocyclization of the resulting dithioesters **174** with Montmorillonite K-10 clay, Li-Montmorillonite or MW/iodine afforded the desired products (Scheme 41).

2.6. Reactions of trithiocarbonates

2.6.1. Cycloaddition reactions

Heimgartner *et al.* investigated the synthetic importance of C=S dipolarophiles of dithioesters in the synthesis of 1,3-dithiolanes in addition to the thiiranes mentioned earlier.[62] The thiocarbonyl *S*-methylides **180a–c**, generated *in situ* by thermal decomposition of the corresponding 2,5-dihydro-1,3,4-thiadiazoles **179**, underwent [3+2] cycloadditions with diphenyl trithiocarbonate (**6c**) to give 1,3-dithiolanes **181**, **182** and **183** (Scheme 42).[62]

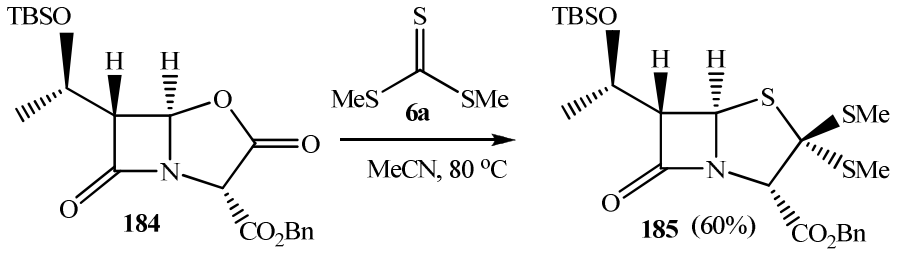


Scheme 42

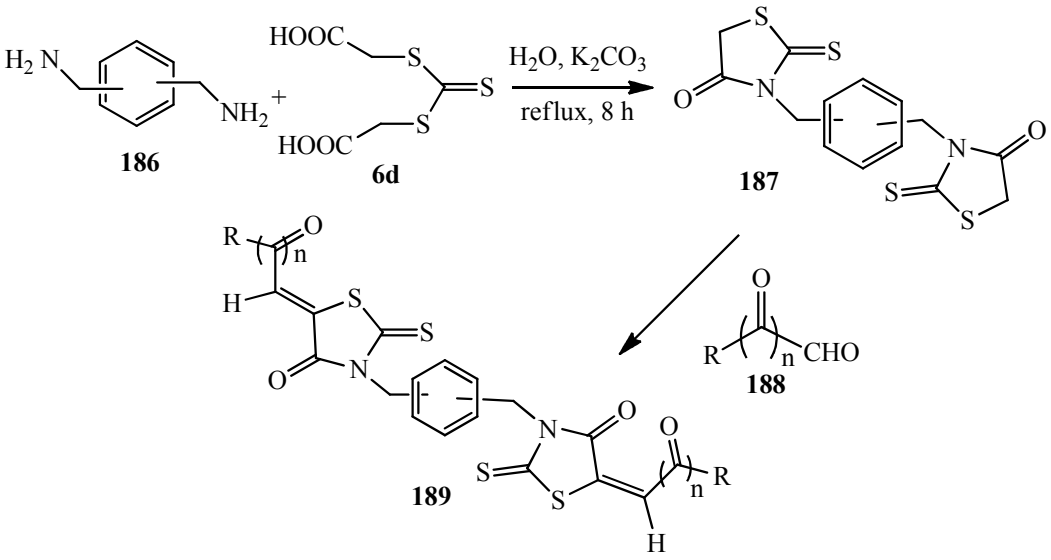
As discussed previously in the case of dithioesters (see Scheme 14), trithiocarbonates can also be employed to assemble the penam/penem skeleton in a single step. Thermolysis of **184** (MeCN, 80 °C, 80 h) in the presence of dimethyl trithiocarbonate **6a** provided the adduct **185** in 60% yield (Scheme 43).[22]

Biehl *et al.*[63] used a trithiocarbonate in a microwave-assisted synthesis of novel bis(2-thioxo-thiazolidin-4-one) derivatives as potential glycogen synthase kinase-3 (GSK-3) inhibitors.

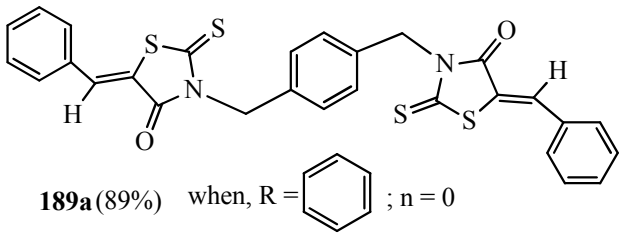
(5Z,5′Z)-3,3′-[(1,4-Phenylene-bis-(methylene)-bis-(5-arylidene-2-thioxothiazolidin-4-one)] derivatives **189** were synthesized by the Knoevenagel condensation reaction of 3,3′-[(1,4- or 1,3-phenylene bis(methylene)]bis(2-thioxo-thiazolidin-4-ones) **187** with suitably substituted aldehydes **188**, under microwave conditions in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidine (TMP) in ethanol (Scheme 44). The bis(2-thioxo-thiazolidin-4-ones) **187** were prepared from the corresponding primary alkyl amines **186** and di(carboxymethyl)trithiocarbonyl **6d**.



Scheme 43



when, R = phenyl, thienyl, furyl; n = 0, 1; yield = 79-94%
when, R = indolyl; n = 0; yield = 80-96%

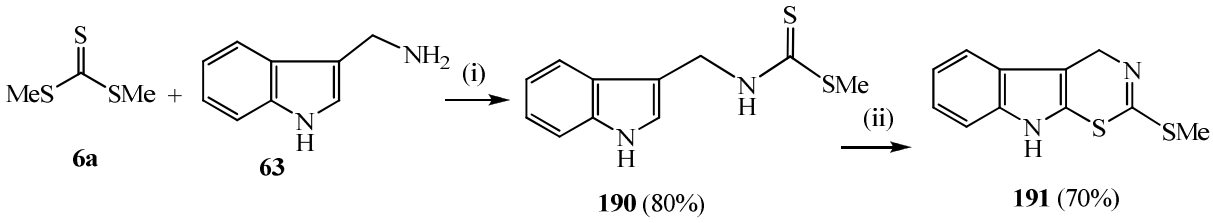


189a (89%) when, R = ; n = 0

Scheme 44

2.6.2. Synthesis of condensed heterocycles using trithiocarbonates

The importance of condensed heterocycles containing indole moieties and their syntheses using methyl dithioesters has already been highlighted in Scheme 18.[29] The same authors have extended the procedure using trithiocarbonates and, based on Hugerschoff reactions of thiobenzamides with phenyltrimethyl-ammonium tribromide, obtained condensed indole **191**. Using phenyltrimethylammonium tribromide as the bromine source, the phytoalexin cyclobrassinin **191** was prepared in a considerably higher yield than that described previously (Scheme 45).

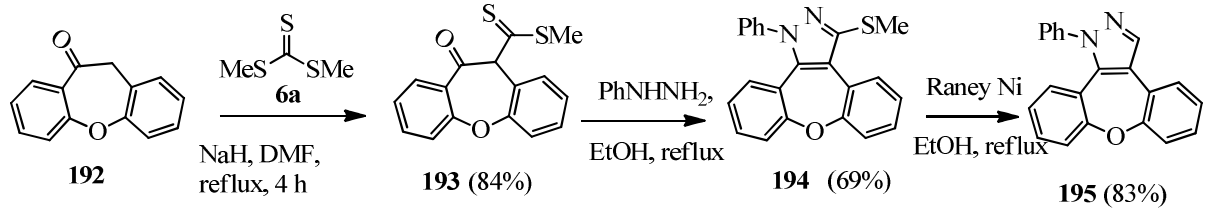


(i) CH_2Cl_2, Et_3N, 6 d

(ii) CH_2Cl_2, $PhMe_3NBr_3$, Et_3N, 5 min, 6 d

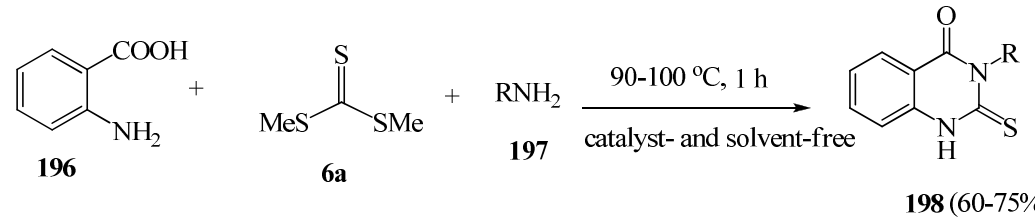
Scheme 45

Junjappa and co-workers used trithiocarbonates and dithioesters for the heteroaromatic annulation of 10,11-dihydro-11-[bis(methylthio)methylene]dibenzoxepin-10-one to access dibenzoxepino[4,5]-fused heterocycles.[64] When ketone **192** was reacted with trithiocarbonate **6a**, dithioester derivative **193** was generated, which was further utilized in cyclocondensation with phenylhydrazine to afford the corresponding regioisomeric 3-(methylthio)-1-phenyldibenzoxepin[4,5-*d*]pyrazole **194**) (Scheme 46). Dethiomethylation of **194** using Raney nickel yielded **195** in 83% yield.

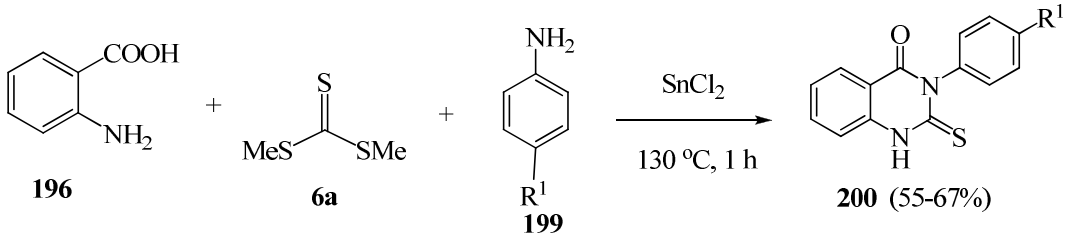


Scheme 46

Singh *et al.*[65] reported the application of dimethyltrithiocarbonate **6a** in the synthesis of 2,3-dihydro-3-alkyl/aryl-2-thioxoquinazoline-4(1*H*)-ones **198** and **200** using a one-pot multicomponent reaction. When a mixture of anthranilic acid **196**, amine **197** and dimethyl trithiocarbonate **6a** was heated at 90–100 °C under neat conditions, in the absence of any catalyst or solvent, the corresponding dihydroquinoxalines **198** were obtained in good to moderate yields.



R = CH_3, C_2H_5, C_3H_7, C_4H_7, $CH_2C_6H_5$, cyclohexyl



R^1 = H, CH_3, Cl. Br

Scheme 47

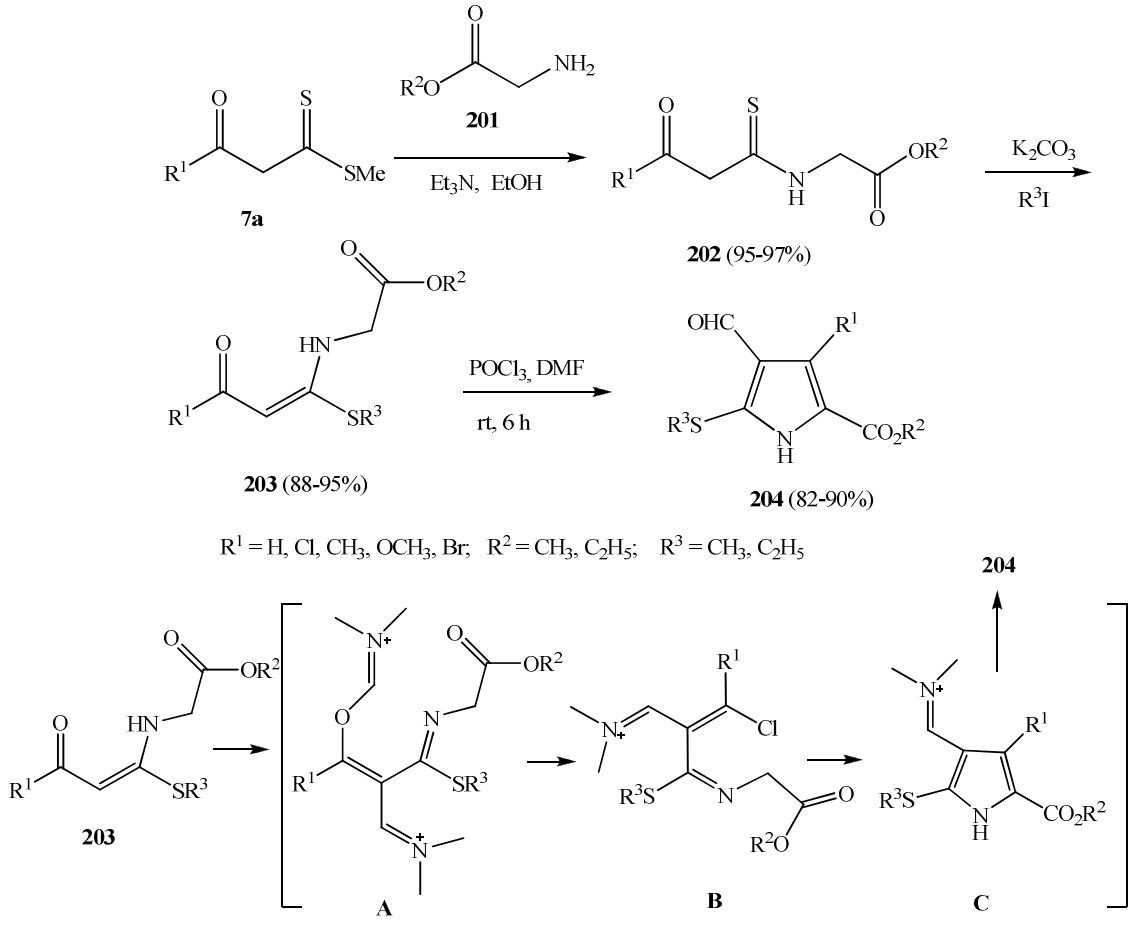
However, in the case of aromatic amines **199**, a catalyst was needed to promote the cyclocondensation. The best yields of dihydroquinazolines **200** were obtained when $SnCl_2$ (10 mol%) was used as the catalyst and the reaction mixture was heated at 130 °C (Scheme 47).

2.7. Reactions of β-oxodithioesters

β-Oxodithioesters are potential multifunctional synthons which are useful for the synthesis of heterocyclic compounds. They are also convenient precursors for the preparation of β-oxothioamides and functionalized ketene *N*,*S*-acetals.

2.7.1. Synthesis of five-membered heterocycles

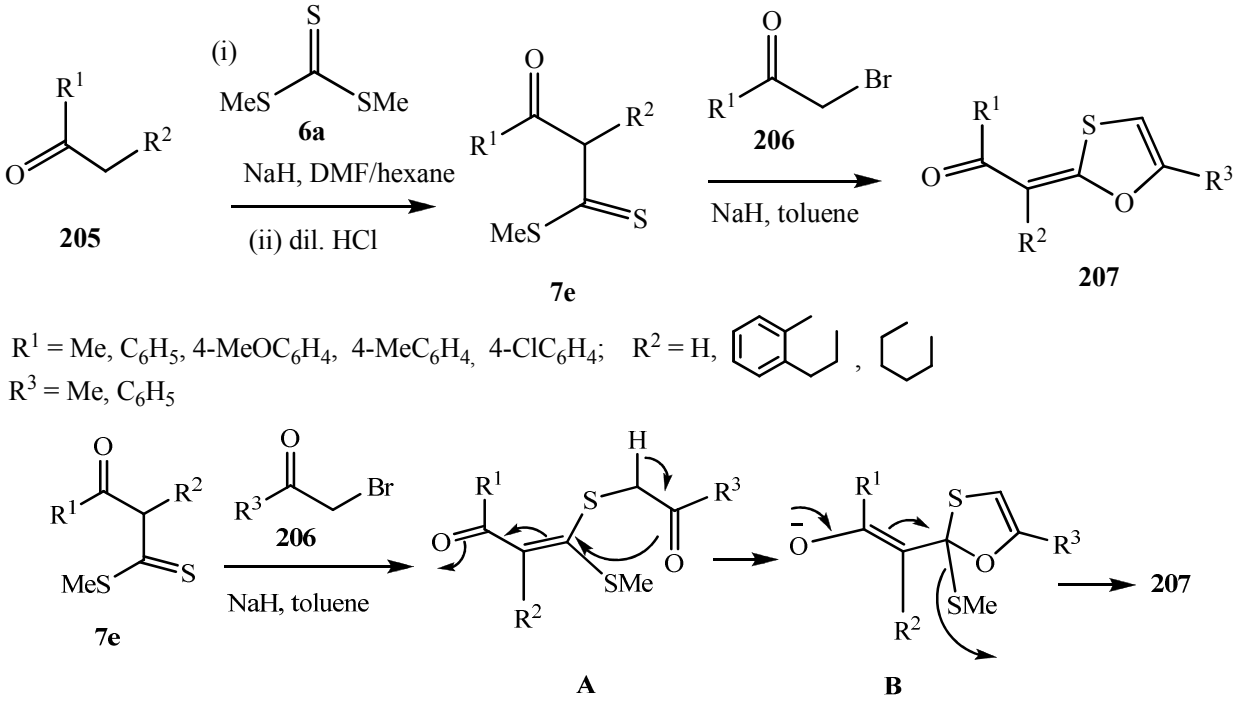
Asokan *et al.*[66] have described a regiocontrolled formation of tetra- and trisubstituted pyrroles **204** starting from readily available and inexpensive dithioesters and glycine esters. Reaction of enolizable carbonyl compounds with dimethyl trithiocarbonates in DMF using sodium hydride as the base afforded β-oxodithiocarboxylates **7a** in excellent yields within one hour at room temperature. Treatment of the dithiocarboxylates **7a** with ethyl glycinate **201**, in absolute ethanol in the presence of triethylamine at room temperature, gave thioamides **202** in nearly quantitative yields. The thioamides **202** underwent facile alkylation in the presence of potassium carbonate using an alkyl iodide in acetone to give the *N*,*S*-acetals **203** in good yields. The ketene-*N*,*S*-acetals **203** thus generated were unstable in strongly basic medium and intractable mixtures of products were formed during their attempted base-catalyzed cyclization. However, in the presence of the Vilsmeier-Haack reagent, prepared from $POCl_3$ and DMF, they underwent iminoalkylation followed by intramolecular cyclization to afford substituted pyrroles **204**.



Scheme 48

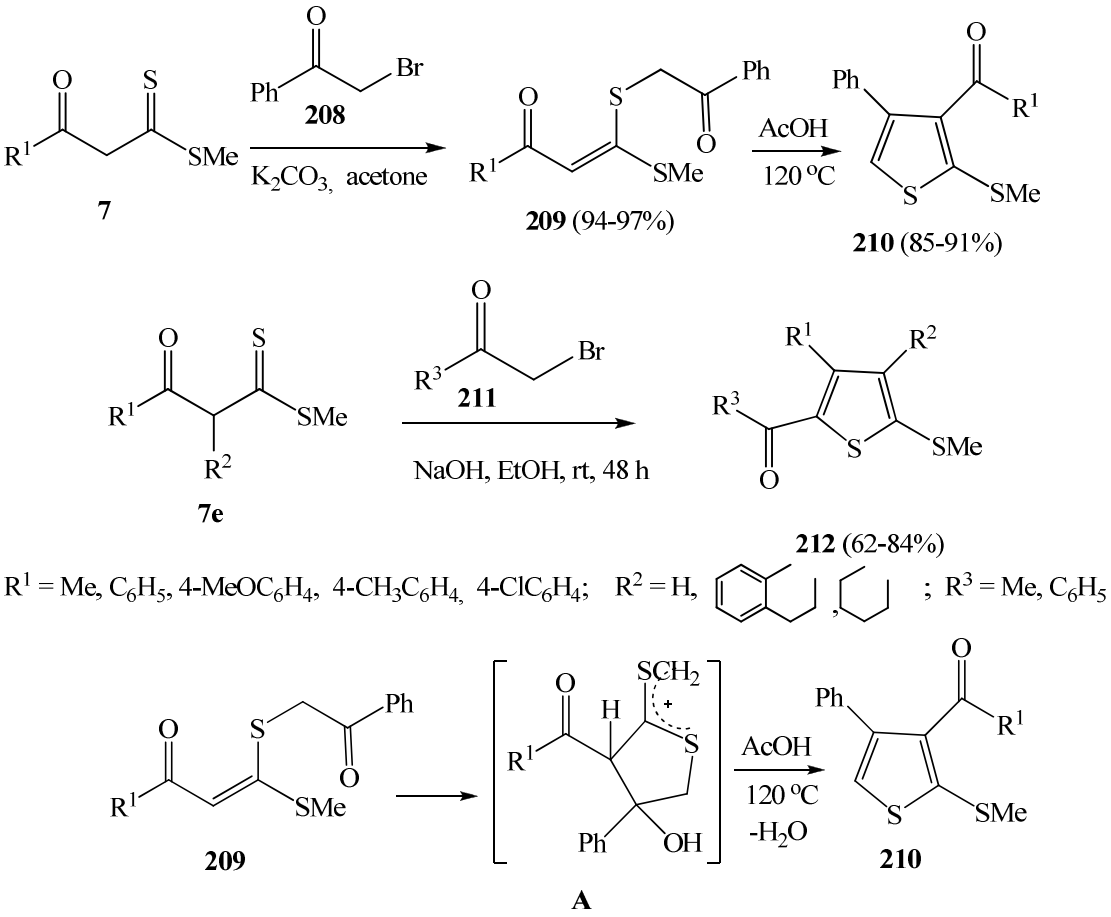
Mechanistically, the formation of pyrrole carbaldehydes **204** can be rationalized as shown in Scheme 48. Sequential iminoalkylations of the ketene-*N*,*S*-acetal moiety and the enaminoketone functionality leads to the intermediates **A** and **B**, respectively. The chlorovinyl iminium salt **B** can be obtained by displacement of the *N*,*N*-dimethyl formamide by a chloride ion originating from **A**. Cyclization of **B**, involving the imino acetate group and the chlorovinyl iminium moiety, leads to the formation of iminium salt **C**, which affords the pyrrole **204** on hydrolysis.

Dithioesters were also utilized for the synthesis of 1,3-oxathioles.[67] β-Oxodithioesters **7e**, prepared from active methylene compounds **205** and trithiocarbonate **6a**, were reacted with α-haloketones, including phenacyl bromide and bromoacetone, in the presence of sodium hydride in toluene. The reactions were monitored by TLC and were complete within 48 hours affording substituted 1,3-oxathioles **207** in good yields (Scheme 49). The formation of 2-ylidene-1,3-oxathioles occurs *via* a two-step reaction by the base-induced intramolecular heteronucleophilic addition of the enolate anion moiety. Probably, the thioacylated product **A** underwent base-induced intramolecular heteronucleophilic addition of the enolate anion to the ketenedithioacetal moiety resulting in the formation of substituted 1,3-oxathioles **207** *via* the intermediate **B** as shown in Scheme 49.



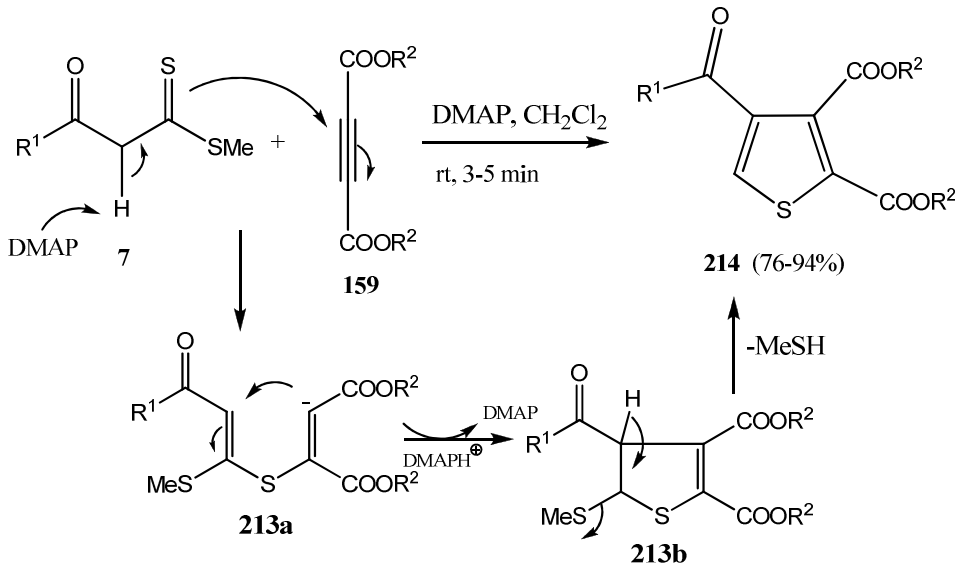
Scheme 49

Alkylations of aryl 3-oxopropanedithioates with α-haloketones yielding differently substituted thiophenes **210** and **212** have been reported by Asokan and co-workers.[68] The mechanism of the reaction is explained by a thermally induced intramolecular cyclization of the intermediate ketene dithioacetal **209**, generated from dithioester **7** and phenacyl bromide **208**. Due to the presence of vinylic alkylsulfanyl groups, the α-carbon atom of the ketene dithioacetal can act as a nucleophile under suitable reaction conditions. The addition of the ketene dithioacetal moiety to the benzoyl group under thermal conditions, followed by elimination of water from the intermediate **209** results in the formation of functionalized thiophenes **210** (Scheme 50). Similarly β-oxodithiocarboxylates of type **7e** could be converted into tetrasubstituted thiophenes **212** under milder reaction conditions.



Scheme 50

Singh and co-workers[69] reported an efficient and experimentally rapid protocol for the synthesis of 2,3-dicarboalkoxy-4-aroyl/heteroaroyl/alkanoyl thiophenes *via* heteroaromatic annulation of β-ketodithioesters **7** with dialkyl acetylenedicarboxylates **159** in dichloromethane, in the presence of 4-dimethylaminopyridine (DMAP) at room temperature.

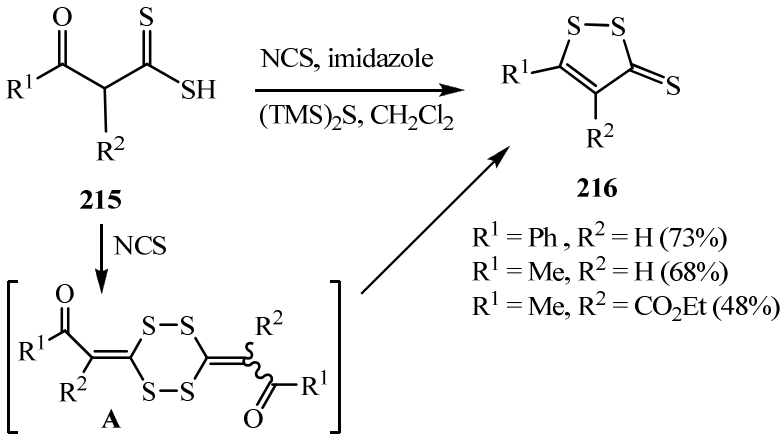


R^1 = C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 3-pyridyl, 3-(*N*-methylpyrrole), ferrocenyl; R^2 = Me, Et

Scheme 51

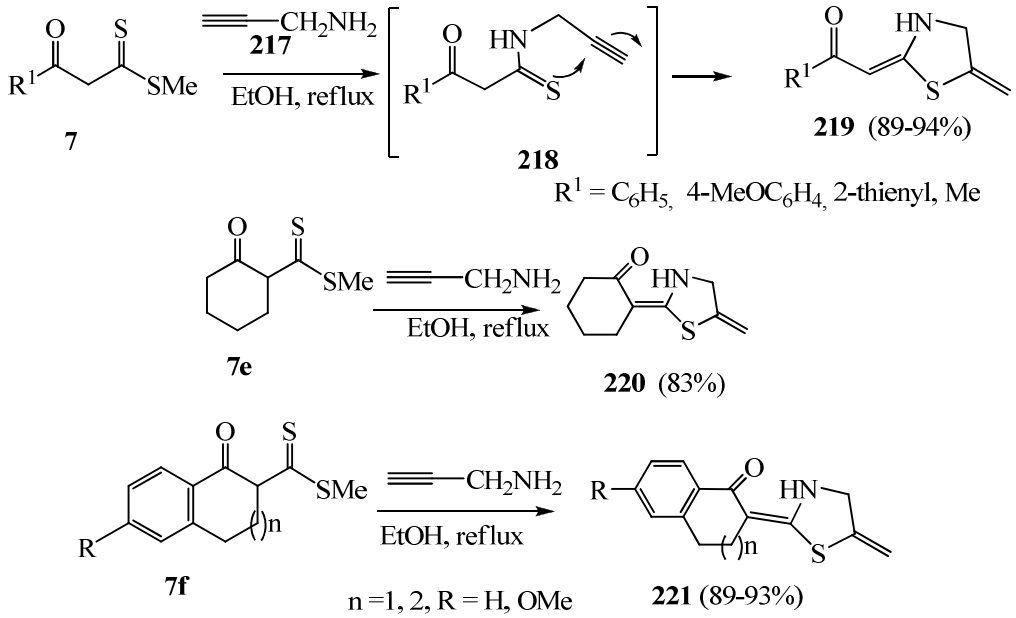
The corresponding 2,3,4-trisubstituted thiophenes **214** were obtained within 3–5 minutes in 76–94% yields (Scheme 51). The mechanism was proposed to involve abstraction of the acidic proton of β-keto-dithioester **7** by DMAP followed by nucleophilic attack on the sp-hybridized carbon of the 2,3-dimethyl acetylenedicarboxylate to generate open-chain adduct **213a**, which underwent intramolecular cyclization with extrusion of MeSH to give the thiophene derivative **214**. The intermediacy of **213a** was confirmed by its isolation and characterization when triethylamine was utilized as the base.

β-Oxodithiocarboxylates **215**, on treatment with $(TMS)_2S$ in the presence of *N*-chlorosuccinimide and imidazole leads to the formation of substituted 3-thioxo-l,2-dithioles **216** (Scheme 52).[70] The mechanism for the formation of the 1,2-dithiolanes is not very clear; however, it is believed that this reaction might proceed *via* the intermediacy of 1,2,4,5-tetrathiane **A**.



Scheme 52

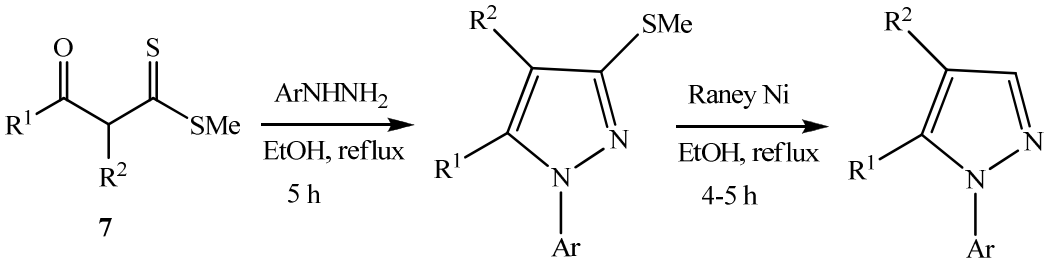
The reactions of β-oxodithioesters derived from acyclic and cyclic ketones with propargylamine **217** afford novel 2-(acylalkylidene)-5-(methylene)thiazolidines **219** in high yields, *via* intramolecular nucleophilic attack of the thiocarbonyl sulfur on the triple bond of the propargyl thioamide intermediate **218** (Scheme 53).[71]



Scheme 53

Cyclic dithioesters derived from cyclohexanone **7e** and 6-methoxytetralone **7f** were also reacted under the same reaction conditions to afford the corresponding thiazolidines **220** and **221** in good yields.

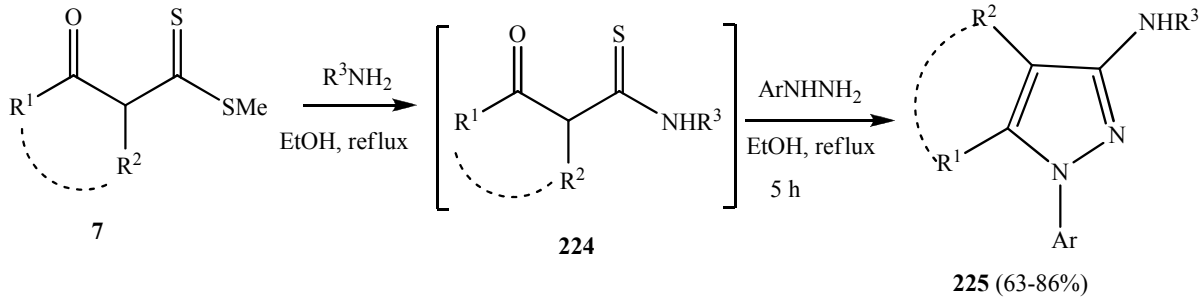
Ila, Junjappa and co-workers[72] have reported a highly efficient and regioselective synthesis of 1-aryl-3,4-substituted/annulated-5-(methylthio)pyrazoles and 1-aryl-3-(methylthio)-4,5-substituted/annulated pyrazoles *via* the cyclocondensation of arylhydrazines with β-oxodithioesters (Scheme 54). Condensation reactions of **7** with the aryl hydrazines occurred in refluxing ethanol with elimination of H_2S to afford the thiomethyl-substituted pyrazoles **222** in good yields. Raney-Ni mediated desulfurization led to 1-aryl-3,4-substituted/annulated pyrazoles **223**.



$R^1 = C_6H_5$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3-pyridyl, Me, *i*-Pr, $CH(OMe)_2$; R^2 = H, Ph;
R^1/R^2 = -$(CH_2)_4$ -; Ar = C_6H_5, 4-FC_6H_4

Scheme 54

Ila and co-workers[73] reported another efficient, highly regioselective protocol for the synthesis of amino-substituted pyrazoles. The reaction involves a one-pot, three-component cyclocondensation of β-oxo-dithioester **7**, an amine and a hydrazine in ethanol, at reflux, in the presence of a catalytic amount of acetic acid. Highly functionalized pyrazoles **225** were constructed through the cyclization of thioamide intermediate **224**, generated in situ from the β-oxodithioester (Scheme 55).



$R^1 = C_6H_5$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 3-pyridyl, Me, *i*Pr
R^2 = H, C_6H_5; R^1/R^2 = -$(CH_2)_4$ -; R^3 = *n*-C_4H_9, $C_6H_5CH_2$, 4-$CH_3C_6H_4CH_2$,
R_3 = cyclohexyl, N⟨ ⟩X where X = CH_2, O, NH, NC_6H_5, $NCO_2C_2H_5$

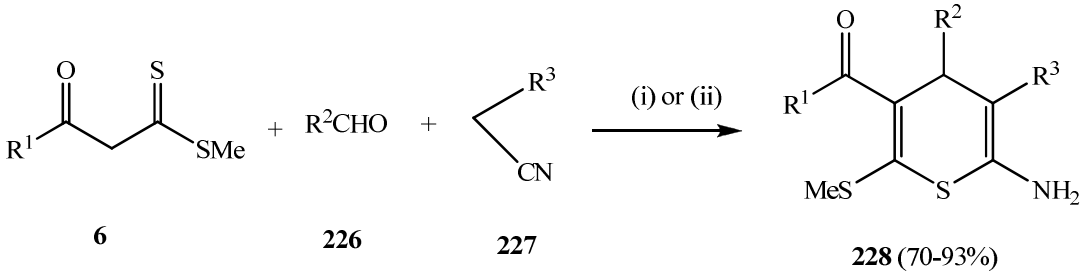
Ar = C_6H_5, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3-FC_6H_4

Scheme 55

2.7.2. Synthesis of six-membered heterocycles

Singh and co-workers[74] have reported a one-pot, three-component regioselective synthesis of highly functionalized 4*H*-thiopyrans *via* the heteroannulation of β-oxodithioesters, to afford a library of 2-amino-4-

(aryl/alkyl)-5-(aroyl/heteroaroyl)-3-(cyano/carboalkoxy)-6-methylthio-4*H*-thiopyran derivatives **228**. This one-pot, three-component domino coupling of β-oxodithioesters **7**, aldehydes **226** and malononitrile or ethyl or methyl cyanoacetate **227** was promoted by 4-dimethylaminopyridine in dichloromethane, as well as under solvent-free conditions (Scheme 56). Systematic optimization of the reaction parameters identified that the three-component coupling (3CC) protocol tolerated a wide array of functionality providing highly functionalized 4*H*-thiopyrans in excellent yields. The merit of this cascade Knoevenagel condensation/Michael addition/cyclization sequence producing three new bonds (two C–C and one C–S), in a single operation, is highlighted by the authors.

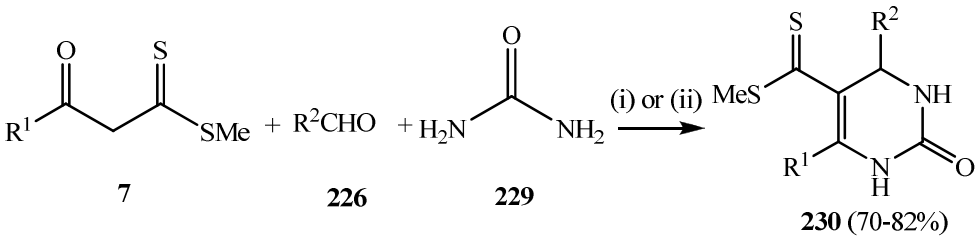


6 **226** **227** **228** (70-93%)

(i) DMAP (20 mol%), CH_2Cl_2, reflux; (ii) DMAP (20 mol%), solvent-free, 70 °C

R^1 = 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 4-binaphthyl, 1-naphthyl R^2 = C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 4-$NO_2C_6H_4$, 4-BrC_6H_4; R^3 = CN, CO_2Me, CO_2Et

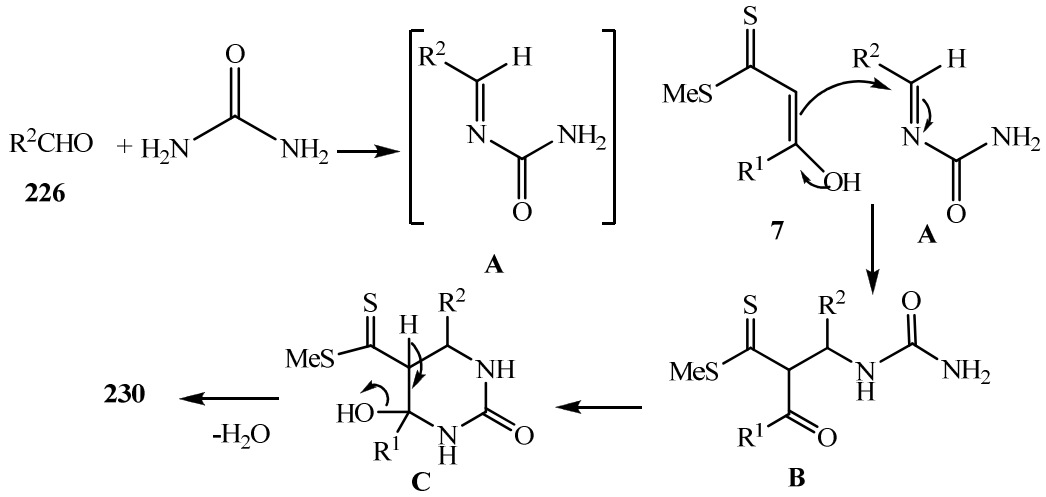
Scheme 56



7 **226** **229** **230** (70-82%)

(i) $SnCl_2$ (10 mol%), solvent-free, 100 °C; (ii) SiO_2-H_2SO_4, EtOH, 80 °C

R^1 = C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 4-binaphthyl, 1-naphthyl; R^2 =Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 4-$NO_2C_6H_4$, 4-BrC_6H_4;

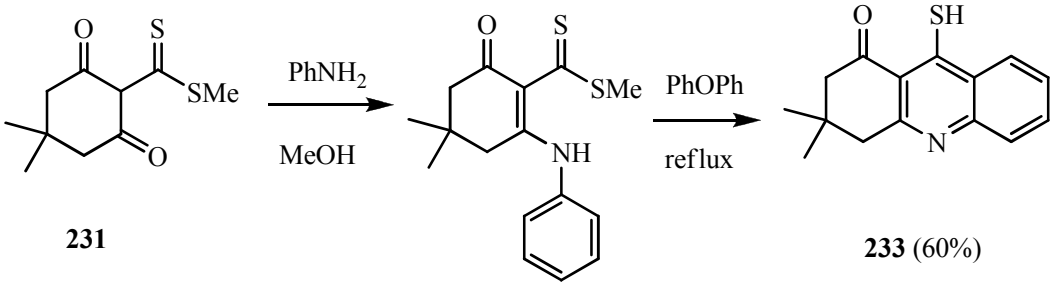


Scheme 57

Dihydropyrimidinone derivatives have attracted considerable interest because of their promising activities as calcium channel blockers, antihypertensive agents and α-1a-antagonists.[75] Moreover, several alkaloids containing the dihydropyrimidine unit have been isolated from marine sources, examples of which exhibit interesting biological properties. Singh *et al.*[76] reported a simple synthesis of dihydropyrimidines utilizing dithioesters. For the first time, β-oxodithioesters **7** have been applied in three-component Biginelli reactions under solvent-free conditions to afford novel 5-methylmercaptothiocarbonyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones **230** in excellent yields (Scheme 57). Tin-catalyzed cyclocondensation of oxodithioesters **7** with a variety of readily accessible aldehydes **226** and urea gave the corresponding dihydropyrimidinones. The yields were good to excellent when the amount of catalyst ($SnCl_2$) was 10 mol%. A plausible mechanism for this reaction is shown in Scheme 57 based on the classical Biginelli reaction. The first step is the acid-catalyzed formation of an acyl imine intermediate **A**, formed by reaction of the aldehyde **226** with urea. Interception of the imine intermediate **A** by β-oxodithioester **7** produces an open-chain ureide **B** that affords **C** on intramolecular *N*-acylation. Finally, dehydration affords the dihydropyrimidinones **230**.

2.7.3. Synthesis of condensed heterocycles

A convenient method for quinazoline synthesis was described by Tominaga *et al.*[77] starting from cyclic dithioesters. β-Phenylamino substituted α,β-unsaturated dithioester **232**, derived by selective addition of aniline to one of the carbonyl groups of methyldithiocarboxylate **231**, underwent thermal cyclization to afford **233** (Scheme 58).



231

232 (70%)

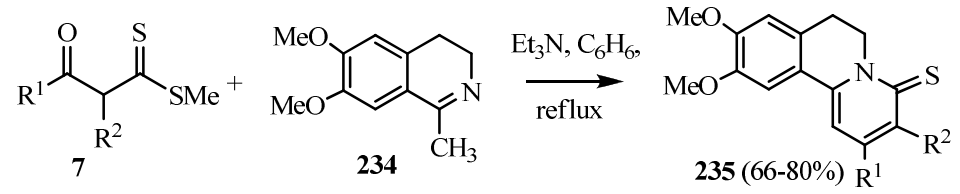
233 (60%)

Scheme 58

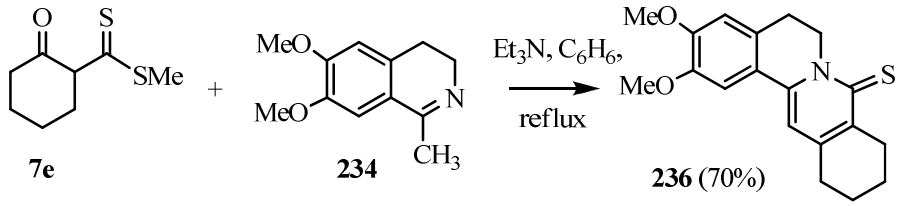
Junjappa *et al.*[78] reported an efficient and highly convergent route to 2,3-substituted and annulated benzo[*a*]quinolizine-4-thiones *via* ring annulation with β-oxodithioesters. The process involved ring annulation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **234** with a variety of readily accessible acyclic and cyclic β-oxodithioesters **7**, in the presence of triethylamine in refluxing benzene, to afford 6,7-dihydro-9,10-dimethoxy-2-methylbenzo[*a*]quinolizine-4-thiones **235** (Scheme 59). The corresponding cyclic dithioesters **7e** and **7f** also reacted smoothly with **234**, under identical conditions, to afford the corresponding 2,3-disubstituted benzo[*a*]quinolozine-4-thiones **236** and **237** in 80% and 71% yields, respectively.

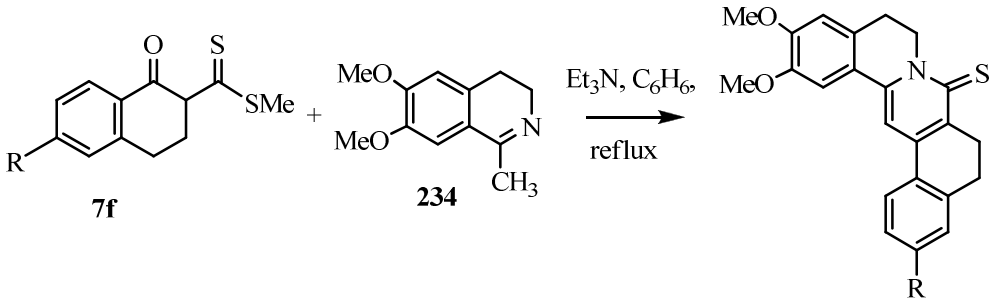
Singh and co-workers[79] reported a highly efficient, one-pot, three-component regioselective synthesis of 4-aryl-3-aroyl-2-methylsulfanyl-4,6,7,8-tetrahydrothiochromen-5-ones by annulation of β-oxodithioesters with aldehydes and cyclic 1,3-diketones under solvent-free conditions promoted by P_2O_5. No co-catalyst or activator was needed. The merit of this process is highlighted by its high efficiency producing three new bonds and a stereocentre in one operation. Thus, when β-oxodithioesters **7** were treated with aldehydes **226**

and cyclic 1,3-diketone **238** under solvent-free conditions in the presence of P_2O_5 at 100 °C, the corresponding 4-aryl-3-aroyl-2-methylsulfanyl-4,6,7,8-tetrahydrothiochromen-5-ones **239** were obtained in 70–90% yields (Scheme 60). A plausible mechanism involves initial Knoevenagel condensation between the aldehyde **226** and cyclic 1,3-diketone **238** generates adduct **A**, which acts as a Michael acceptor. The enol form of β-oxodithioester **7** attacks Knoevenagel adduct **A** in a Michael-type addition to produce open-chain intermediate **B**. This then underwent regioselective *S*-alkylation to afford the product **239**.



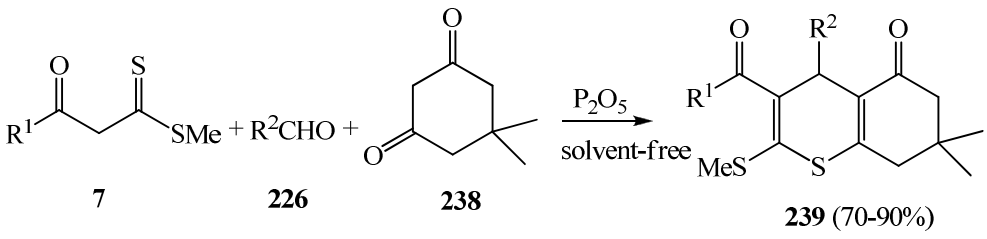
R^1 = Ph, 4-$MeOC_6H_4$, Me; R^2 = H, Me



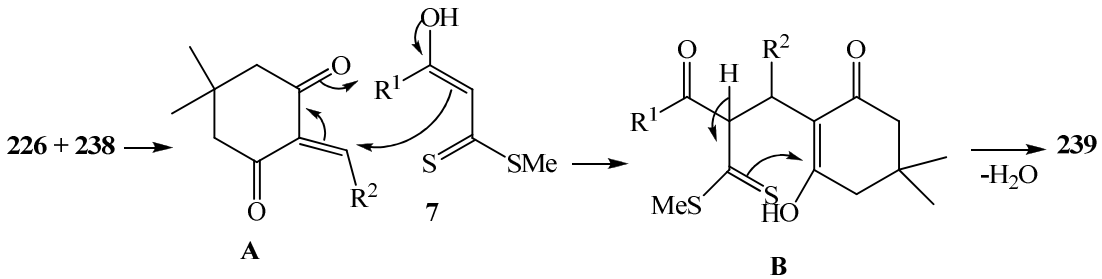


R = H, OMe **237** (54-78%)

Scheme 59

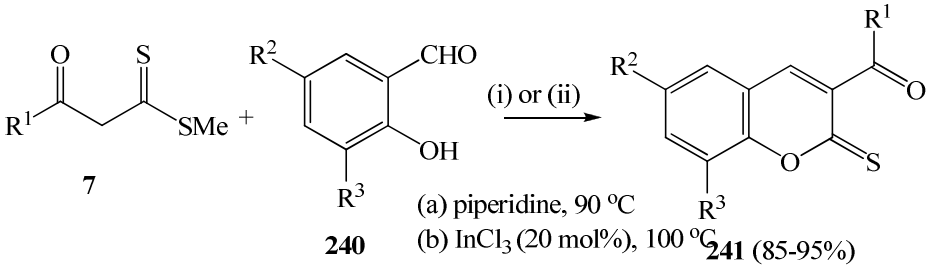


R^1 = C_6H_5, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 3-pyridyl;
R^2 =Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 4-BrC_6H_4



Scheme 60

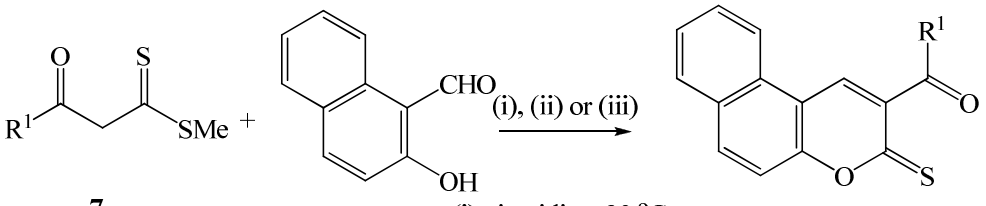
Molecules with a chromene framework are important synthetic targets in the pharmaceutical industry, displaying rich chemistry and numerous applications. They occur widely as key structural motifs in many natural products such as alkaloids, flavonoids, tocopherols and anthocyanins.[80] A facile, convenient and high yielding synthesis of a combinatorial library of 3-alkanoyl/aroyl/heteroaroyl-2*H*-chromene-2-thiones **241** has been developed *via* the condensation of easily accessible β-oxodithioesters **7** and salicyl-aldehyde/substituted 2-hydroxybenzaldehydes **240** under solvent-free conditions.[81] The reaction was performed in the presence of piperidine by heating at 90 °C for 1−2 hours. The extent of the radical scavenging ability of these compounds towards the stable free radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH) was measured; these compounds were found to scavenge DPPH free radicals efficiently. They were also able to protect curcumin from the attack of sulfur free radicals generated by radiolysis of glutathione (GSH) and exhibited excellent antioxidant activities (Scheme 61).



R^1 = Me, C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 4-pyridyl; R^2 = H, Br; R^3= H, MeO

Scheme 61

The same authors[82] extended the above work to the synthesis of 3-thioxo-3*H*-benzo[*f*]chromen-2-yl methanone under solvent-free conditions. Thus, based on the applications of cupric chloride as an efficient catalyst in various organic transformations, the facile synthesis of 3-thioxo-3*H*-benzo[*f*]chromen-2-ylmethanones **243** from 2-hydroxynaphthaldehyde **242** and β-oxodithioesters **7**, *via* domino Knoevenagel cyclocondensations under solvent-free conditions, was described. The use of $CuCl_2$ (10 mol%) and heating at 90 °C for 1−2 hours gave the desired products in 87−93% yields (Scheme 62).



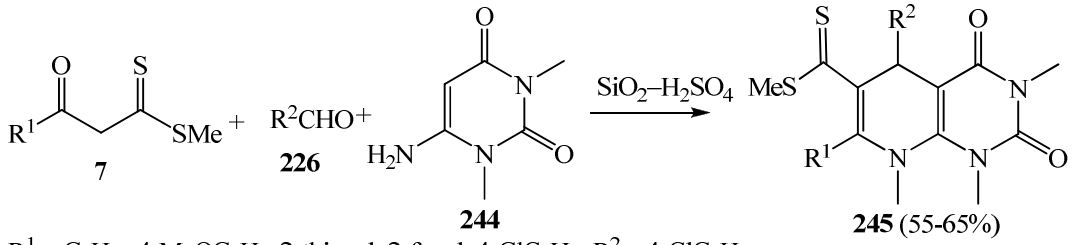
R^1 = Me, C_6H_5, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 2-thienyl

Scheme 62

On the other hand, these compounds [**241** (Scheme 61) and **243** (Scheme 62)] were synthesized in improved yields using $InCl_3$ as the catalyst.[83] The reactions of β-oxodithioesters **7** (1 mmol), aldehyde **226** (1.2 mmol), and $InCl_3$ (10 mol%) under solvent-free conditions at 100 °C afforded compounds **245** in excellent yields. Aldehydes with several nitro substituents on the aryl ring were tolerated when using $InCl_3$.

Further, these compounds were screened for biological activities such as antileishmanial activity against *Leishmania donovani.*[84] Based on docking statistics and *in vitro* analysis, these compounds were found to show high levels of antileishmanial activity together with minimal toxicity to human peripheral blood mononuclear cells.

Applications of dithioesters in multicomponent reactions were used as a central point for diversity oriented synthesis of several heterocycles using the catalyst, SiO_2-H_2SO_4. Dihydropyrimidines **230** (prepared earlier according to Scheme 57) could be synthesized in relatively higher yields using this catalyst.[85] The results were very similar with those of earlier methods, however, the new catalyst was found to tolerate more substituted benzaldehydes possessing electron-withdrawing groups such as nitro. Encouraged by the successful application of β-oxodithioesters **7** in the Biginelli reaction as described earlier, the scope of this methodology was further expanded through the synthesis of highly functionalized dihydropyrido-pyrimidinones **245** using a Hantzsch-type reaction. The synthesis commenced with commercially available 6-amino-1,3-dimethyluracil **244**, which upon treatment with β-oxodithioesters **7** and aldehydes **226**, resulted in dihydropyridopyrimidinones **245** in 55−66% yields (Scheme 63).



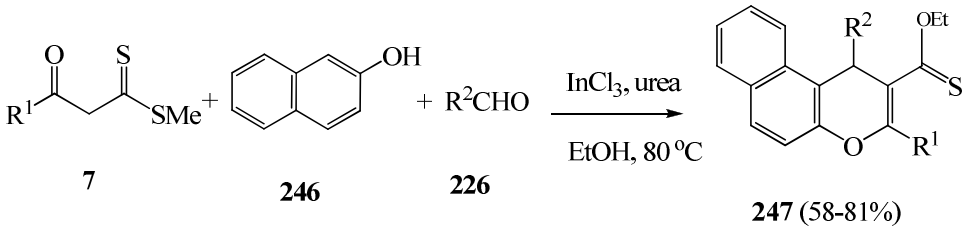
$R^1 = C_6H_5$, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 4-ClC_6H_4; $R^2 = 4$-ClC_6H_4, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 3-$NO_2C_6H_4$, 3-ClC_6H_4

Scheme 63

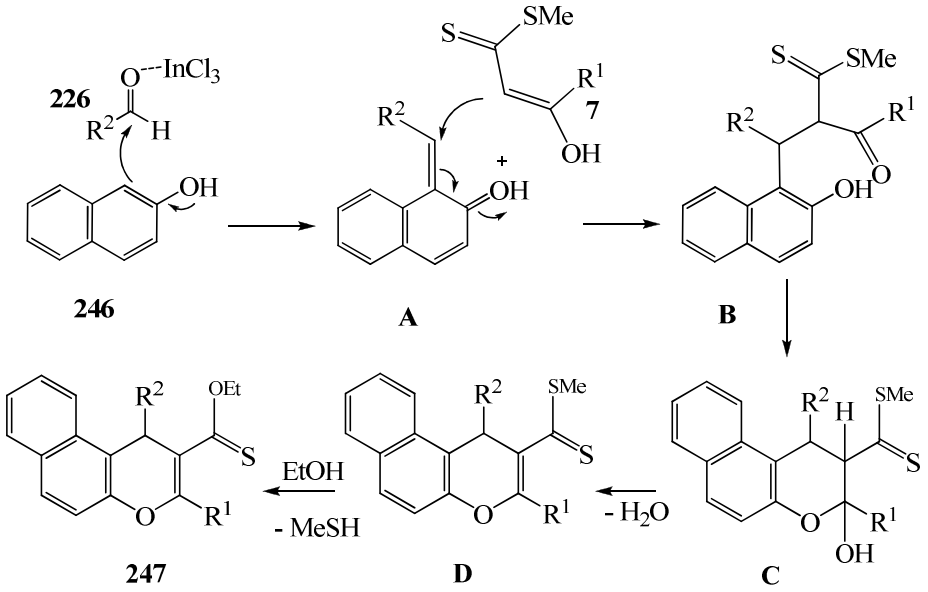
Singh *et al.*[86] reported a highly efficient regioselective protocol for the synthesis of another series of 4*H*-benzo[*f*]chromenes **247** by the one-pot, four-component coupling of aromatic aldehydes, β-naphthol, β-oxodithioesters and primary alcohols in the presence of $InCl_3$ as the catalyst. This transformation presumably proceeds *via* a domino Knoevenagel condensation/Michael addition/intramolecular cyclo-dehydration/transesterification sequence creating four new bonds and one stereocentre in a single operation. Further, the alcohol plays a dual role as a reactant as well as the reaction medium (Scheme 64). Thus β-naphthol **246**, the aromatic aldehydes **226** and β-oxodithioesters **7**, in equimolar amounts, were reacted under one-pot conditions to yield benzo[*f*]chromenes **247**.

Michael acceptor *ortho*-quinonemethide intermediate **A**, formed by nucleophilic addition of β-naphthol **246** to aldehyde **226** is proposed initially in the mechanism. The enol form of β-oxodithioester **6** attacks **A** in a Michael-type fashion to produce open-chain intermediate **B**. This undergoes regiospecific intramolecular ring cyclization *via O*-acylation, followed by dehydration to give the benzo[*f*]chromene **D**, which could not be isolated and immediately undergoes transesterification with the alcohol to give benzo[*f*]chromene **247**.

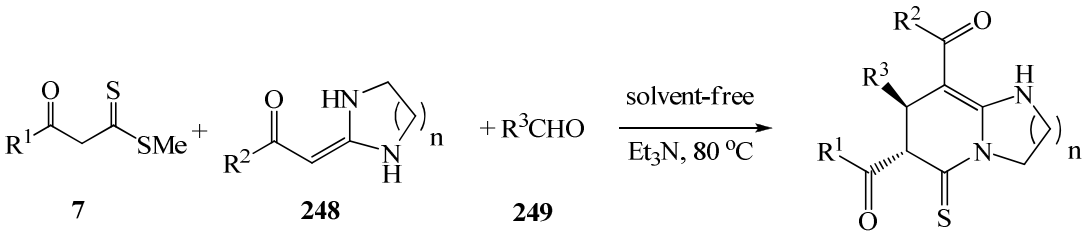
Wen *at al.*[87] employed β-oxodithioesters for the synthesis of imidazo[1,2-*a*]pyridine derivatives *via* a one-pot, three-component reaction under solvent-free conditions. The method represents a green and convenient protocol for the regioselective synthesis of imidazo[1,2-*a*]pyridines **250** *via* the tandem annulation of β-oxodithioesters **7**, heterocyclic ketene aminals (HKA) **248** and aldehydes **249** (Scheme 65).



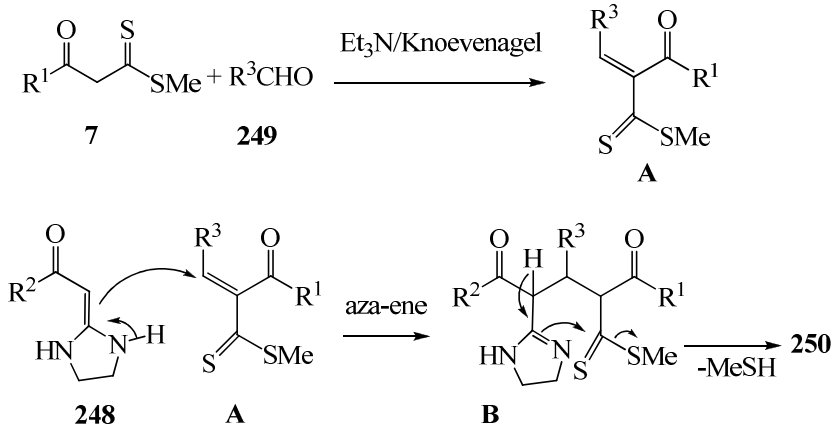
$R^1 = C_6H_5$, 4-$MeOC_6H_4$, 2-thienyl, 4-ClC_6H_4;
$R^2 = C_6H_5$, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-FC_6H_4, 2-$MeOC_6H_4$, 2-ClC_6H_4, 4-OHC_6H_4



Scheme 64



$R^1 = C_6H_5$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$;
$R^2 = C_6H_5$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4; $R^3 = C_6H_5$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-thienyl, CH_2CH_3

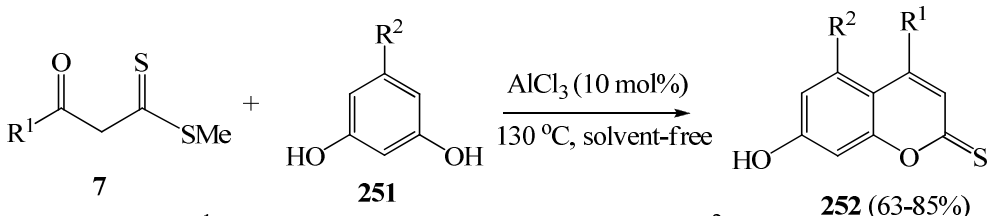


Scheme 65

The aza-ene type reaction was optimized using Et_3N (1.0 equiv) as the catalyst and heating the three components at 80 °C. The three components used have highly functionalized aryl groups and the scope of this reaction was demonstrated by the generation of a library of 27 heterocyclic compounds of type **250** in 73–91% yields.

A proposed mechanism for this novel domino reaction is outlined in Scheme 65. The Knoevenagel adduct **A**, readily prepared *in situ* from β-oxodithioester **7** and aldehyde **249** reacts with the HKA **248** to form the intermediate **B** *via* an aza-ene reaction. Next, **B** undergoes a rapid imine-enamine tautomerization, and finally, intramolecular cyclization with loss of methanethiol leads to the heterocyclic imidazo [1,2-*a*]pyridines **250**.

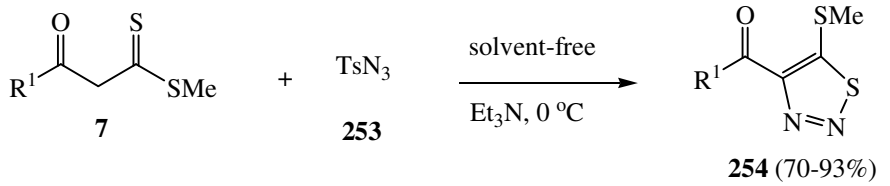
Singh *et al.*[88] have described a facile synthesis of thiocoumarins **252** *via* Pechmann condensation of phenols **251** and β-oxodithioesters **7** catalyzed by $AlCl_3$ under solvent-free conditions. This method offers wide scope for the synthesis of coumarins in good yields over short periods of time (Scheme 66).



$R^1 = C_6H_5$, 4-$MeOC_6H_4$, 2-thienyl, 4-ClC_6H_4; R^2 = H, OH

Scheme 66

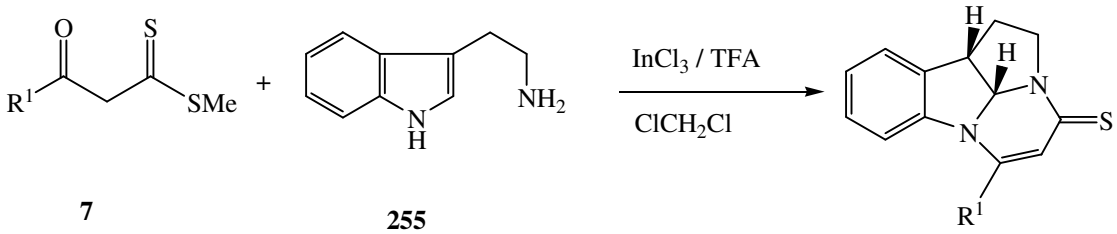
An efficient regioselective one-pot synthesis of 4-aroyl/hetaroyl/alkanoyl-5-alkyl/allyl/benzylsulfanyl-1,2,3-thiadiazoles **254** has been achieved by [3+2] cycloaddition of α-enolic dithioesters with tosyl azide through cascade 1–2 (S–N) and 3–4 (C–N) bond connections involving Wolff-type heterocyclization (Scheme 67).[89] Optimally, the reactions are very fast and completed within 2–15 minutes, when a mixture of β-oxodithioesters **7** and tosyl azide **253** was stirred at 0 °C in the presence of Et_3N under solvent-free conditions. Furthermore, no co-catalyst or activator is necessary. The eco-compatibility, mild conditions, excellent yields, easy purification and avoidance of expensive/toxic reagents are advantages of this protocol to access this medicinally privileged substructure.



R^1 = CH_3, C_6H_5, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 2-ClC_6H_4, 3, 4 - $(CH_2O)_2C_6H_3$, 4-biphenyl, 1-naphthyl, 2-*N*-methylpyrryl, 2-furyl, 2-thienyl, 3-pyridyl.

Scheme 67

Finally and very recently, Singh *et al.*[90] reported a cycloannulation of β-oxodithioesters and tryptamine in dichloromethane in the presence of catalytic amount of $InCl_2$ and TFA gave the novel 5-aryl/heteroaryl 2a[1],9b-dihydro-1*H*-2a,5a-diaza-cyclopenta[*jk*]fluorene-3(2*H*)-thiones in moderate to good yields. The reaction was proposed to involve a tandem transformation of thioamide, protonation and dehydrative cyclization. $KMnO_4$-oxidation of these newly prepared compounds yielded oxidative-desulfurization products in good yields (Scheme 68).



7 **255** **256** (75-92%)

R^1 = C_6H_5, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 2-FC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 1-naphthyl, 2-naphthyl, 2-pyrryl, 2-furyl, 2-thienyl, 3-pyridyl

Scheme 68

3. Conclusion

This review on the applications of dithiocarboxylates in the synthesis of diverse heterocycles has revealed that these compounds can play many roles including as dipolarophiles and one carbon, two atom or three carbon electrophiles, thus making them versatile intermediates in many cyclization processes. The dithioesters act as building blocks for a wide range of heterocycles starting from small three-membered rings to medium-sized and various condensed and fused heterocyclic systems. The reactions of dithioesters in heterocyclic syntheses include cycloadditions, addition-eliminations, intramolecular ring cyclizations, cyclocondensation reactions with various nucleophiles and multicomponent reactions (MCR) generating libraries of bioactive heterocycles. These substrates can be prepared easily from readily available starting compounds and their applications in the synthesis of bioactive heterocycles require further detailed exploration.

Acknowledgments

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METAL-CATALYZED INTRAMOLECULAR HYDROAMINATIONS OF UNSATURATED AMINES WITH TERMINAL DOUBLE BOND – PART 2[#]

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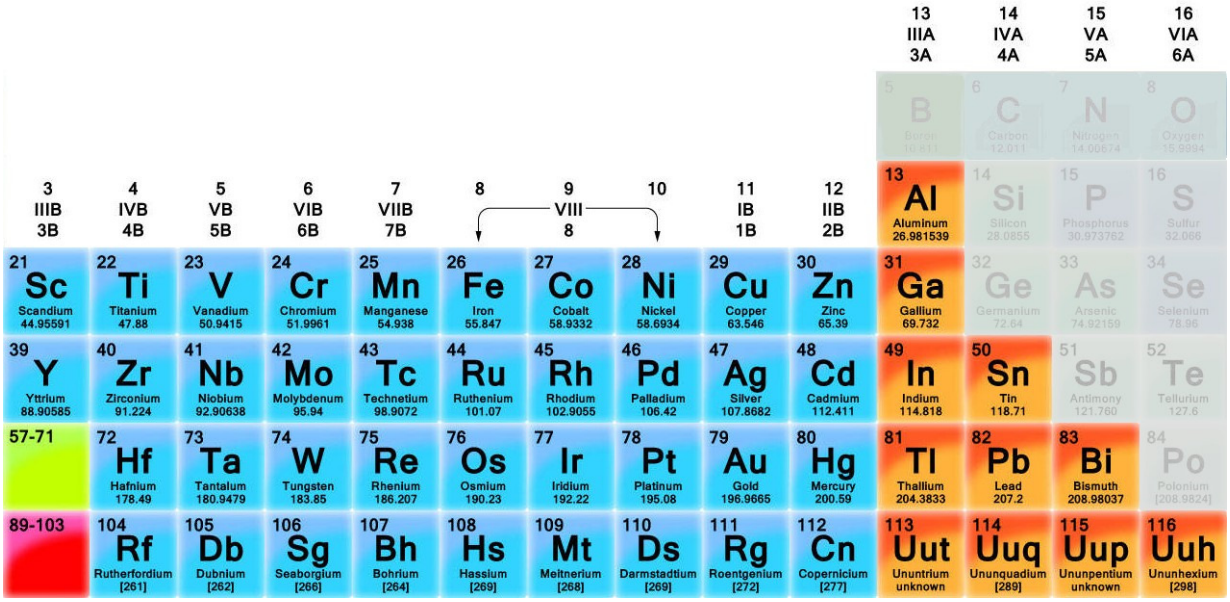
Abstract. *The two-part critical review deals with the metal-catalyzed intramolecular hydroaminations of alkenyl amines having terminal double bond. Following the first part, this second one summarizes the employment of known hydroamination catalysts based on various transition metals in the direct preparation of pyrrolidines and piperidines. The focus is given to the efficiency and stereoselectivity of respective aminocyclizations. The plausible mechanistic proposals of metal catalysis are presented. The last section highlights the use of Brønsted acids as hydroamination catalysts. The review covers the respective literature published until October 2012.*

Contents

1. Transition metals



[#] Part 1: Mathia, F.; Zálupský, P.; Szolcsányi, P. In *Targets in Heterocyclic Systems*; Attanasi, O. A.; Spinelli, D., Eds., 2011; Vol. 15, pp. 226–262.

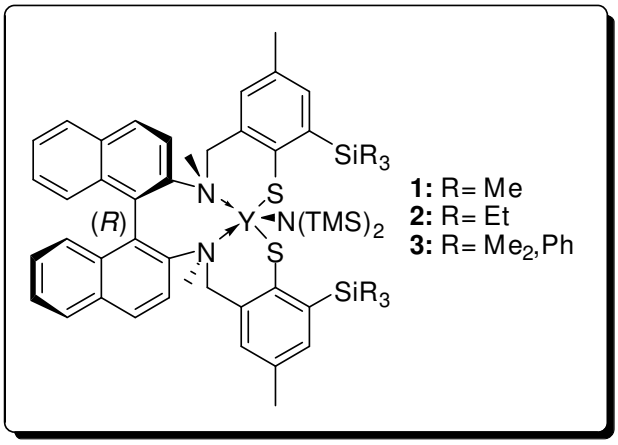
1.1. Synthesis of pyrrolidines

Elements in groups *p* and *d* can be subdivided into four categories:

- Early transition metals (Elements of group IIIB)
- Metallocenes (Elements of group IVB)
- Late transition metals (Elements of groups VB–IIB)
- Post transition metals (Elements of group IIIA and VA)

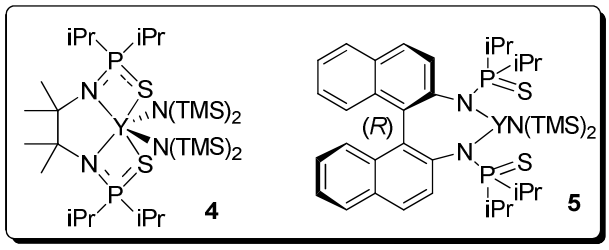
Early transition metals – scandium and yttrium – *elements of the IIIB group*, show, as do La and Ac, chemical behaviour similar to that of elements that follow them, *i.e.* lanthanides and actinides. Out this group, yttrium, which has been often used as central metal in complexes catalyzing hydroaminations, resembles most the above-mentioned lanthanides and actinides. Catalysts on the basis of Y represent highly oxophilic complexes capable of catalyzing only hydroamination of simple aminoalkenes and only rarely tolerating oxygenated solvents. Y^{3+} catalysts are usually derivatives of lanthanide catalysts, the most common being ytriocenes,[1–7] Y-amides,[8–22] Y-thiophosphidamidates,[23] Y-thiolates,[24] and Y-oxides.[25,26]

Ytrium-thiolates (Scheme 1) belong to medium activity pre-catalysts of hydroamination of aminoalkenes. They give by a wide margin the best *ee* values of all yttrium-based catalysts, transforming *N*-unsubstituted aminoalkenes to cyclic amines faster and with better enantioselectivity than the *N*-methylated analogues (Table 1, entries 1–3 *vs*. 16–18). The obvious positive steric influence of the silyl functional group on the final *ee* allows merely by exchanging one methyl group for a phenyl to increase enantioselectivity from *ee* 69% to 81% (Table 1, entries 1 *vs.* 3). Contrary to what has been observed so far, the introduction of a Thorpe-Ingold activation segment into the molecule led to lower reaction rates. On the other hand, caused probably by higher steric interactions between the substrate and bulky catalyst, enantiomeric excess improved by about 10% (Table 1, entries 1–3 *vs.* 51–53).

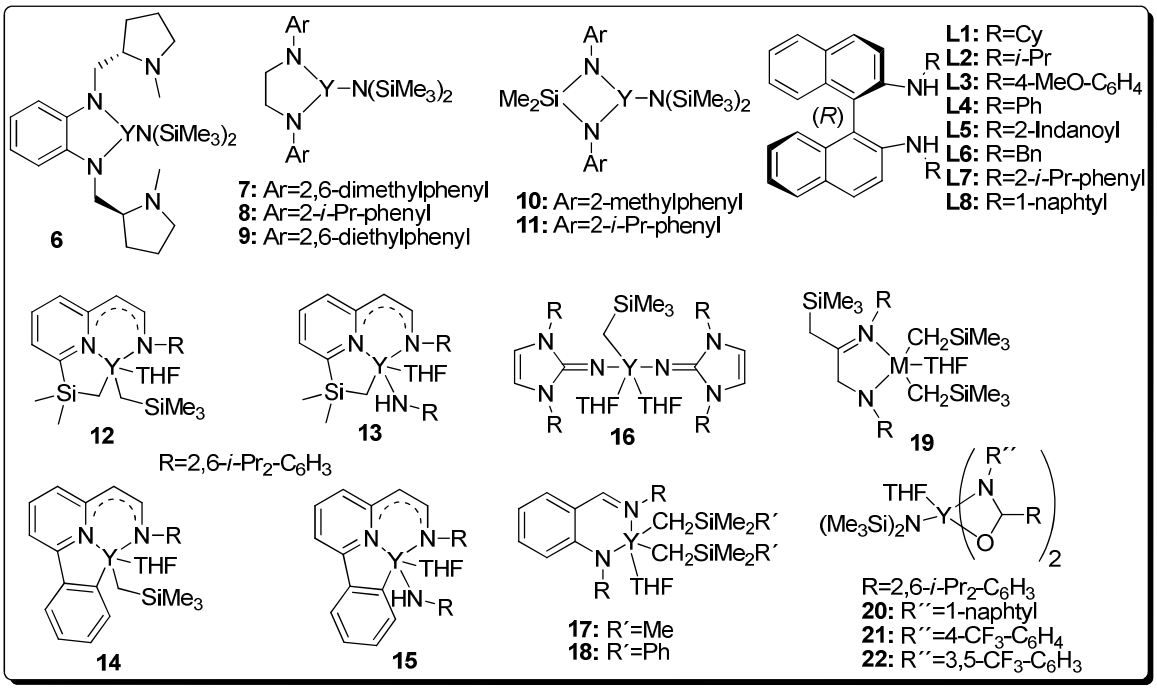


Scheme 1

Both yttrium-thiophosphoimidates (Scheme 2) and Y-amides (Scheme 3) belong to active catalytic complexes with activity similar to that of T-thiolates. These pre-catalysts achieve average *ee* values of 56–76%. In hydroaminations of secondary aminoalkenes, yttrium^{3+} amides **7–11** afford disubstituted pyrrolidines in diasteromeric ratios of up to 1:23 (Table 1, entries 52–440). The employment of sub-stoichometric amount of *O*-bridged ligands moderately increases the activity and diastereoselectivity of Y(III)-amides. However, this is applies only for secondary alkenyl amines, while the hydroamination´s rate enhancement was not observed in the case of their primary counterparts.

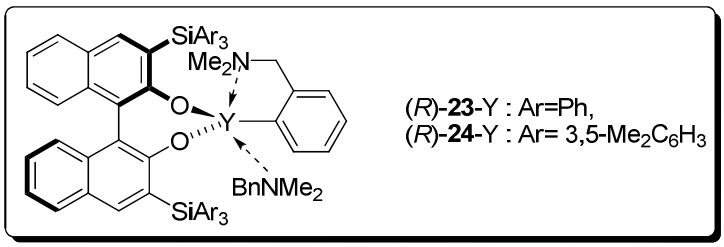


Scheme 2

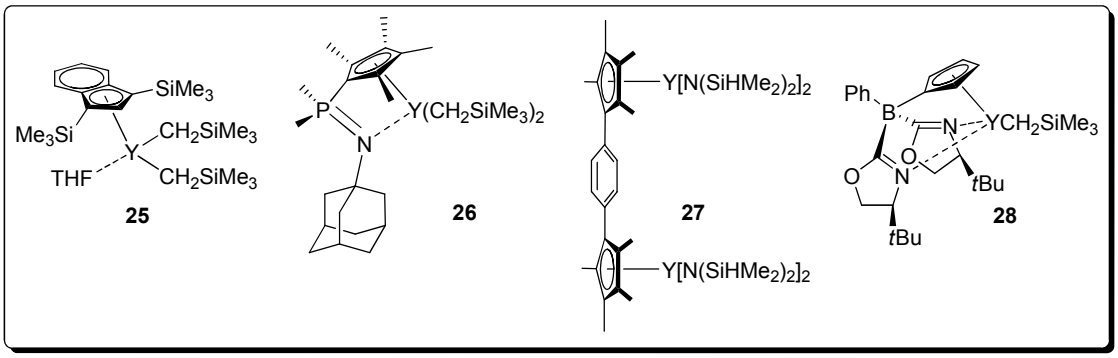


Scheme 3

Yttrium-oxides give *ee* values second only to Y-thiolates (Scheme 4). Their steric demands match those of thio-complexes. Introduction of *gem*-dimethyl group into the substrate reduces the reaction time by an order of magnitude, although at the cost of halving the *ee* (Table 1, entries 5 and 6 *vs.* 102 and 103).



Scheme 4

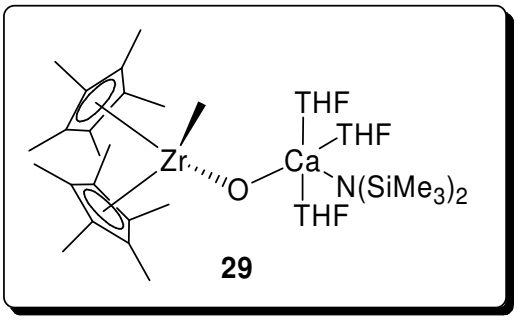


Scheme 5

Ytriocenes as catalysts are inferior to lanthanocenes, being less active, much less selective, with *ee* values reaching 11–94% (Table 1, entries 9, 10, 115, 116, 119, 462–463) (Scheme 5).

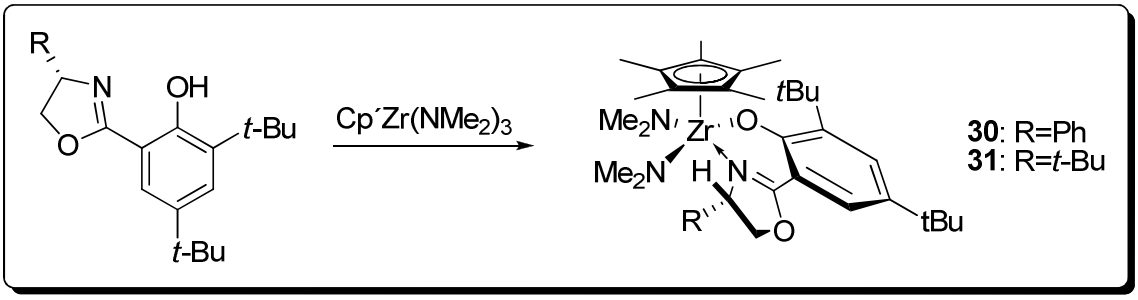
Elements of the IVB group – Ti, Zr, Hf – differ in their properties markedly from the rest of *d*-elements and form a group of their own. Structurally, they are catalysts based on them similar to complexes of the IIIB group, lanthanides and actinides. The main differences lie in the mechanism of hydroamination and the resulting limitations for their use in synthesis. Just like the above-mentioned complexes they are highly oxophilic, so that they have not been used in hydroaminations in oxygenated solvents. The most common are titanocenes, zirconocenes and hafniocenes, CGC-catalysts, -amides, -amidates, -thiophosphidamidates and oxides.

Metallocenes with central metal from the IVB group[25,27–34] represent complexes with poor activity. In order to achieve effective transformation of aminoalkenes to cyclic amines, they require high reaction temperatures (~105 °C) and reactions times of up to tens of hours.As if these limitations were not enough, they can be used only for substrates with the Thorpe-Ingold activation effect, as there has been no recorded successful hydroamination of unsubstituted aminoalkene yet. However, the employment of bimetallic catalytic complex **29** with an equimolar amount of additive $[PhNMe_2H][B(C_6F_5)_4]$ allows the cyclization of secondary amines (Scheme 6). An interesting feature is also formation of the opposite enantiomer simply by replacing yttrium for zirconium as a central metal of the catalytic complex (Table 1, entries 349 and 350).



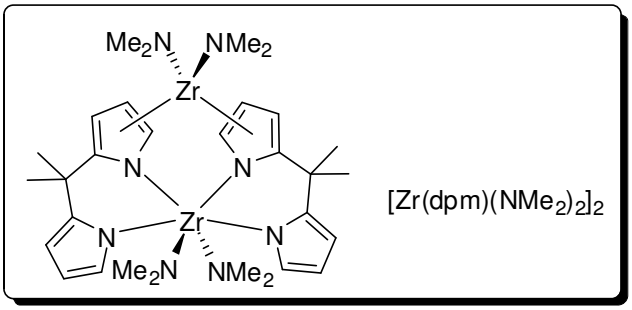
Scheme 6

The so-called "half-sandwich" zirconium^{3+} catalysts[36] were prepared by ligand exchange of one $-NMe_2$ group of the $Cp'Zr(NMe_2)_3$ complex by a chiral ligand (Scheme 7). They are rated as medium active catalysts, at 110 °C they cyclize 2,2-dimethylpent-4-en-1-amine to the 2,4,4-trimethylpyrrolidine within several tens of minutes, with enantioselectivity on the order of 51% and 70% *ee*, respectively (Table 1, entries 109 and 110).



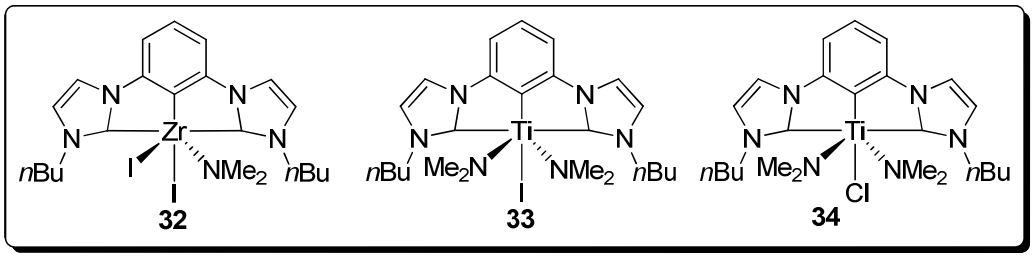
Scheme 7

Zirconium^{3+} CGC-catalyst[37] (Scheme 8) has activity similar to that of catalysts **30** and **31**. Hydroamination of substrates activated by the Thorpe-Ingold effect proceeds relatively fast, total conversion or yields over 86% can be achieved within hours at 100 °C. Transformation of the substrate with a single activation substituent on the chain (Table 1, entry 41) requires for its 57% yield elevated reaction temperature and a significantly extended reaction time. A substrate totally lacking activation could not be cyclized with this complex.

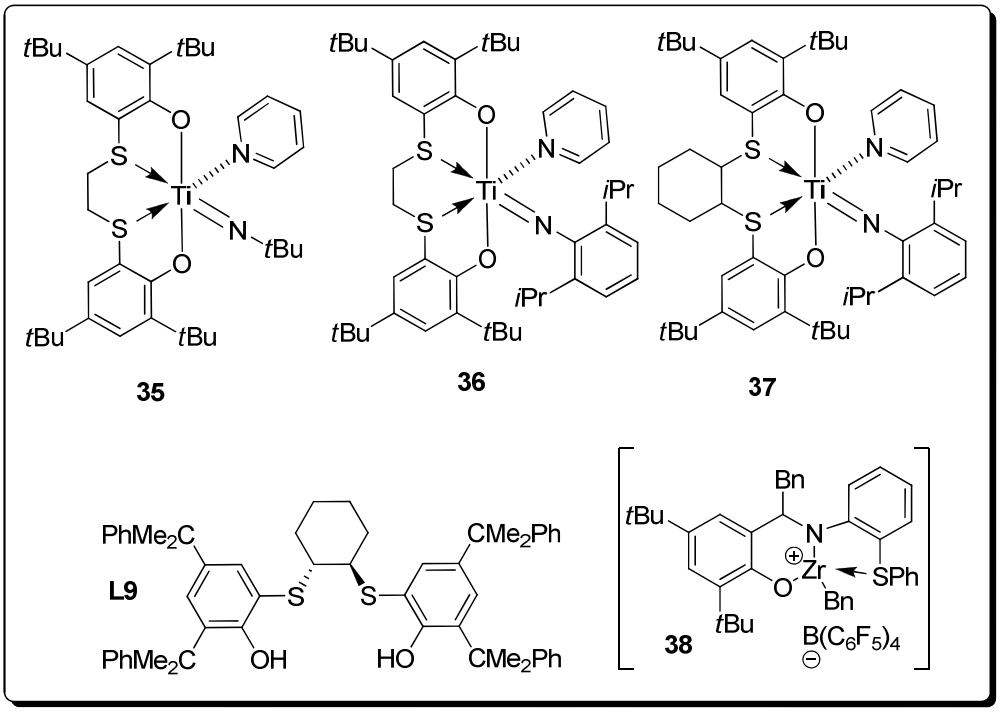


Scheme 8

Zr-*pincer*-complex[36,38] **32** (Scheme 9) requires for achieving acceptable reaction rates of cyclization of sterically activated aminoalkenes temperature of up to 160 °C, in the absence of activation even such conditions are insufficient (Table 1, entry 11).



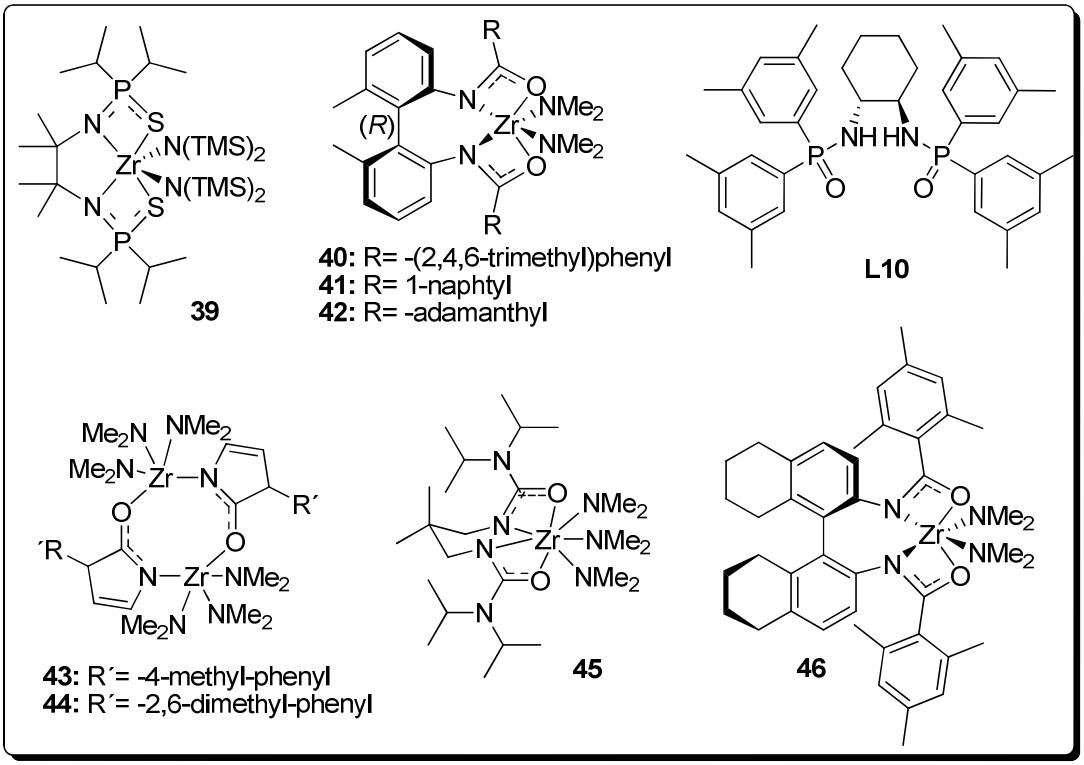
Scheme 9



Scheme 10

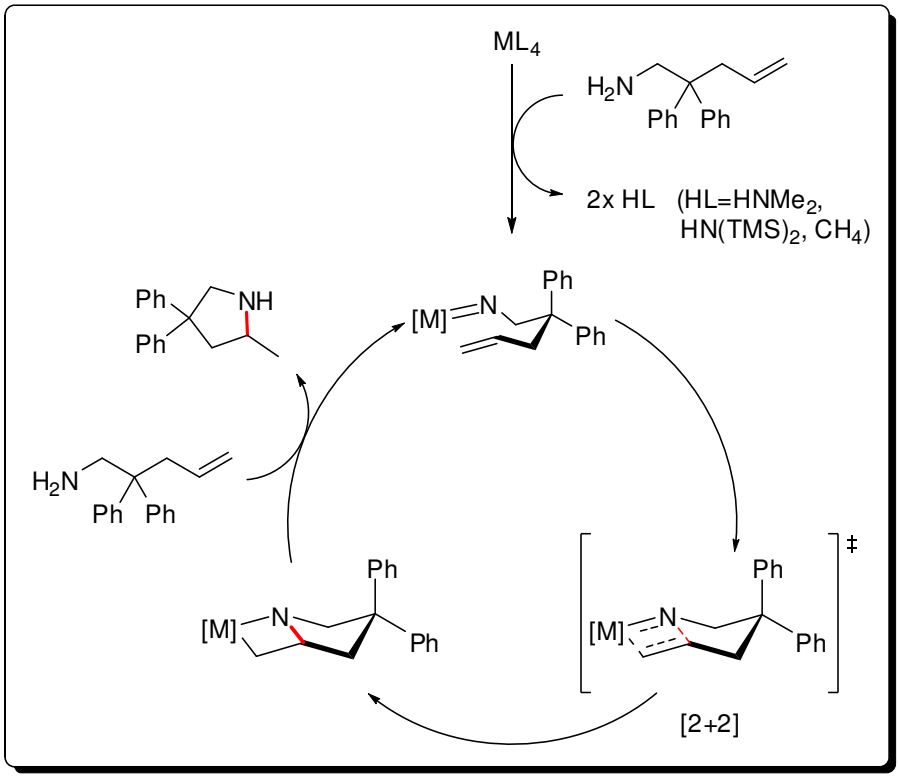
First viable representative of titanium and zirconium oxides[39] has been the catalyst generated *in situ* from the ligand **L9** and metal amide $M(NMe_2)_4$ (Scheme 10). It is capable of converting *gem*-diphenyl activated aminoalkene to a corresponding cyclic amine in very good yield (Table 1, entries 185 and 186). The employment of complexes **35–37** do not represent any improvement in either higher yields or faster reaction.[40] On the other hand, significantly more active cationic Zr-komplex **38** is capable to shorten the reaction time down to 3 hours at 100 °C.[41]

Amides,[42–46] amidates,[47–55] phosphidoamidates,[56] thiophosphoamidates,[57a,23] sulfamides[58,59] and halides of group IVB metals represent the last group of pre-catalysts among these metals (Scheme 11). Generally, they belong to medium to little active catalysts. Catalysis by these metals proceeds usually at temperatures of 70–160 °C, with reaction times on the order of hours or tens of hours. Amidates **40–42**, **46** and the phosphoimidates, prepared *in situ* by the reaction of **L10** with $Zr(NMe_2)_4$, furnish the best enantioselectivities, with *ee* of up to 93% (Table 1, entries 96 and 97).



Scheme 11

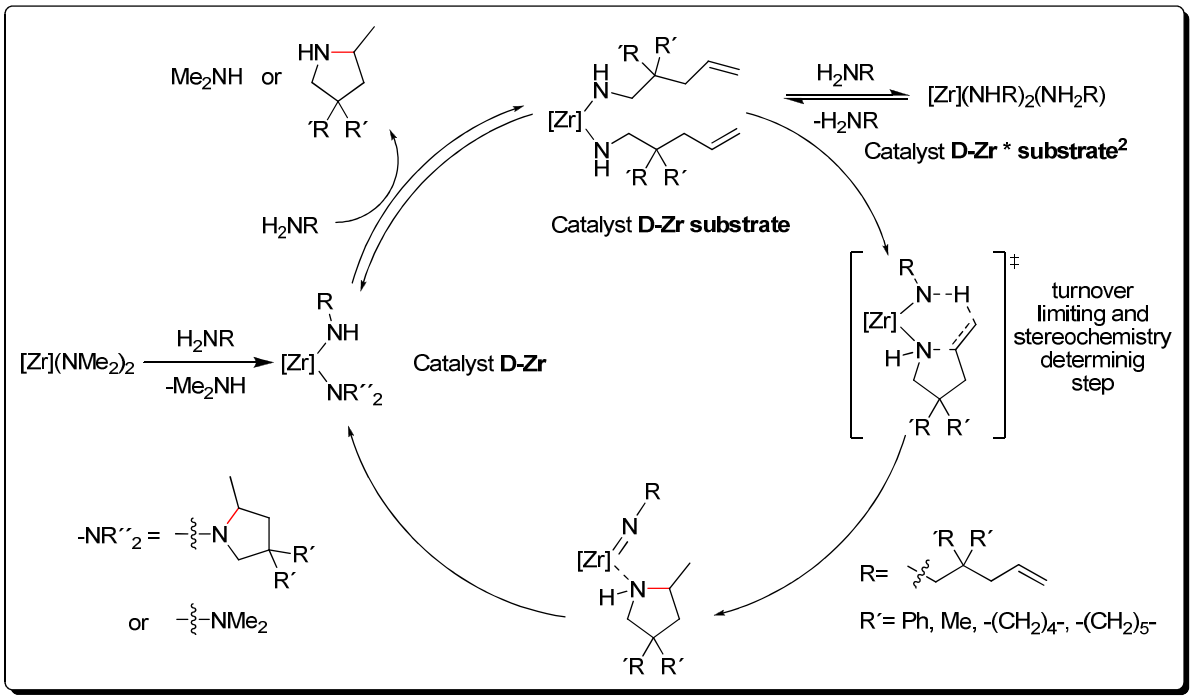
It has been assumed that catalysis by group IVB metals proceeds by either of two possible mechanisms. A single case of hydroamination of secondary amine by metals of this group has been described in the literature (Table 1, entry 235); the overwhelming majority of attempted experiments remained unsuccessful (for example Table 1, entries 19 and 234). Hydroaminations of primary amines have been explained by operation of the metal-imide mechanism, suggested by Bergman (Scheme 12).[56] In the first step, a ligand exchange takes place between the precatalyst and the substrate. As a result, the above-mentioned metal-imide complex is formed, accompanied by reductive removal of two ligands, most often $HNMe_2$ or $HN(TMS)_2$, confirmed on several occasions by ^1H NMR analysis. The metal-imide complex as the active catalyst *per se* generates by a subsequent [2+2] cycloaddition a cyclometallobutane intermediate, which, after another ligand exchange with the molecule of substrate, takes place in the formation of the target pyrrolidine, regenerating at the same time the metal-imide catalyst.



Scheme 12

The other alternative, suggested by Marks,[60] assumes an insertion of olefinic double bond into the M–N bond, analogously to the mechanism involving lanthanides or actinides (see Scheme 25, Part 1). This has been the only mechanism accounting for hydroamination of secondary amines by group IVB metals.

Another plausible mechanism was independently postulated in 2011 by Sadow[34] and Schafer[61] in order to explain the cyclizative hydroamination of secondary amines by IVB group metals. This proposal is based on results of control experiments revealing that (substoichiometric) amount of primary amine is essential for the successful transformation.



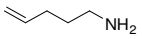
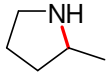
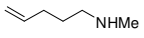
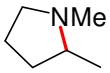
Scheme 13

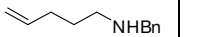
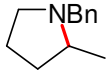
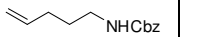
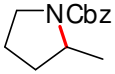
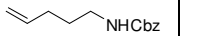
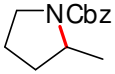
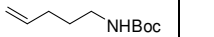
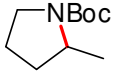
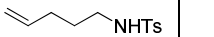
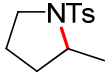
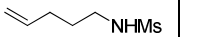
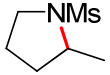
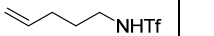
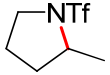
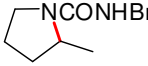
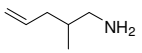
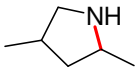
Thus, both authors consider the formation of 6-membered cyclic transition state as key turnover limiting and stereochemistry determining step. Moreover, authors do not envisage [2+2] cycloaddition of Zr=N and C=C bonds, instead they propose an incorporation of N–H bond of primary amine into the respective intermediate (Scheme 13).

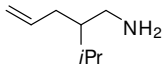
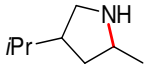
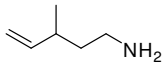
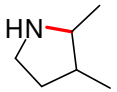
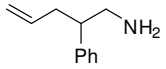
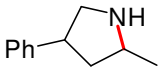
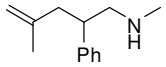
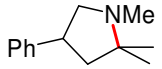
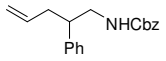
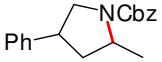
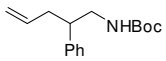
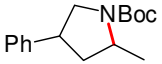
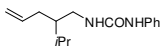
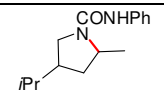
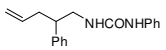
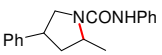
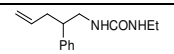
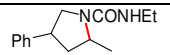
In conclusion, we can summarize the drawbacks preventing wider practical use of group IVB metals in the catalysis of hydroaminations of aminoalkene substrates as follows:

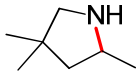
- Oxophility – inability to use oxygenated solvents and/or substrates.
- Metal-imide mechanism – does not tolerate secondary amines as substrates.
- Necessity of having activating substituents on the substrate chain.
- Low activity – high reaction temperatures are required.

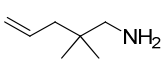
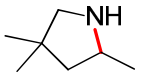
Table 1.

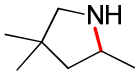
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
1	(*R*)-**1**-Y/5			>95[a]	C_6D_6		60	10	*ee*=69 (*S*)	24
2	(*R*)-**2**-Y/5							5	*ee*=73 (*S*)	
3	(*R*)-**3**-Y/5							8	*ee*=81 (*S*)	
4	**39**-Zr/10			89[a]	C_6D_6		120	41		57
5	(*R*)-**23**-Y/4			98[a]	C_6D_6	1.2	22	24	*ee*=69	25
6	(*R*)-**24**-Y/4			98[a]		2.2	22	20	*ee*=83	
7	$Ti(NMe_2)_4$/5			0	toluene		110	24		42
8	**L10**+$Zr(NMe_2)_4$/20			33[b,c]	toluene		135	72	*ee*=62	56
9	(Cp-(+)-neomenthyl)$_2$Y(Ph-2-[$CH_2(NMe_2)$])/4			96[a]	C_6D_6	0.4	65	65	*ee*=22 (*R*)	1
10	(Cp-(−)-phenylmenthyl)$_2$-YN(TMS)$_2$/3			82[a]		0.8	100	65	*ee*=35 (*S*)	
11	**32**-Zr/5			0	toluene-d_8		160	41		38
12	$Zr(NMe_2)_4$/5			25[a]	toluene		150	28		36
13	**20**-Y/10			>95[a]	C_6D_6		110	24		20
14	**21**-Y/10			>95[a]	C_6D_6		110	6		20
15	**22**-Y/10			88[a]	C_6D_6		110	6		20
16	(*R*)-**1**-Y/5			>95[a]	C_6D_6		60	36	*ee*=60 (*S*)	24
17	(*R*)-**2**-Y/5							38	*ee*=63 (*S*)	
18	(*R*)-**3**-Y/5							30	*ee*=69 (*S*)	
19	**39**-Zr/5			0	toluene-d_8		150	18		57

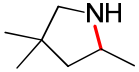
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
20	**L20**+$PtCl_2$/5			48	diglyme		80	96		78
21	(Au[P*t*-Bu_2(*o*-biphenyl)]Cl) +AgOTf/10			87	dioxane		100	68		91
22	2x$AgBF_4$+**53**-Pd +2x$Cu(OTf)_2$/5			82	DCM		r.t.			77
23	2x$AgBF_4$+**53**-Pd +2x$Cu(OTf)_2$/5			88	DCM		r.t.			77
24	$Bi(OTf)_3$/20			>95	DCE		40	72		113
25	$Bi(OTf)_3$/5			>95	DCE		40	192		113
26	$Sc(OTf)_3$/20			>95	DCE		60	192		113
27	$In(OTf)_3$/20			>95	DCE		80	168		113
28	$Al(OTf)_3$/20			>95	DCE		100	216		113
29	$BiBr_3$/20			>95	DCE		100	192		113
30	$InCl_3$/20			>95	DCE		100	288		113
31	$Bi(OTf)_3$/20			88	DCE		60	96		113
32	$Bi(OTf)_3$/20			68	DCE		80	192		113
33	[Au(**L13**)Cl]+AgOTf/10			98	MeOH		45	43		92
34	**55**-Au+AgOTf/10			86[a]	dioxane		60	48		94
35	$Ti(NMe_2)_4$/5			38[a]	toluene		110	96		42
36	**9**-Y/5			>95[a]	C_6D_6		60	61	*cis*:*trans*=1:1.5	9

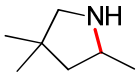
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
37	2x PPh_3+[$PtCl_2(CH_2{=}CH_2)$]/2.5			62	dioxane		120	11		76
38	**9**-Y/5			>95[a]	toluene-d_8		120	14	*cis*:*trans*=1:9	9
39	$Ti(NMe_2)_4$/5			26	toluene		110	168	*cis*:*trans*=1.4:1	42
40	**32**-Zr/5			18	toluene-d_8		160	11		38
41	[$Zr(dpm)(NMe_2)_2]_2$/2.5			57	toluene		150	120		36
42	$Zr(NMe_2)_4$/5			97[a]						
43	1.2x**L11**+[$Rh(COD)_2$]BF_4/7.5			80	dioxane		120	7		65
44	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			96	DCM		r.t.		*cis*:*trans*=2.3:1	77
45	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			84	DCM		r.t.		*cis*:*trans*=2.3:1	77
46	[Au(**L13**)Cl]+AgOTf/5			98	MeOH		r.t.	24	*cis*:*trans*=5.5:1	92
47	[Au(**L13**)Cl]+AgOTf/10			99	MeOH		45	24	*cis*:*trans*=2.9:1	92
48	**55**-Au+AgOTf/10			49[a]	MeOH		45	48	*cis*:*trans*=2.1:1	94
49	**55**-Au+AgOTf/10			98	dioxane		45	30	*cis*:*trans*=2.1:1	94
50	[Au(**L13**)Cl]+AgOTf/5			84	MeOH		45	24	*cis*:*trans*=3.3:1	92

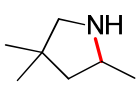
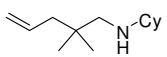
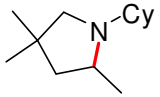
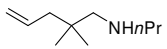
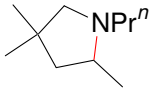
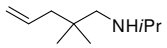
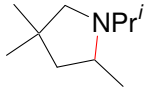
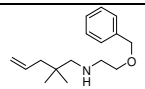
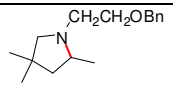
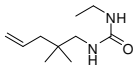
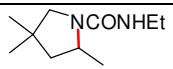
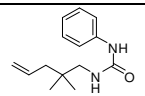
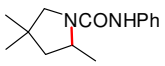
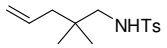
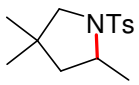
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
51	(*R*)-**1**-Y/5			>95[a]	C_6D_6		60	15	*ee*=78 (*S*)	24
52	(*R*)-**2**-Y/5							12	*ee*=83 (*S*)	
53	(*R*)-**3**-Y/5							9	*ee*=87 (*S*)	
54	**25**-Y/1			>95[a]	C_6D_6	196	60	0.5		3
55	**26**-Y/5			>93[a]	C_6D_6		27	4.58		4
56	**26**-Y/5			>92[a]			60	1.37		
57	**27**-Y/3-5			>95[a]	C_6D_6	0.3	25			2
58	**12**-Y/2.5			96[a]	C_6D_6	38.4	60	1		16
59	**13**-Y/2.5			97[a]		66.5	60	0.58		
60	**14**-Y/2.5			97[a]		19.4	60	2		
61	**15**-Y/2.5			98[a]		33.6	60	1.16		
62	**16**-Y/3			90[a]	C_6D_6		r.t.	5.5		21
63	**16**-Y/3			96[a]	C_6D_6		60	1		21
64	**17**-Y/5			>93[a]	toluene-d_8		25	0.83		18
65	**19**-Y/5			>95[a]	toluene-d_8		r.t.	0.16		19
66	**19**-Sc/5			>95[a]	toluene-d_8		60	5		19
67	**20**-Y/10			88[a]	C_6D_6		25	4.5		20
68	**21**-Y/10			88[a]	C_6D_6		25	2.5		20
69	**22**-Y/10			93[a]	C_6D_6		25	2.5		20

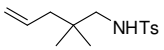
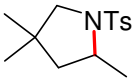
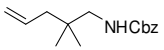
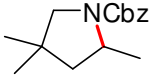
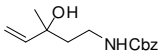
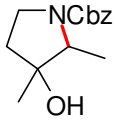
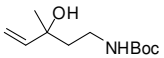
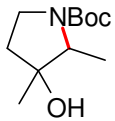
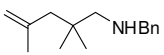
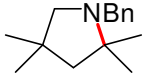
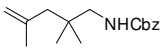
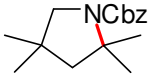
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
70	$Y[N(TMS)_2]_3$/2.8			>95[a]	C_6D_6		25	6		22
71	$Y[N(TMS)_2]_3$/2.8			>95[a]	THF		25	336		22
72	$Y[N(TMS)_2]_3$/2.8			>95[a]	diglyme		25		*no reaction*	22
73	$Y[N(TMS)_2]_3$/2.8			>95[a]	dioxane		25		*no reaction*	22
74	$Y[N(TMS)_2]_3$+5x*i*Pr_2O/2.8			>95[a]	C_6D_6		25	6		22
75	$Y[N(TMS)_2]_3$+5xMTBE/2.8			>95[a]	C_6D_6		25	6		22
76	$Y[N(TMS)_2]_3$+5xTHF/2.8			>95[a]	C_6D_6		25	6		22
77	$Y[N(TMS)_2]_3$+10xTHF/2.8			>95[a]	C_6D_6		25	8		22
78	$Y[N(TMS)_2]_3$+20xTHF/2.8			>95[a]	C_6D_6		25	9		22
79	$Y[N(TMS)_2]_3$+5xTHT/2.8			>95[a]	C_6D_6		25	6		22
80	$Y[N(TMS)_2]_3$+HMPA/2.8			>95[a]	C_6D_6		25	96	<5% isomerization	22
81	$Y[N(TMS)_2]_3$+*t*-BuONa/2.8			>95[a]	C_6D_6		60	216	21% isomerization	22
82	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			83[a]	THF		r.t.	24	*ee*=76	8
83	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			85[a]	C_6D_6		r.t.	23	*ee*=76	8
84	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			49[a]	C_6D_6		25	180	*ee*=64	10
85	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			96[a]	C_6D_6		60	22	*ee*=68	
86	(*R*)-**L1**+$[(TMSCH_2)_3Y(THF)_2]$/6			>95[a]	C_6D_6		23	48	*ee*=72	15
87	(*R*)-**L5**+$[(TMSCH_2)_3Y(THF)_2]$/6			>95[a]	C_6D_6		23	108	*ee*=70	15
88	(*R*)-**L6**+$[(TMSCH_2)_3Y(THF)_2]$/6			>95[a]	C_6D_6		23	168	*ee*=75	15

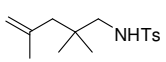
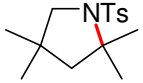
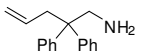
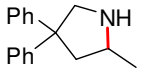
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
89	(*R*)-**L7**+[$(TMSCH_2)_3Y(THF)_2$]/6			>95[a]	C_6D_6		60	12	*ee*=28	15
90	(*R*)-**L8**+[$(TMSCH_2)_3Y(THF)_2$]/6			>95[a]	C_6D_6		60	27	*ee*=12	15
91	**39**-Zr/10			94[a]	C_6D_6		120	12		57
92	**6**-Y/5			95[a]	C_6D_6		25	22	*ee*=56	23
93	**6**-Y/5						10	168	*ee*=66	
94	**5**-Y/5				toluene-d_8		25	15	*ee*=61	
95	**5**-Y/5				C_6D_6		25	18	*ee*=61	
96	(*R*)-**40**-Zr/10			80	toluene		110	3	*ee*=93 (*R*)	47
97	(*S*)-**40**-Zr/10			98[a]			110	3	*ee*=93 (*S*)	
98	$Ti(NMe_2)_4$/5			87[e]	toluene		105	96		28
99	Ind_2TiMe_2/5			74[e]						
100	Ind_2ZrMe_2/5			58[e]						
101	Ind_2HfMe_2/5			19[e]	toluene		105	96		28
102	(*R*)-**23**-Y/4			98[a]	C_6D_6	8	22	3	*ee*=43	25
103	(*R*)-**24**-Y/4			98[a]		14	22	2	*ee*=53	
104	$Ti(NMe_2)_4$/5			32[a]	toluene		110	24		42
105	$Ti(NMe_2)_4$/5			52[a]				96		
106	**L10**+$Zr(NMe_2)_4$/20			95[b,c]	toluene		115	24	*ee*=80	56
107	**L10**+$Zr(NMe_2)_4$/10			78[b,d]				48	*ee*=80	

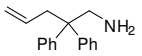
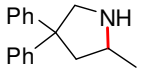
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref
108	**32**-Zr/5			88[a]	toluene-d_8		160	38		38
109	**30**-Zr/10			95[a]	toluene	2.35	110	0.83	*ee*=51	36
110	**31**-Zr/10			95[a]				0.33	*ee*=70	
111	$Ti(NMe_2)_4$/5			87[e]	toluene		105	96		27
112	Ind_2TiMe_2/5			74[e]						
113	Cp_2TiMe_2/5			<5[e]						
114	$[Me_2Si(Cp)(t\text{-}BuN)]Ti(NMe_2)_2$/5			8[e]						
115	(Cp-(+)-neomenthyl)$_2$Y[Ph-2-($CH_2(NMe_2)$)]/3			96[a]	C_6D_6	3.8	25	12.7	*ee*=21 (*R*)	1
116	(Cp-(-)-phenylmenthyl)$_2$YN(TMS)$_2$/3			97[a]		48	60	1	*ee*=26 (*S*)	
117	(R)-**46**-Zr/10			100[a]	C_6D_6		90	48	*ee*=93 (*S*)	48
118	(R)-**46**-Zr/10			57[a]	C_6D_6		70	160	*ee*=93 (*S*)	48
119	(Ind-1-(+)-neomenthyl)$_2$YN(TMS)$_2$/3			80[a]	C_6D_6		25	6.25	*ee*=11 (*S*)	1
120	$Ti(NMe_2)_4$/5			87[a]	toluene		105	96		27
121	**47**-V/10			89[a]	C_6D_6		140	24	*ee*=76	63
122	**48**-V/10			85[a]	C_6D_6		140	24	*ee*=68	63

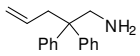
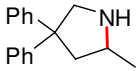
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
123	**48**-V/10			85[a]	C_6D_6		140	24	*ee*=68	63
124	**48**-V/10			32[a]	C_6D_6		130	48	*ee*=70	63
125	**49**-Ta/5			>95[a]	C_6D_6		140	34	*ee*=41 (*S*)	62
126	**58**-Zn/13.3			99[a]	C_6D_6		120	72		97
127	**58**-Zn+[$PhNMe_2H$][$B(C_6F_5)_4$]/5			46[a]	C_6D_6		120	52		
128	**56**-Zn/5			100[a]	C_6D_6		120	90		101
129	**57**-Zn/5			100[a]	C_6D_6		120	65		
130	(*S,S,S*)-**74**-Zn/5			94[a]	C_6D_6		90	140	*ee*=2 (*S*)	104
131	(*R,S,S*)-**75**-Zn/10			>99[a]	toluene-d_8		100	89	*ee*=3 (*R*)	104
132	**39**-Zr/5			92[a]	toluene-d_8		150	104		57
133	2xPPh_3+[$PtCl_2(CH_2{=}CH_2)$]/2.5			65	dioxane		120	9		76
134	**58**-Zn+[$PhNMe_2H$][$B(C_6F_5)_4$]/2.5			60	C_6D_6		80	13		98
135	**59**-Zn+[$PhNMe_2H$][$B(C_6F_5)_4$]/2.5			83	C_6D_6		80	13		
136	**50**-Ir/2.5			90[a]	C_6D_6		110	16	<5% substrate isomerization	73
137	1.2x**L11**+[$Rh(COD)_2$]BF_4/2.5			83	dioxane		70	7		65
138	**27**-Y/3-5			>95[a]	C_6D_6		90		no reaction	2

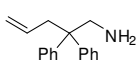
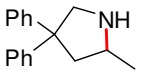
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
139	**27**-Y/3-5			>95[a]	C_6D_6	0.04	120			2
140	**29**-Zr+[$PhNMe_2H$][$B(C_6F_5)_4$]/10			68[a]	C_6D_6		110	48		31
141	ZnI_2+8-hydroxyquinoline/10			92	dioxane		110	36		108
142	Et_2Zn+[$PhNHMe_2$][$B(C_6F_5)_4$]/2.5			89	C_6D_6		r.t.	5.5		106
143	2xPPh_3+[$PtCl_2(CH_2{=}CH_2)$]/2.5			57	dioxane		120	17		76
144	**50**-Ir/2.5			80[a]	C_6D_6		110	16	10% substrate isomerization	73
145	**50**-Ir/2.5			90[a]	C_6D_6		110	16	5% substrate isomerization	73
146	2xPPh_3+[$PtCl_2(CH_2{=}CH_2)$]/2.5			70	dioxane		120	22		76
147	[Au(**L13**)Cl]+AgOTf/5			99	MeOH		r.t.	24	*cis*:*trans*=3.9:1	92
148	[Au(**L13**)Cl]+AgOTf/5			92	MeOH		r.t.	24	*cis*:*trans*=3.6:1	92
149	$FeCl_3{\cdot}6H_2O$/10			97	DCE		80	2		64
150	$FeCl_3{\cdot}6H_2O$/10			52[a]	hexane			1		
151	$FeCl_3{\cdot}6H_2O$/10			19[a]	benzene					

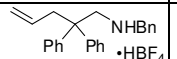
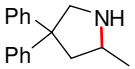
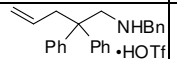
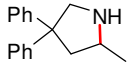
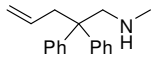
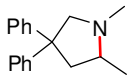
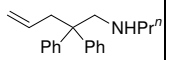
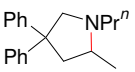
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
152	$FeCl_3 \cdot 6H_2O$/10			9[a]	dioxane		80	1		64
153	$FeCl_2 \cdot 4H_2O$/10			73[a]	DCE			2		
154	$Cu(OTf)_2$/10			99				16		
155	AgOTf/10			78				16		
156	Au:PVP/5			81	EtOH		50	16	3 eq. Cs_2CO_3, air	90
157	2x$AgBF_4$+**53**-Pd+10x$Cu(OTf)_2$/20			98[b]	DCM		r.t.			77
158	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			93[b]						
159	2x$AgBF_4$+**53**-Pd+20x$Cu(OTf)_2$/0.5			84[b]						
160	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			80	DCM		r.t.		*cis*:*trans*=4:1	77
161	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			88	DCM		r.t.		*cis*:*trans*=4:1	77
162	**58**-Zn+[$PhNMe_2H$][$B(C_6F_5)_4$]/2.5			86[a]	C_6D_6		80	480		98
163	**59**-Zn+[$PhNMe_2H$][$B(C_6F_5)_4$]/2.5			82	C_6D_6		80	168		
164	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			0	DCM		r.t.			77

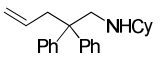
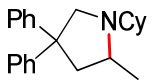
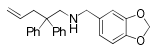
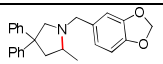
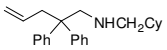
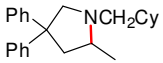
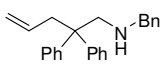
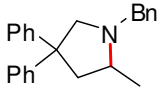
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
165	$FeCl_3 \cdot 6H_2O$/10			99	DCE		80	2		64
166	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			>95[a]	THF		r.t.	0.75	*ee*=75	8
167	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			90[a]	C_6D_6		r.t.	0.6	*ee*=77	
168	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			94[a]	C_6D_6		0	94	*ee*=75	10
169	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			100[a]			25	5	*ee*=75	
170	**26**-Y/5.2			>92[a]	C_6D_6		27	0.25		4
171	**28**-Y/5			93	C_6D_6		r.t.	0.16	*ee*=94 (S)	6
172	**28**-Zr/10			95[a]	C_6D_6		r.t.	18	*ee*=93 (R)	6
173	**16**-Y/5			quant.	C_6D_6		r.t.	0.08		21
174	**17**-Y/5			>95[a]	C_6D_6		25	0.66		18
175	**18**-Y/5			>95[a]	C_6D_6		25	0.66		18
176	**20**-Y/10			95	C_6D_6		25	<0.25		20
177	**21**-Y/10			94	C_6D_6		25	<0.25		20
178	**22**-Y/10			93	C_6D_6		25	<0.25		20
179	**33**-Ti/5			91[a]	toluene-d_8		160	96		38
180	**34**-Ti/5			67[a]	toluene-d_8		160	96		38
181	(*R*)-**40**-Zr/10			93	toluene-d_8		110	1.25	*ee*=74 (*R*)	47
182	(*S*)-**40**-Zr/10			93				1.25	*ee*=74 (*S*)	

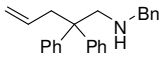
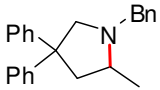
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
183	(*R*)-**41**-Zr/10			98[a]	toluene-d_8			18	*ee*=31	47
184	(*R*)-**42**-Zr/10			98[a]				3	*ee*=39	
185	*rac*-**L9**/Ti(NMe_2)$_4$/5			76	toluene		105	24		39
186	*rac*-**L9**/Zr(NMe_2)$_4$/5			82				24		
187	Ti(NMe_2)$_4$/5			92	toluene		110	24		42
188	Ti(NMe_2)$_4$/5			91	toluene		105	1		27
189	Ind_2TiMe_2/5			97				15		
190	Cp_2TiMe_2/5			86	toluene		105	24		27
191	[Me_2Si(Cp)(*t*-BuN)] Ti(NMe_2)$_2$/5			74				24		
192	Ti(NMe_2)$_4$/5			97[a]	toluene		105	24		28
193	Ind_2TiMe_2/5			96[a]						
194	Ind_2ZrMe_2/5			96[a]						
195	Ind_2HfMe_2/5			98[a]						
196	**32**-Zr/5			98[a]	toluene-d_8		160	0.84		38
197	**35**-Ti/10			61[a]	toluene-d_8		150	29d		40
198	**36**-Ti/10			78[a]	toluene-d_8		150	23d		40
199	**37**-Ti/10			85[a]	toluene-d_8		150	14d		40
200	**38**-Zr/10			>95[a]	C_6D_5Br		100	3		41

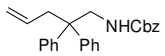
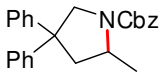
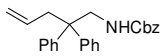
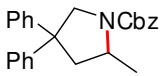
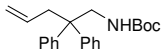
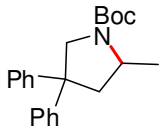
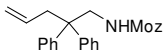
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
201	$[Zr(dpm)(NMe_2)_2]_2$/2.5			92	toluene		100	1		36
202	$Zr(NMe_2)_4$/5			92[a]						
203	$TiCl_4$/20			11[b,c]	toluene		120	18	+ 1.2 eq. *t*-$BuNH_2$	57b
204	$TiCl_4$/20			29[c]					+ 1.2 eq. *t*-$BuNH_2$ and 2,6-(*t*-$Bu)_2C_5H_3N$	
205	$TiCl_4$/20			26[c]					+ 1.2 eq. TMP	
206	$TiCl_4$/20			37[b,c]					+ 0.8 eq. LDA	
207	$HfCl_4$/20			59[c]					+ 0.8 eq. LDA	
208	$ZrCl_4$/20			87[c]					+ 0.8 eq. LDA	
209	43-Zr/5			>95[a]	toluene-d_8		70	7.5		44
210	44-Zr/5			>95[a]	toluene-d_8		70	4.5		44
211	**58**-Zn/10			69	toluene		100	24		97
212	**58**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			99[a]	C_6D_6		120	5		
213	**56**-Zn/1			92[a]	C_6D_6		120	13		101
214	**57**-Zn/1			100[a]						
215	(*S,S,S*)-**74**-Zn/5			88[a]	C_6D_6		60	140	*ee*=13 (*S*)	104
216	(*R,S,S*)-**75**-Zn/10			>99[a]	C_6D_6		100	71	*ee*=29 (*R*)	104

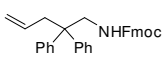
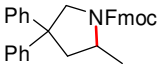
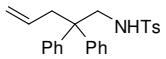
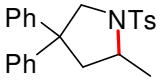
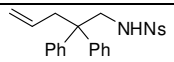
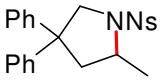
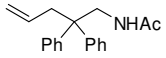
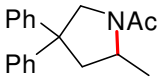
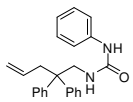
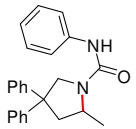
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
217	**50**-Ir/2.5			0	C_6D_6		110	16	50% substrate isomerization	73
218	**51**-Rh/2.5			0					75% substrate isomerization	
219	1.2x**L11**+$[Rh(COD)_2]BF_4$/5			83	dioxane		100	10		65
220	$[Ir(COD)Cl]_2$+2x$HNEt_3Cl$/5			89	dioxane		110	24		68
221	Cu(O*t*-Bu)(Xantphos)/10			92	toluene/MeOH		100	72		85
222	**72**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			12[a]	C_6D_6		120	7.5		105
223	**73**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			98[a]	C_6D_6		120	7.5		105
224	**76**-Al/10			81[a]	C_6D_6		150	38		109
225	**77**-Al/10			75[a]	C_6D_6		150	100		110
226	**78**-Al/10			70[a]	C_6D_6		135	28	15% substrate isomerization	111
227	**79**-Al/10			70[a]	C_6D_6		135	39	10% substrate isomerization	111
228	**80**-Al/10			50[a]	C_6D_6		135	70		111
229	**81**-Al/10			30[a]	C_6D_6		135	70	10% substrate isomerization	111
230	**82**-Al/10			83[a]	C_6D_6		135	3		111
231	**83**-Al/10			90[a]	C_6D_6		135	0.25		111

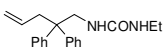
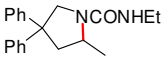
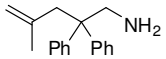
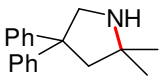
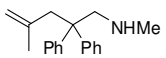
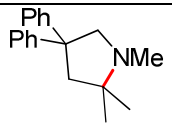
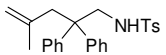
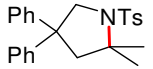
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
232	**L15**+AuCl+AgOTf/5			94	toluene		80	24		96
233	**L15**+AuCl+AgOTf/5			43[b]	toluene		80	24		96
234	(*R*)-**40**-Zr/10			0	toluene		140	76		47
235	$[Zr(dpm)(NMe_2)_2]_2$/2.5			35	toluene		150	120	+ other side products	36
236	**L12**+$[Rh(COD)_2]BF_4$/2.5			86[b]	dioxane		70	7		65
237	2x**L11**+$[Rh(COD)_2]BF_4$/2.5			93[b]						
238	2x**L11**+$[Rh(MeCN)_2COD]BF_4$/2.5			92[b]						
239	2x**L11**+$[Rh(COD)Cl]_2$/1.25			9[b]						
240	**28**-Zr/10			0	C_6D_6		170	24		51
241	**28**-Zr/10			20[a]	C_6D_6		r.t.	1	10–30% $^{n}PrNH_2$	51
242	Cu(O*t*-Bu)(Xantphos)/10			80	MeOH		60	18		85
243	$CuBr_2$+dppe+2x$AgBF_4$/5			80[a]	$C_2H_2Cl_4$		150	24		87
244	**50**-Ir/2.5			95[a]	C_6D_6		110	16	<5% substrate isomerization	73
245	**51**-Rh/2.5			75[a]					<5% substrate isomerization	
246	Cu(O*t*-Bu)(Xantphos)/10			93	toluene/MeOH		100	48		85

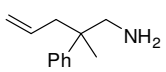
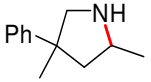
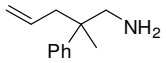
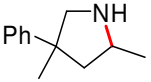
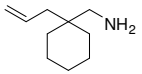
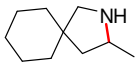
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
247	**45**-Zr/10			91	C_6D_6		145	15		51
248	ZnI_2+8-hydroxyquinoline/10			58	dioxane		110	36		108
249	**45**-Zr/10			86	C_6D_6		100	4		51
250	1.2x**L11**+$[Rh(COD)_2]BF_4$/2.5			91	dioxane		70	7		65
251	$[Ir(COD)Cl]_2$/1			87	dioxane		110	7		67
252	**52**-Pt+2x$AgBF_4$/3			92	benzene		80	48		80
253	$CuBr_2$+dppe+2x$AgBF_4$/5			94	$C_2H_2Cl_4$		150	20		87
254	**32**-Zr/5			0	toluene-d_8		160	29		38
255	**29**-Zr+$[PhNMe_2H][B(C_6F_5)_4]$/10			98[a]	C_6D_6		110	20		31
256	Cu(O*t*-Bu)(Xantphos)/10			99	toluene/MeOH		100	48		85
257	**58**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			100[a]	C_6D_6		80	1.5		98
258	**59**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			95				0.33		
259	**60**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			92[a]	C_6D_6		80	1.58		99
260	**61**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			29[a]	C_6D_6		80	1.58		99
261	**62**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			100[a]	C_6D_6		80	1		99
262	**63**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			64[a]	C_6D_6		80	12		99
263	**64**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			93	C_6D_6		80	0.67		99
264	**65**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			100[a]	C_6D_6		80	0.67		99
265	**66**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			87[a]	C_6D_6		80	12		99

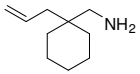
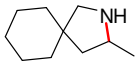
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
266	**L18**+$PtCl_2$/5			86	diglyme		60	14		78
267	**50**-Ir/2.5			98[a]	C_6D_6		110	18		73
268	**50**-Ir/2.5			98[a]	H_2O		100			
269	**51**-Rh/2.5			95[a]	C_6D_6		110			
270	**51**-Rh/2.5			95[a]	H_2O		100			
271	1.2x**L11**+$[Rh(COD)_2]BF_4$/2.5			91	dioxane		70	7		65
272	$[Ir(COD)Cl]_2$/0.25			88	dioxane		110	3		67
273	1.2x**L13**+$[Rh(COD)_2]BF_4$/5			96[b]	dioxane		70	7-15	*ee*=53 (*S*)	66
274	1.2x**L14**+$[Rh(COD)_2]BF_4$/5			98[b]	dioxane		70	7-15	*ee*=70 (*S*)	
275	1.2x**L15**+$[Rh(COD)_2]BF_4$/5			95[b]	dioxane		70	7-15	*ee*=75 (*S*)	
276	1.2x**L16**+$[Rh(COD)_2]BF_4$/5			94[b]	dioxane		70	7-15	*ee*=80 (*S*)	
277	**52**-Pt+2x$AgBF_4$/3			83	toluene		90	48		80
278	**52**-Pt+2x$AgBF_4$/3			>99	benzene		80	48		80
279	**52**-Pt+2x$AgBF_4$/3			84	DCE		80	48		80
280	**52**-Pt+2xAgOTs/3			82	benzene		80	48		80
281	**52**-Pt+2x$AgSbF_6$/3			90	benzene		80	48		80
282	$CuBr_2$+dppe+2x$AgBF_4$/5			85	$C_2H_2Cl_4$		150	30		87
283	ZnI_2+8-hydroxyquinoline/20			93[a]	dioxane		110	24		108
284	Et_2Zn+$[PhNHMe_2][B(C_6F_5)_4]$/2.5			94	C_6D_6		r.t.	1.33		106

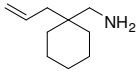
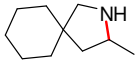
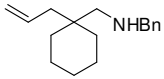
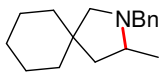
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
285	[Au(PPh_3)Cl]+AgOTf/5			59[a]	toluene					91
286	[Au(PPh_3)Cl]+AgOTf/5			49[a]	CH_3CN					
287	[Au(PPh_3)Cl]+AgOTf/5			33[a]	$C_2H_4Cl_2$					
288	[Au(PPh_3)Cl]+AgOTf/5			75[a]	dioxane					
289	[Au(PMe_2Ph)Cl]+AgOTf/5			7[a]						
290	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			98[a]				24		
291	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			97[a]			60	18		
292	[Au(**L13**)Cl]+AgOTf/5			96	dioxane		45	15		92
293	[Au(**L13**)Cl]+AgOTf/5			20[a]			r.t.	18		
294	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			96[a]	dioxane		60	18	1 eq. H_2O added	91
295	[$(Ph_3PAu)_3O$]BF_4/40			49	$CDCl_3$		r.t.	12	2 eq. Et_3N	95
296	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			96[a]	dioxane		60	20		91
297	[$(Ph_3PAu)_3O$]BF_4/40			53	$CDCl_3$		r.t.	12	2 eq. Et_3N	95
298	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			95[a]	dioxane		60	16		91

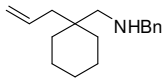
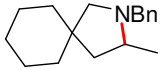
E	Catalyst / mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
299	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			93[a]	dioxane		60	24		91
300	[Au(PPh_3)Cl]+AgOTf/5			96	toluene		85	17		89
301	**52**-Pt+2x$AgBF_4$/3			90	benzene		80	48		80
302	Au:PVP/5			99	EtOH		50	1	3 eq. Cs_2CO_3, air	90
303	[Au(PPh_3)Cl]+AgOTf/5			99	toluene		85	48		89
304	[Au(**L13**)Cl]+AgOTf/5			99	dioxane		45	15		92
305	[Au(**L13**)Cl]+AgOTf/5			83			r.t.	18		
306	[Au(**L13**)Cl]+AgOTf/5			93	dioxane		45	15		92
307	[Au(**L13**)Cl]+AgOTf/5			96			r.t.	18		
308	**54**-Au+2x$AgOTf$/5			95	dioxane		r.t.	3	*ee*=36 (+)	93
309	**54**-Au+2x$AgOTf$/5			96	DCM		r.t.	3	*ee*=0	93
310	**54**-Au+2x$AgOTf$/5			85	THF		r.t.	3	*ee*=19 (+)	93
311	**54**-Au+2x$AgOTf$/5			90	Et_2O		r.t.	3	*ee*=10 (+)	93
312	**54**-Au+2x$AgOTf$/5			96	toluene		r.t.	3	*ee*=42 (+)	93
313	[$(Ph_3PAu)_3O$]BF_4/40			66	$CDCl_3$		r.t.	2	2 eq. Et_3N	95
314	**55**-Au+$AgOTf$/5			98	dioxane		r.t.	15		94
315	**55**-Au+$AgOTf$/5			99	MeOH		r.t.	6		94

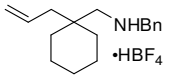
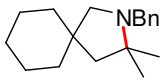
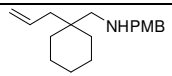
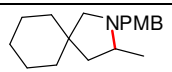
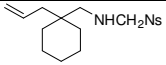
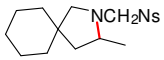
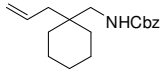
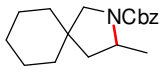
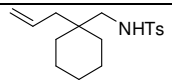
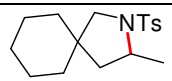
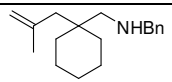
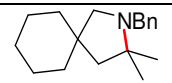
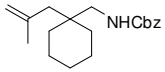
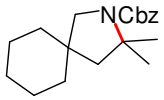
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
316	[Au(**L13**)Cl]+AgOTf / 5			91	dioxane		r.t.	24		92
317	[Au(**L13**)Cl]+AgOTf/1			97	MeOH		r.t.	24		
318	[Au(**L13**)Cl]+AgOTf/5			95	$MeOH/H_2O$		r.t.	24		
319	**32**-Zr/5			98[a]	toluene-d_8		160	8		38
320	(*R*)-**L11**+YCl_3+4*n*-BuLi/6			90[a]	C_6D_6		25	1		14
321	1.2x**L11**+$[Rh(COD)_2]BF_4$/5			96	dioxane		100	24		65
322	$[Ir(COD)Cl]_2$+2x$HNEt_3Cl$/10			87	dioxane		110	48		68
323	**72**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			12[a]	C_6D_6		120	96		105
324	**73**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			98[a]	C_6D_6		120	96		105
325	**76**-Al/10			87[a]	C_6D_6		150	12		109
326	**78**-Al/10			78[a]	C_6D_6		135	5		111
327	**79**-Al/10			74[a]	C_6D_6		135	5		111
328	**82**-Al/10			85[a]	C_6D_6		135	34		111
329	**83**-Al/10			83[a]	C_6D_6		135	3		111
330	1.2x**L11** +$[Rh(COD)_2]BF_4$/2.5			96	dioxane		70	7		65
331	$[Au(PPh_3)Cl]$+AgOTf/5			91	toluene		85	15		89
332	Au:PVP/5			99	EtOH		50	3	3 eq. Cs_2CO_3, air	90

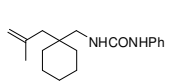
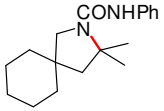
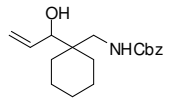
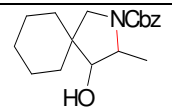
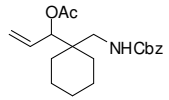
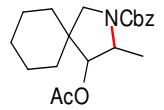
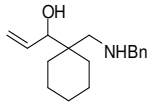
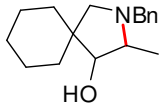
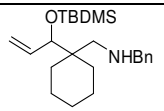
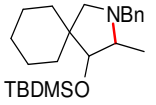
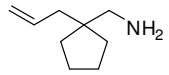
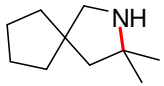
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
333	(*R*)-**40**-Zr/10			94	toluene		110	12	*cis*:*trans*=1.9:1	47
334	$Ti(NMe_2)_4$/5			52	toluene		110	24	*cis*:*trans*=1.4:1	42
335	$Ti(NMe_2)_4$/5			57[e]	toluene		105	24	*cis*:*trans*=1.5:1	97
336	Ind_2TiMe_2/5			58[e]					*cis*:*trans*=1.6:1	
337	Ind_2ZrMe_2/5			58[e]					*cis*:*trans*=1.7:1	
338	Ind_2HfMe_2/5			70[e]					*cis*:*trans*=2.4:1	
339	(*R*)-**L1**+YCl_3+3*n*-BuLi/6			91[a]	C_6D_6		r.t.	5	*ee*=75	8
340	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			94[a]				2	*ee*=75	
341	(*R*)-**L1**+0.5YCl_3+2*n*-BuLi/6			94[a]				5	*ee*=75	
342	(*R*)-**L1**+YCl_3+4*n*-BuLi/3			72	THF		r.t.	3	*ee*=73	
343	(*R*)-**L1**+YCl_3+4*n*-BuLi/6			54[a]	C_6D_6		0	144	*ee*=75	10
344	(*R*)-**L1**+YCl_3+4*n*-BuLi/8			93[a]			25	15	*ee*=81	
345	(*R*)-**L9**+YCl_3+4*n*-BuLi/7			100	C_6D_6		r.t.	20	*ee*=67	11
346	(*R*)-**L10**+YCl_3+4*n*-BuLi/6			95[a]	C_6D_6		r.t.	0.25	*ee*=5	14
347	(*R*)-**L11**+YCl_3+4*n*-BuLi/6			90[a]				0.30	*ee*=5	
348	(*R*)-**40**-Zr/10			96	toluene		110	3	*ee*=82 (*R*)	47
349	**29**-Y/5			95	C_6D_6		r.t.	0.17	*ee*=93 (S)	6
350	**29**-Zr/10			92[a]	C_6D_6		r.t.	32	*ee*=87 (R)	6
351	**16**-Y/5			96[a]	C_6D_6		r.t.	0.13		21

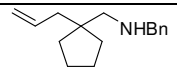
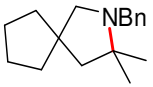
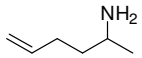
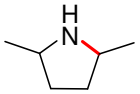
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
352	**20**-Y/10			>95[a]	C_6D_6		25	<0.25		20
353	**21**-Y/10			>95[a]	C_6D_6		25	<0.25		20
354	**22**-Y/10			>95[a]	C_6D_6		25	<0.25		20
355	**33**-Ti/5			98[a]	toluene-d_8		160	67		38
356	**34**-Ti/5			26[a]	toluene-d_8		160	69		38
357	**35**-Ti/10			92[a]	toluene-d_8		150	16d		40
358	**36**-Ti/10			<1[a]	toluene-d_8		150	20		40
359	**37**-Ti/10			94[a]	toluene-d_8		150	22d		40
360	**32**-Zr/5			98[a]	toluene-d_8		160	3		38
361	(*R*)-**46**-Zr/10			98[a]	C_6D_6		120	24	*ee*=74	48
362	**47**-V/10			100[a]	C_6D_6		140	24	*ee*=56	63
363	**47**-Ta/10			>95[a]	C_6D_6		120	30	*ee*=81	62
364	Cu(O*t*-Bu)(Xantphos)/10			79	toluene/MeOH		100	72		85
365	$[Zr(dpm)(NMe_2)_2]_2$/2.5			86	toluene		100	3		36
366	$Zr(NMe_2)_4$/5			100[a]						
367	**58**-Zn/10			87	C_6D_6		120	30		97
368	**58**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			80[a]	C_6D_6		120	8		
369	**56**-Zn/5			100[a]	C_6D_6		120	72		65

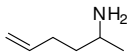
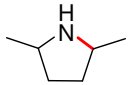
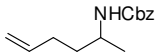
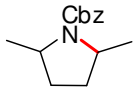
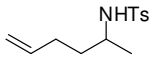
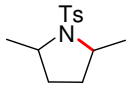
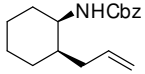
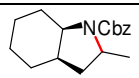
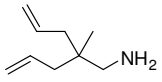
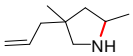
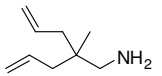
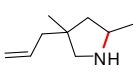
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
370	**57**-Zn/5			97[a]	C_6D_6		120	50		
371	1.2x**L11**+$[Rh(COD)_2]BF_4$/5			74[a]	dioxane		100	10		
372	$[Ir(COD)Cl]_2$+2x$HNEt_3Cl$/5			75[a]	dioxane		110	24		68
373	(*S,S,S*)-**74**-Zn/5			97[a]	C_6D_6		80	50	*ee*=5 (*S*)	104
374	(*R,S,S*)-**75**-Zn/10			>99[a]	C_6D_6		100	20	*ee*=0	104
375	Et_2Zn/10			>99[a]	C_6D_6		60	100		104
376	**72**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			15[a]	C_6D_6		120	8.5		105
377	**73**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/5			91[a]	C_6D_6		120	8.5		105
378	**76**-Al/10			63[a]	C_6D_6		150	90		109
379	**78**-Al/10			84[a]	C_6D_6		135	110		111
380	**82**-Al/10			85[a]	C_6D_6		135	103		111
381	**83**-Al/17.5			88[a]	C_6D_6		135	1		111
382	2xPPh_3+$[PtCl_2(CH_2{=}CH_2)]$/2.5			82	dioxane		120	2		76
383	2xPPh_3+$[PtCl_2(CH_2{=}CH_2)]$/2.5			92[b]	dioxane		120	2	0.5 eq. H_2O added	
384	2xP(*o*-tolyl)$_3$+ $[PtCl_2(CH_2{=}CH_2)]$/2.5			55[b]	diglyme		80	6		78
385	2xP(*m*-tolyl)$_3$+ $[PtCl_2(CH_2{=}CH_2)]$/2.5			22[b]						
386	**L13**+$PtCl_2$/5			45[b]				3		

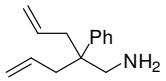
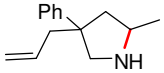
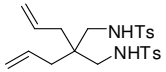
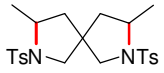
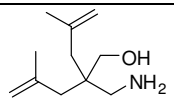
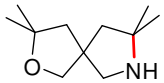
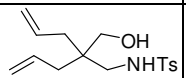
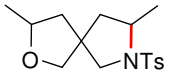
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
387	**L14**+$PtCl_2$/5			20[b]	diglyme		80	3		78
388	**L15**+$PtCl_2$/5			72[b]				6		
389	**L16**+$PtCl_2$/5			82[b]						
390	$[Ir(COD)Cl]_2$/2.5			86	dioxane		110	7		67
391	**29**-Zr+$[PhNMe_2H][B(C_6F_5)_4]$/10			99[a]	C_6D_6		110	20		31
392	**L17**+$PtCl_2$/5			79[b]	diglyme		80	6		78
393	**L18**+$PtCl_2$/5			100[b]						
394	**L19**+$PtCl_2$/5			98[b]						
395	**L20**+$PtCl_2$/5			100[b]						
396	**51**-Rh/2.5			79	C_6D_6		110	22		73
397	1.2x**L11**+$[Rh(COD)_2]BF_4$/2.5			92	dioxane		70	7		65
398	**67**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			100[a]	C_6D_6	53	80	0.75		100
399	**68**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			59[a]	C_6D_6	2.4	80	10		100
400	**69**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			16[a]	C_6D_6	0.6	80	10		100
401	**70**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			94[a]	C_6D_6	3.8	80	10		100
402	**71**-Zn+$[PhNMe_2H][B(C_6F_5)_4]$/2.5			97[a]	C_6D_6	3.9	80	10		100
403	ZnI_2+8-hydroxyquinoline/10			94	dioxane		110	36		108
404	Et_2Zn+$[PhNHMe_2][B(C_6F_5)_4]$/2.5			95	C_6D_6		r.t.	0.58		106

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
405	**L13**+AuCl+AgOT/5			3[b]	dioxane		60	22		96
406	**L19**+AuCl+AgOTf/5			11[b]						
407	**L19**+AuCl+AgOTf/5			48[b]	MeOH					
408	**L19**+AuCl+AgOTf/5			15[b]	THF					
409	**L19**+AuCl+AgOTf/5			37[b]	EtOAc					
410	**L19**+AuCl+AgOTf/5			61[b]	toluene					
411	**L20**+AuCl+AgOTf/5			77[b]						
412	**L15**+AuCl+AgOTf/5			82						
413	**L20**+$PtCl_2$/5			86	diglyme		60	10		78
414	**L18**+$PtCl_2$/5			84	diglyme		60	13		78
415	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			96	dioxane		60	23		91
416	[Au(PPh_3)Cl]+AgOTf/5			99	toluene		85	15		89
417	**L18**+$PtCl_2$/5			85	diglyme		80	64		78
418	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			88	dioxane		80	40		91

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
419	[Au(**L13**)Cl]+AgOTf/5			92	dioxane		r.t.	24		92
420	**55**-Au+AgOTf/5			98	dioxane		r.t.	24		94
421	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			91	dioxane		60	22		91
422	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			63	dioxane		60	18		91
423	1.2x**L11**+$[Rh(COD)_2]BF_4$/2.5			65	dioxane		70	7	*cis*:*trans*=1:11	65
424	2xPPh_3+$[PtCl_2(CH_2{=}CH_2)]$/2.5			79	dioxane		120	14	*de*=3.5:1	76
425	(*R*)-**40**-Zr/10			91	toluene		110	5	*ee*=88 (*R*)	47
426	**28**-Y/5			95	C_6D_6		r.t.	3	*ee*=89 (S)	6
427	**32**-Zr/5			92[a]	toluene-d_8		160	18		38
428	**20**-Y/10			96[a]	C_6D_6		25	1.8		20
429	**21**-Y/10			88[a]	C_6D_6		25	1		20
430	**22**-Y/10			>95[a]	C_6D_6		25	1		20
431	**33**-Ti/5			14[a]	toluene-d_8		160	67		38
432	**34**-Ti/5			7[a]	toluene-d_8		160	45		38

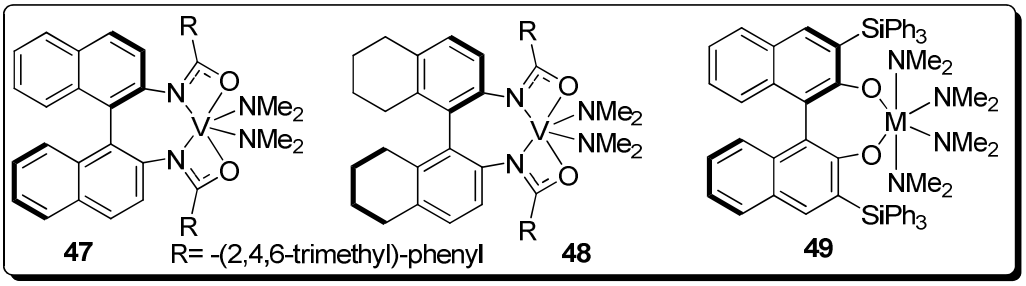
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
433	**51**-Rh/2.5			98[a]	C_6D_6		110	16		73
434	**39**-Zr/5			>98[a]	C_6D_6		120	172	*cis*:*trans*=1:1.3	57
435	**4**-Y/5			95[a]	C_6D_6		60	1	*cis*:*trans*=1:7	23
436	**7**-Y/5			>95[a]	C_6D_6		60	1.2	*cis*:*trans*=1:19	9
437	**8**-Y/5				C_6D_6		60	0.25	*cis*:*trans*=1:19	
438										
439	**10**-Y/5			>95[a]			60	11	*cis*:*trans*=1:19	
440	**11**-Y/5			>95[a]	C_6D_6		60	2	*cis*:*trans*=1:16	
441	(**R**)-24-Y/2			52[a]	C_6D_6		22	26	*ee*=80	1
442	(**R**)-24-Sc/2			50[a]	C_6D_6		40	94	*ee*=73	
443	**16**-Y/3			99[a]	C_6D_6		120	2	*cis*:*trans*=1:5	21
444	**17**-Y/5			>95[a]	C_6D_6		25	36	*cis*:*trans*=1:17	18
445	**18**-Y/5			80[a]	C_6D_6		0	48	*cis*:*trans*=1:23	18
446	**18**-Y/5			>95[a]	C_6D_6		25	36	*cis*:*trans*=1:17	18
447	**18**-Y/5			>95[a]	C_6D_6		65	1.5	*cis*:*trans*=1:11	18
448	$Y[N(TMS)_2]_3$/5			>95[a]	C_6D_6		90	146	*cis*:*trans*=1:6	22
449	$Y[N(TMS)_2]_3$+5xTHF/5			>95[a]	C_6D_6		90	120	*cis*:*trans*=1:9	22
450	$Y[N(TMS)_2]_3$/5			>95[a]	THF		90	209	*cis*:*trans*=1:5	22

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
451	Y[N(TMS)$_2$]$_3$/5			>95[a]	MTBE		90	106	*cis*:*trans*=1:9	22
452	Y[N(TMS)$_2$]$_3$/5			>95[a]	$C_6H_5(CF_3)$		90	53	*cis*:*trans*=1:8	22
453	**58**-Zn+[PhNMe$_2$H][B(C_6F_5)$_4$]/10			19[a]	C_6D_6		120	36		97
454	[Au(P*t*-Bu$_2$(*o*-biphenyl)Cl]+AgOTf/10			91	dioxane		100	55		91
455	$FeCl_3 \cdot 6H_2O$/10			97	DCE		80	2	*cis*:*trans*=3.8:1	64
456	[Au(P*t*-Bu$_2$(*o*-biphenyl)Cl]+AgOTf /5			95	dioxane		100	30		91
457	(*R*)-**40**-Zr/10			82	toluene		110	2	*cis*:*trans*=2.3:1	47
458	(*R*)-**23**-Y/2			98[a]	C_6D_6	75	22	1		25
459	(*R*)-**24**-Y/2			98[a]	C_6D_6	70	22	1.2		25
460	**28**-Y/5			95			r.t.	0.16	*dr*=1.2:1	6
461	(Cp-(+)-neomenthyl)$_2$Y(Ph-2-CH_2NMe_2)/3			100[a]		16	25	2.6		1
462	(Cp-(−)-phenylmenthyl)$_2$-YN(TMS)$_2$/3			100[a]		0.5		68		
463	(Ind-1-(+)-neomenthyl)$_2$-YN(TMS)$_2$/1.5			96[a]	C_6D_6	225	25	0.5		

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
464	**32**-Zr/5			98[a]	toluene-d_8		160	1		38
465	$[Zr(dpm)(NMe_2)_2]_2$/2.5			96	toluene		100	3		36
466	$Zr(NMe_2)_4$/5			100[a]						
467	**28**-Y/5			96	C_6D_6		r.t.	0.16	*dr*=1.2:1	6
468	$FeCl_3 \cdot 6H_2O$/10			82	DCE		80	38		64
469	$[Au(PPh_3)Cl]$+AgOTf/5			97	toluene		85	10		89
470	$FeCl_3 \cdot 6H_2O$/10			95	DCE		80	11		64

[a]Conversion determined by NMR. [b]Conversion determined by GC. [c]Isolated as *N*-trifluoroacetamide. [d]Isolated as 2-naphtoylamide. [e]Isolated as benzylcarbamate.

Group VB metals –V, Nb, Ta – form a similar catalytic complexes as group IVB metals. These are characteristic by their relatively low catalytic activity and thus, they require higher reaction temperatures. Due to the fact that **47–49** are able to cyclize mostly the Thorpe-Ingold type of activated substrates and/or primary amines only, they do not represent synthetically useful catalysts yet (Scheme 14).[62,63]

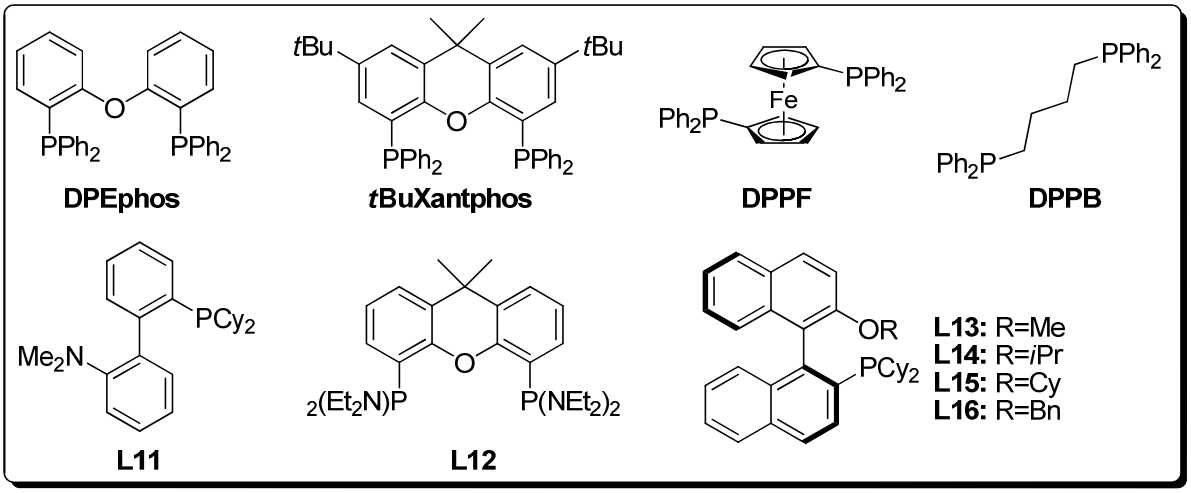


Scheme 14

When crossing the periodic table going from *elements of the group VIB to IIB* from the left – there is an element rarely encountered in hydroaminations, but one of the cheapest available – the iron. In 2006, Takaki and co-workers successfully cyclized *N*-tosylated aminoalkenes using 10 molar % $FeCl_3 \cdot 6H_2O$.[64] Screening of the reaction conditions (temperature, Fe-salt, solvent) allowed the authors to arrive at optimized experimental conditions (Table 1, entries 149–153). To be more specific, the use of 10 molar % of $FeCl_3 \cdot 6H_2O$ at 80 °C in 1,2-dichloroethane for 2–5 hours allows the cyclization of substituted tosylated aminoalkenes (Thorpe-Ingold effect) to the corresponding pyrrolidines (Table 1, entries 165, 455 and 468). An OH group, suitably located on the substrate chain can be added to an olefin. Extension of reaction time both competing reaction can be brought to total conversion and thus prepare the 2-oxa-7-aza-spiro [4.4]nonane (Table 1, entry 470). The single biggest drawback of Fe^{3+}-based catalysts remains their inability to cyclize aminoalkenes to piperidines or azepanes. Such substrates undergo double bond isomerization followed by hydroamination leading to 2-ethyl- or 2-propylpyrrolidines. The desired 6- or 7-membered amines either fail to form at all, or arise only as minor products.

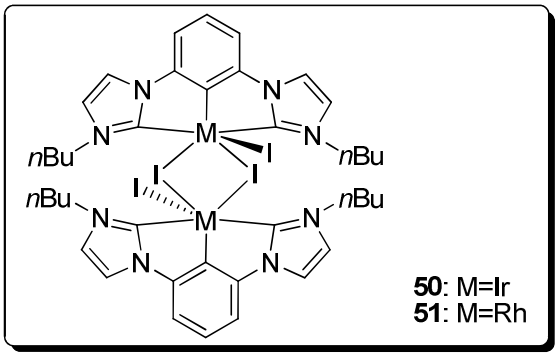
In 2008, Hartwig carried out hydroaminations catalyzed by a rhodium catalyst, one which had already proved useful in additions of amines to vinylarenes.[65] When used in cyclizations however, ligands commonly used in intramolecular hydroaminations failed to produce comparable results. Phosphine ligands such as DPEphos, *t*-BuXantphos, DPPB, DPPF, PCy_3 and PPh_3 (Scheme 15) showed no selectivity. The desired hydroamination products either does not form at all, or only as minor products, accompanying products of olefin reduction or double bond isomerization. *N,P*-ligands **L11** and **L12** were highly selective (Scheme 15). In combination with 2.5 mol% $[Rh(COD)_2]BF_4$ (relative to substrate), they successfully transformed both secondary and primary aminoalkenes to cyclic amines. Aminoalkenes carrying an electron-donating substituent at nitrogen generally react much more readily, while, for achieving mildly lower yields or conversion, analogous to primary amines, they require the use of higher reaction temperature and longer reaction times (Table 1, entries 271 *vs.* 219, 330 *vs.* 321, 397 *vs.* 371). Rhodium perfectly tolerates a free hydroxyl group in the substrate (Table 1, entry 423) and allows also hydroamination of 2,2-disubstituted alkenes (Table 1, entries 43, 321 and 330). Since the catalysts tolerate fairly well H_2O and atmospheric oxygen, thorough drying of solvents and/or their deoxygenation is no longer necessary. Later, Buchwald developed an axially chiral binaftyl ligands **L13–L16** that were reaching enantioselectivities in the range of 53–80%.[66]

Similarly to the $[Rh(COD)_2]BF_4$ catalyst, Stradiotto[67–69] employs $[Ir(COD)Cl]_2$ as hydroamination catalyst as well as Ir-phosphino-phenolates[70] with comparable success. Already known are also half-sandwich catalysts of Rh and Ir that allow the cyclization of Thorpe-Ingold-type activated aminoalkenes at 50 °C.[71,72]



Scheme 15

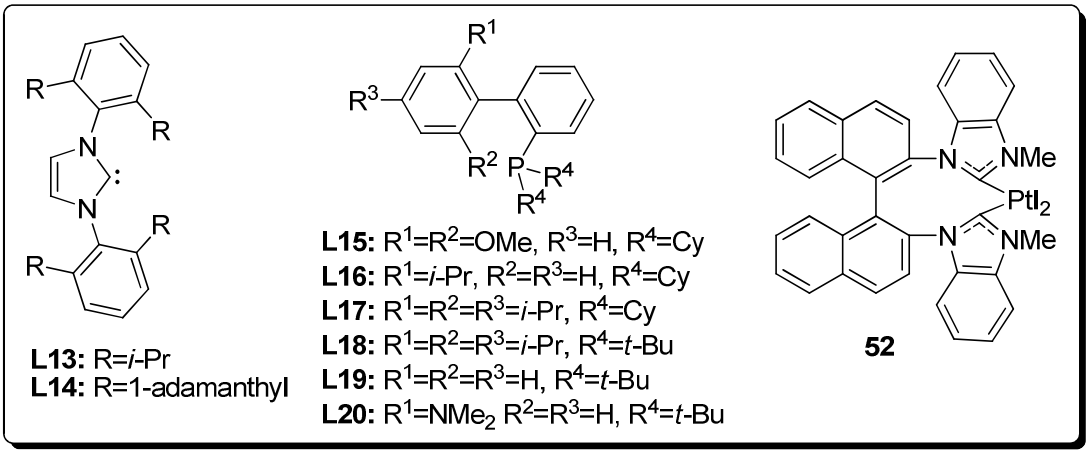
The exchange of the central zirconium ion of the catalytic complex **32** (Scheme 9) for rhodium or iridium gave rise to dimeric catalysts **50** and **51**, active in hydroaminations of secondary amines (Scheme 16).[73] These *N*-heterocyclic carbene complexes make possible cyclization of secondary amines with electron-withdrawing substituents and the Thorpe-Ingold effect; the process takes place in 16 hours at 110 °C (Table 1, entries 136, 144, 145, 244, 245, 396 and 433). Primary amines lacking of an electron-rich substituent are insufficiently activated for hydroamination to occur and undergo a double bond isomerization instead. In spite of only average activity of catalysts, they stand out from the range of other catalysts so far used in hydroaminations, or mentioned in this work. The character of complexes and their insensitivity to moisture make these catalysts truly **green** – they can catalyze hydroaminations in water without any loss of activity or selectivity whatsoever (Table 1, entries 267–270).



Scheme 16

It is interesting to note, that although ***Pd and Pt metals*** have been widely used in organometallic chemistry for the formation of C–C, C–O, C–N and C–P bonds, their use in hydroaminations has been rare. Apart from the stoichiometric cyclizations of aminoalkenes from the seventies,[74,75] the first intramolecular hydroaminations of non-activated aminoalkenes, catalyzed by these metals, appeared only in 2005[76] and

2006.[77] Up to that time only hydroaminations of activated amines and/or activated olefins were known and a catalytic system for hydroamination of non-activated aminoalkenes was yet to be discovered. According to authors,[76] it may have been caused by the stability of Pt-alkyl or Pt-olefin complexes. In their groundbreaking paper,[76] authors cyclized aminoalkenes with terminal (also 2,2-disubstituted) double bond. The used reaction conditions (2.5 mol% $[PtCl_2(CH_2{=}CH_2)_2]$, 5% PPh_3, dioxane, 120 °C, 2–40 hours) are fairly hard; in addition, the selection of substrate is limited by the need of electron-donating substituent at nitrogen and the presence of steric activators (utilization of the Thorpe-Ingold effect) in the substrate chain. In spite of limitations, this paper opened up new possibilities for utilization of late transition metals in hydroaminations of aminoalkenes. Three years later, authors[78] carried out screening of ligands in order to find less drastic reaction conditions. Starting from the tentative mechanism (*vide infra*) involving final protonolysis as the rate determining step and observation that sterically demanding ligands can accelerate the reaction, they replaced PPh_3 for P(*o*-tolyl)$_3$ a P(*m*-tolyl)$_3$. After comparing the rates of thus catalyzed hydroaminations (Table 1, entries 384 *vs.* 385), they decided to use *ortho*-biphenyls and *N*-heterocyclic carbenes as ligands (Scheme 17). The influence of *P,P*- and *P,N*-ligands on the reaction rate using their respective Pd and/or Pt-complexes for the hydroamination was scrutinized by Stradiotto.[79] However, none of the tested ligands displayed such an increased activity that would allow to either significantly reduce the reaction temperature or to remove the Thorpe-Ingold activators from substrates.



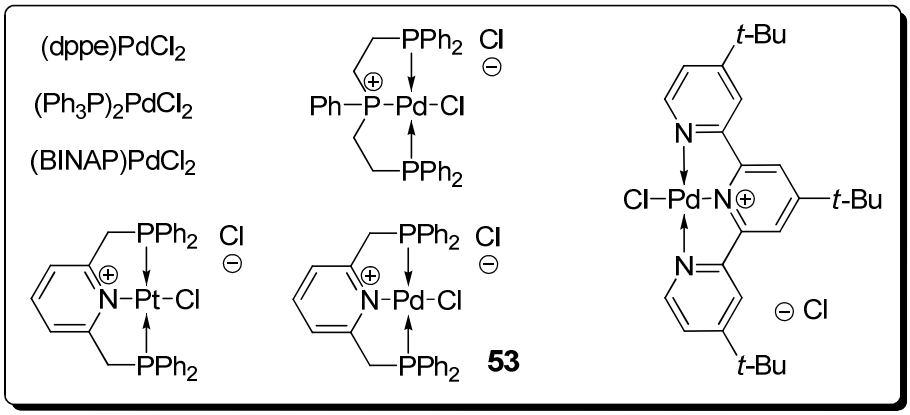
Scheme 17

The hypothesis by Widenhoefer[78] has been borne out by practical experiments, since by using sterically encumbered phosphine ligands, they were indeed able to reduce the reaction temperature to 60–80 °C, (Table 1, entries 266, 386–389, 392–395, 417), or else to cyclize even aminoalkenes without the Thorpe-Ingold effect (Table 1, entry 20).

Recently, *N*-heterocyclic carbenes were tested as Pt-ligands by Shi.[80] They successfully performed the hydroamination using the complex **52**; however, the elevated reaction temperature (80 °C) and prolonged reaction time (48 hours) were necessary for the cyclization of Thorpe-Ingold activated substrate.

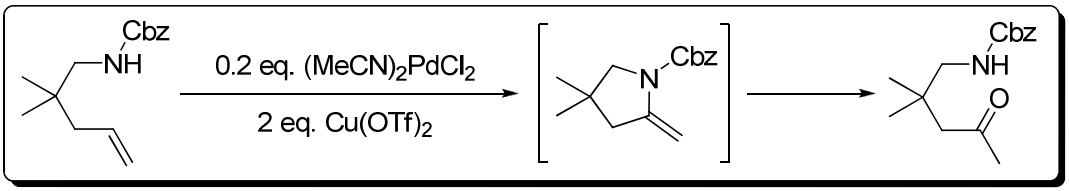
In 2006, Michael and Cochran presented the first Pd-catalyzed intramolecular hydroamination of non-activated alkenes.[77] Their success was based on preventing the unwanted β-H-elimination of the primary alkyl-Pd-complex, formed after closure of the heterocyclic ring. It is exactly the strong tendency of alkyl-Pd-complexes to β-H-elimination that accounts for the rarity of Pd-catalyzed hydroaminations, or their absence until 2006. Authors assumed that by blocking the free coordination positions at the central metal cation of

the alkyl-Pd-complex, they could suppress the elimination. Since one coordination place has been taken by the alkyl itself, for testing the viability of their hypothesis, they needed tridentate ligands. Out of all tested bi- and tri-dentate ligands (Scheme 18), no more than one ligand (forming the catalytic complex **53**) could catalyze hydroamination.



Scheme 18

Unlike Pt-catalysts, Pd(PNP)Cl_2 complex **53** made hydroamination of aminoalkenes possible under considerably milder reaction conditions – at laboratory temperature – in dichloromethane. Also, in contrast to Pt-complexes, substrates catalyzed by the palladium complex **53** had the nitrogen of aminoalkenes substituted by an electron-withdrawing protecting group, most frequently by Boc or Cbz. The probable reason is, according to authors,[81] the essentially irreversible coordination of free amines to Pd-complexes. As the conformation of the indispensability of PNP-ligand at palladium authors made a control experiment, in which they attempted hydroamination in analogous conditions using the acetonitrile $PdCl_2$ complex. As a result, they isolated aminoketone as the product of formal Wacker oxidation of olefin, proceeding, according to authors, *via* an unstable enamide formed after *β*-hydride elimination. In our view, this experiment gives no irrefutable proof of the necessity to use (PNP)-ligands in order to suppress the *β*-H-elimination. We believe the isolated aminoketone is the consequence of anhydrous reaction system. Moreover, successful Wacker oxidation does not need to produce a cyclic enamide (Scheme 19).



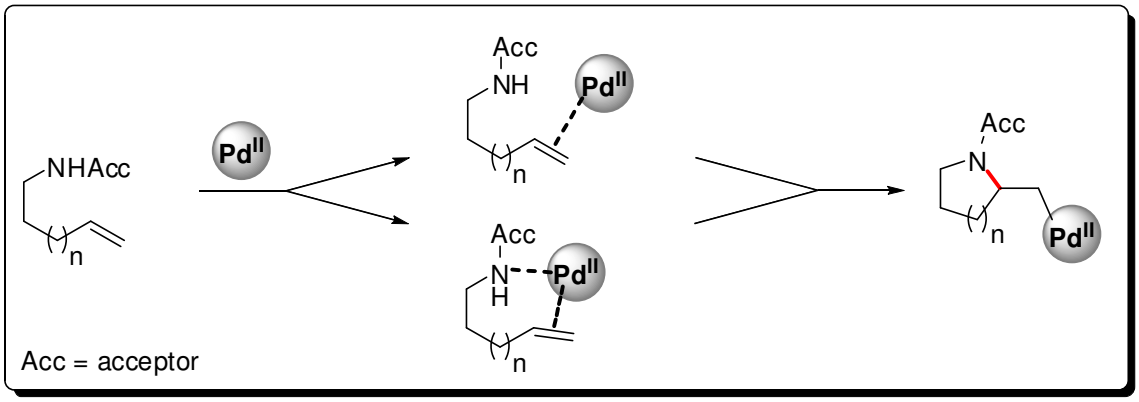
Scheme 19

In a subsequent paper, authors excluded the co-catalyst $Cu(OTf)_2$ from the reaction mixture, confirming it was not needed for this reaction. By this they also removed the suspicion that the reaction was acid-catalyzed (*vide infra*), or proceeds by catalysis at the central copper atom.

Generally, the comparison of Pt- *versus* Pd-catalyzed hydroaminations unequivocally favours the Pd-PNP complex, allowing aminoalkenes with or without the Thorpe-Ingold effect to cyclize, with nitrogen protected as carbamate, in dichloromethane at laboratory temperature. It also tolerates the presence of OH group in the substrate. Hydroaminations of aminoalkenes with electron-donating substituents at nitrogen are better carried under Pt-catalysis in combination with *ortho*-substituted phenylphosphine ligands.

1.1.1. Mechanism of catalysis with Pt and Pd

The catalysis by Pt- and Pd-complexes usually begins with coordination of olefin and metal. Next olefin loses electrons and is attacked by a nucleophile. New bonds C–Nu and C–M are created. Already the attack of nucleophile can proceed in two fold way. In case the coordination of substrate to central metal is mediated by the olefin, we speak of the so-called "outer-sphere", or an *anti*-attack. If both substrate and olefin are coordinated directly with the central metal, (in *syn*-arrangement) an "inner-sphere", or *syn*-attack takes place (Scheme 20).[81] Of course in terminal olefins the result of whichever attack is the same, but on internal olefins different attack provides products with reversed configuration at the newly created stereogenic centre.



Scheme 20

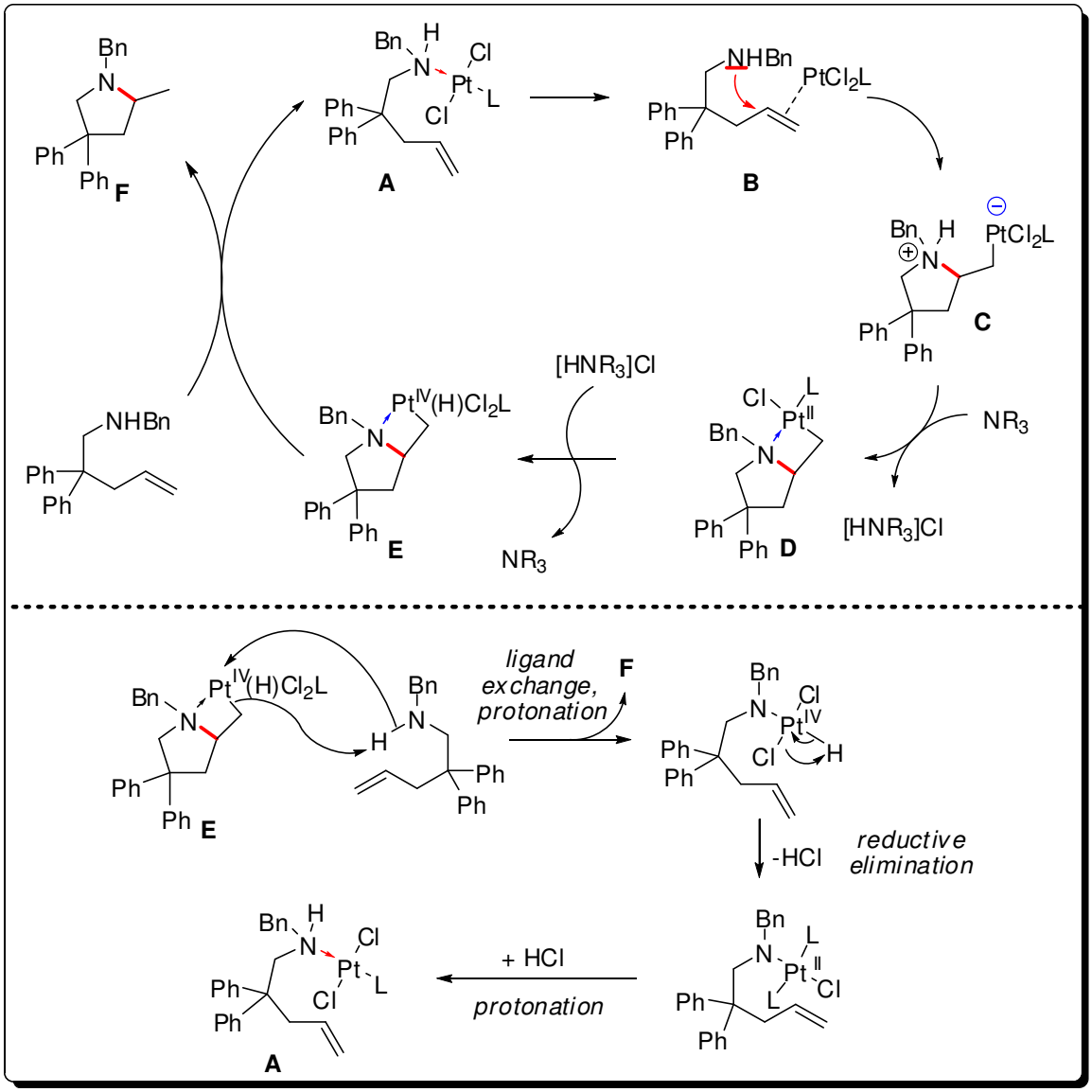
In the following step, three types of reactions can take place, a β-H-elimination, a reductive elimination or a ligand exchange.

The β-hydride elimination leads to an undesirable enamine with *exo*-double bond which, after a rearrangement (isomerization), gives rise to the energetically more favourable cyclic enamine with an internal double bond. It has been known that Pt(II)-alkyl complexes are much less prone to undergo the β-hydride elimination than are their Pd(II) analogues.[82] Pd(PNP)-complexes do not undergo β-hydride elimination owing to their ligand. The tridentate (PNP) ligand fully occupies all coordination places at the central metal, hence attack of hydride on Pd is not possible.

The reductive elimination, involving breaking of the M–C bond, has been suggested in cases with Pt as central metal. The mechanistic hypothesis however does not suppose the process as being of the type $Pt^{II} \rightarrow Pt^{0}$, but rather as protonation $Pt^{II} \rightarrow [Pt^{IV}]$, followed by the reductive elimination itself as $[Pt^{IV}] \rightarrow Pt^{II}$ (Scheme 21).

In mechanistic studies with the stoichiometric amount of Pt-catalyst, authors isolated an amino-Pt complex (**A**) as a stable compound. The *trans*-arrangement of ligands at the central metal was confirmed by large interaction constant (J_{P-N}=48 Hz) between atoms P and N (^{31}P NMR spectrum of the ^{15}N-labelled isotopomer).[81] Authors assumed a ligand exchange takes place whereby nitrogen of secondary amine is replaced by an olefin, whereupon the Pt-activated olefin (**B**) undergoes a nucleophilic nitrogen attack. No insertion of olefin into the N–Pt bond takes place. Instead, a zwitterion (**C**) is formed (and confirmed by NMR), which when heated in a stoichiometric experiment at 80 °C degraded without giving the product **F**. An alternative experiment with addition of a secondary amine ($HNEt_2$) produced smoothly the heterobicyclic Pt-amine complex (**D**). The authors claim that protonolysis of the Pt–C bond proceed by way of a Pt(IV)-

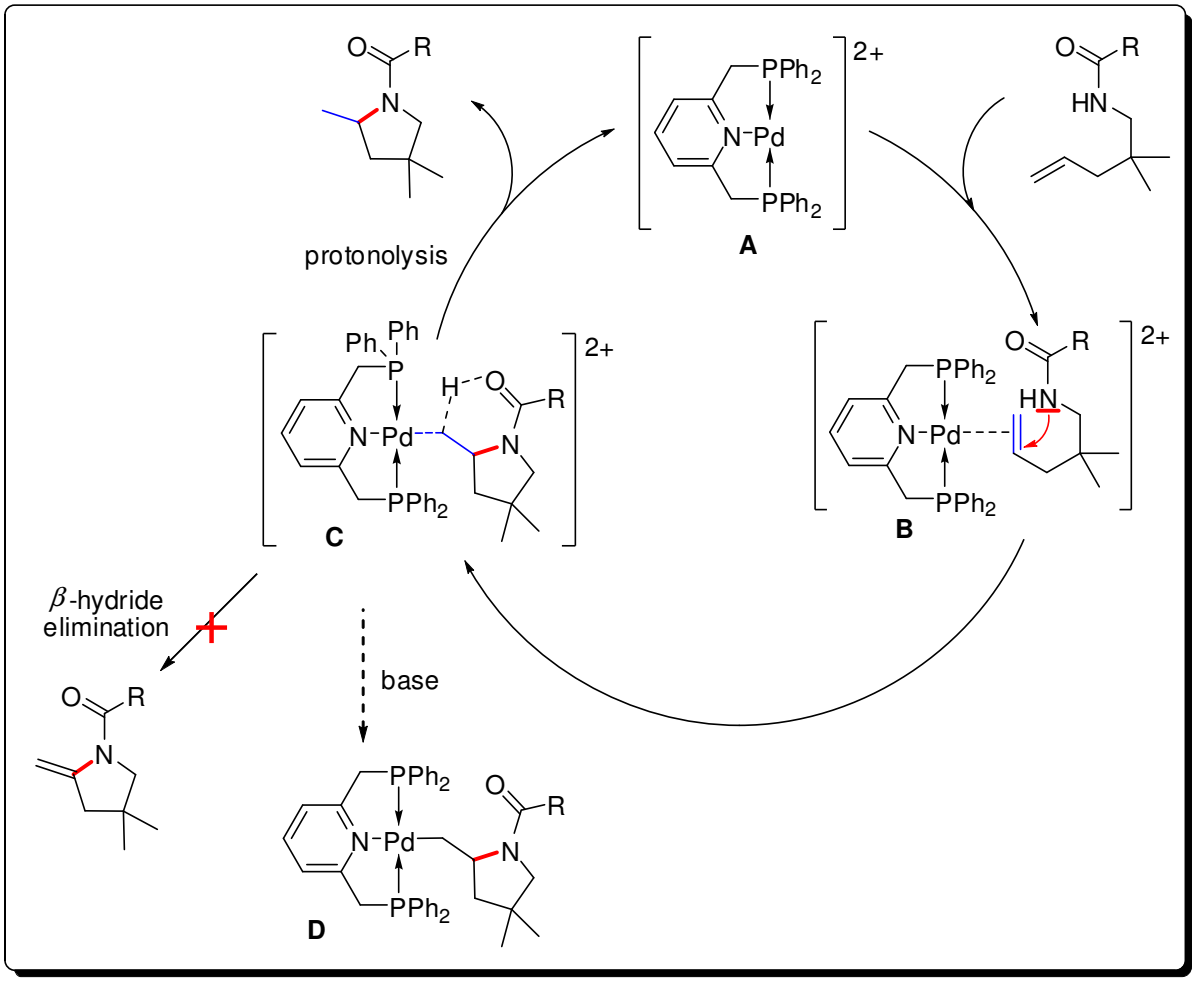
hydride intermediate (**E**), which in due course undergoes the reductive elimination to the desired pyrrolidine (**F**) and regenerates itself into the Pt-amine complex (**A**) (Scheme 21). In this place, it should be noted that authors do not give any fine mechanistic details of the transformation of **E** to **A** and leave out several intermediary stages, through which most likely proceeds oxidation as well as changes of type and number of ligands. Because of this and to clarify the transformation for the reader, we suggest the following mechanism of transformation of **E** to **A**: in the first step, proton from secondary amine attacks the Pt–C bond with simultaneous attack of the central metal by the electron pair of nitrogen from the N–H bonds. The desired product – cyclic amine (**F**) – is released. The formed Pt(IV)-amidoalkene next loses HCl by reductive elimination, thus lowering oxidation number of the metal from (+IV) to (+II). Since in the Pt(II)-complex (**A**) amine coordinates with the metal solely by its free electron pair, the last required step is the protonolytic cleavage of the N–Pt bond by HCl (Scheme 21).



Scheme 21

Pd-catalyzed hydroaminations of aminoalkenes have so far been possible only on *N*-carbamates as substrates. Such "deactivated" nitrogen cannot bind palladium tightly, that is why the preferred mechanism starts with activation of olefin (Scheme 22). The attack of carbamate nitrogen at the electron-poor double bond of the π-Pd-complex (**B**) forms the σ-Pd-complex (**C**). Due to favourable ligand neighbourhood, no

β-hydride elimination takes place and the protonolysis now generates the desired cyclic carbamate and regenerates the Pd(II)-catalysts **A**. As an indirect evidence of existence of the σ-Pd-complex (**C**), authors present the results of experiment with the stoichiometric amount of Pd salt. By the action of base, they could convert the formed Pd-alkyl complex (**C**) to a stable, isolable compound **D**. Moreover, addition of acid to this complex converted it to the desired product and the (PNP)Pd chelate (**A**). An NMR study of this step was used to exclude Pd(IV)-hydride complex as possible intermediate. (The expected shift of H^-anion in the range of 0 to −60 ppm was not observed). Authors also admitted they were fairly lucky in their choice of *N*-protecting group, as carbamate facilitated an intramolecular attack of hydrogen at the C–Pd bond, making possible and accelerating the protonolysis (Scheme 22).

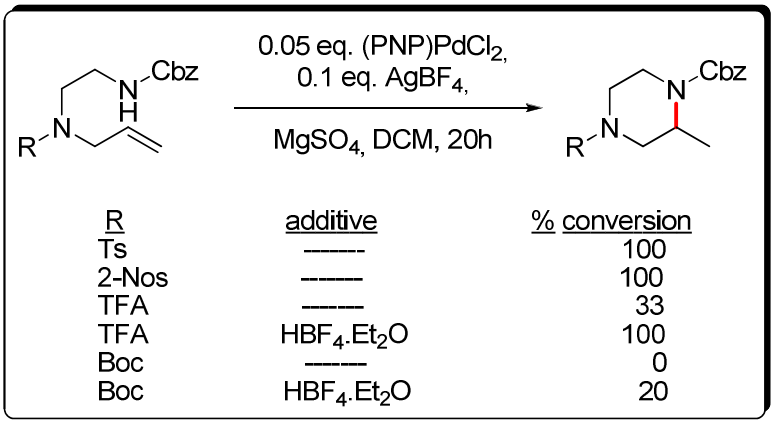


Scheme 22

Authors try to give indirect support to their theory by observed hydroaminations leading to piperazines (Scheme 23).[83]

In case of protection of the substrate nitrogen not taking part in hydroamination as trifluoroacetamide *vs.* sulphonamide (Ts, 2-Ns-), they observed slowing down of this transformation up to its total inhibition. Authors account for this by assuming that the slightly more basic trifluoroacetic group inhibits carbamate protonation (quenching the H^+ present in the reaction system) and prevents hydrogen attack at the newly formed Pd–C bond, thus inhibiting catalysis. This explanation however cannot be extended to an analogous case, namely secondary amine nitrogen protected by the Boc group, in which hydroamination is totally inhibited. The authors left the fact without comment. After acid ($HBF_4 \cdot OEt_2$) has been added as

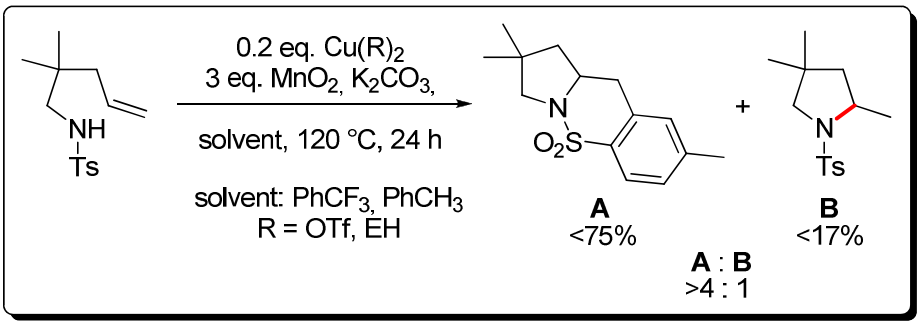
co-catalyst, providing plenty of H^+ to protonate the carbamate and amide, an almost total conversion of the TFA-protected carbamate was achieved. Unfortunately, addition of acid also removed the acid-sensitive protecting Boc group.



R	additive	% conversion
Ts	-------	100
2-Nos	------	100
TFA	------	33
TFA	$HBF_4.Et_2O$	100
Boc	------	0
Boc	$HBF_4.Et_2O$	20

Scheme 23

In the group of **metals**– Cu, Ag, Au – gold has been most often used to catalyze hydroaminations of non-activated aminoalkenes. Both copper and silver in the form of salts with the trifluoromethanesulphonic acid (triflates) catalyze hydroamination of unsaturated sulphonamides with the Thorpe-Ingold effect in DCE at 80 °C (Table 1, entries 154 and 155).[64] In 2007, Chemler isolated apart from the products of carboamination catalyzed by Cu(II)-salts[84] also hydroamination products as minor components of the reaction mixture (Scheme 24). Later in 2009, Sawamura described a catalytic activity of Cu(O*t*-Bu)(Xantphos) complex.[85] This catalyst is capable to cyclize primary and secondary alkenyl amines in alcoholic solvents at temperatures of 60–140 °C. Moreover, Cu(O*t*-Bu)(Xantphos) effectively cyclizes alkenyl aminodiols to the corresponding pyrrolidines and/or piperidines. However, only activated substrates displaying Thorpe-Ingold effect were successfully hydroaminated and even those often required prolonged reaction time.[86] The analogous prerequisite in necessary for the cyclizative hydroamination of secondary aminoalkenes using $CuBr_2$ and $AgBF_4$.[87] To the best of our knowledge, any other attempts to catalyze intramolecular hydroamination of non-activated aminoalkenes with silver are unknown.

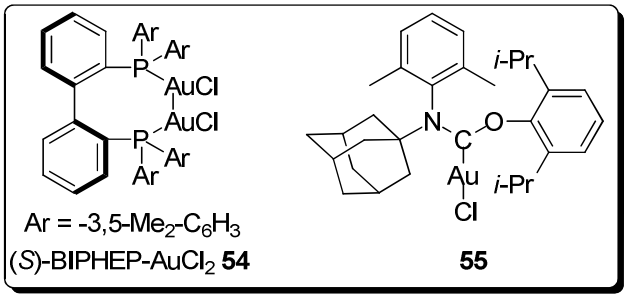


Scheme 24

The homogeneous catalysis by Au-complexes has in the recent decade evolved from mere rarity to the intensely studies wellspring of novel catalytic transformations.[88] The first intramolecular hydroamination of aminoalkenes (protected as sulphonamides) was published in 2006, in which He used catalyst effective in intramolecular hydroaminations – Ph_3PAuCl.[89] He cyclized substrates activated by the Thorpe-Ingold effect at 85 °C in toluene. Similarly, Sakurai showed the cyclization of analogous substrates using gold

nanoclusters stabilized by a hydrophilic polymer, poly(*N*-vinyl-2-pyrrolidone) (Au:PVP) in EtOH under aerobic and basic conditions at 50 °C.[90] The particular condition that mitigates the synthetic utility of these methodologies is the necessity to protect amine as sulphonamide, synthetically demanding reduction of tosyl protecting group at nitrogen and poor atom economy of (de)protection.

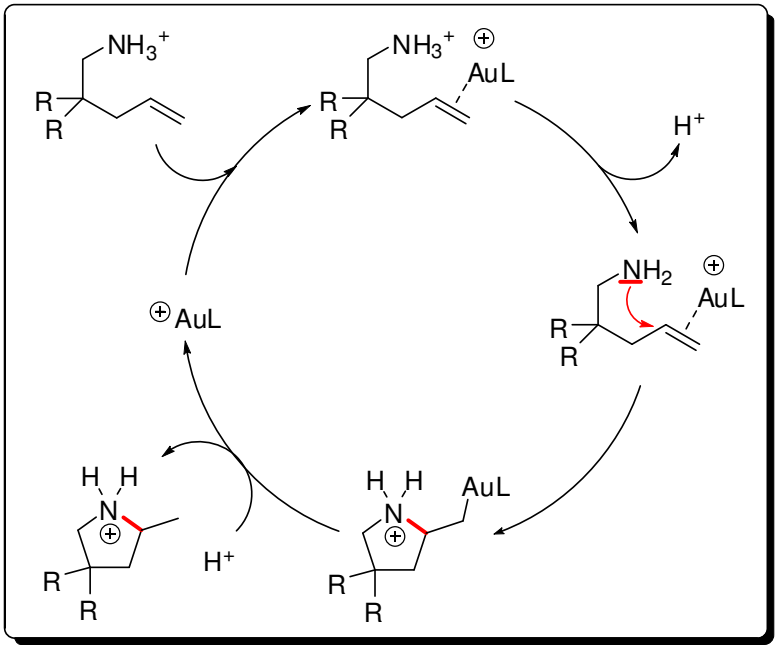
Widenhoefer dissatisfied with activity of the $[PtCl_2(CH_2{=}CH_2)_2]$ catalyst, with which he cyclized aminoalkenes at relatively high reaction temperature, sought a more active complex among Au(I) salts.[76] He carried out a study of the effect of phosphine ligand on the activity of $Au(PR_3)Cl$ in the cyclization of alkenyl carbamates as substrates (Table 1, entries 21, 285–291, 294, 296, 298–299, 415, 418, 421–422, 454, 456).[91] He observed that as far as the activity of complex is concerned in this class of substrates steric effects prevails over the electronic ones. The catalytic system consisting of 5 mol % [Au(P*t*-Bu_2(*o*-biphenyl)Cl] + AgOTf/dioxane/60 °C can tolerate a protected OH group or one equivalent of H_2O in the system. The Thorpe-Ingold effect facilitates the reaction (or alternatively thus activated substrates react at by 40 °C lower temperature than do their sterically non-activated analogues), but its utilization is not a condition. Later Widenhoefer expanded the range of substrates by *N*-alkenylureas, which underwent successful hydroamination reaction, catalyzed by Au-catalyst with NHC ligand.[92] The selected ligand (**L13**) (Scheme 17) represents an NHC-analogue of the successful *t*-Bu_2P(*o*-biphenyl)-Au – and it is not only a very good electron-donor, but it has also appropriate steric demands. The use of *N*-alkenylureas as substrates in combination with Au(**L13**)Cl allowed the reaction to be carried out at as low as room temperature. By exchanging dioxane for methanol, authors doubled the reaction rate, moreover super-equivalent amount of H_2O had no negative effect on either rate or yield. These results were a truly fruitful inspiration for others, as evidenced by the recent development of $AuCl_2$(BIPHEP) (**54**),[93] Au-aminooxycarbene (**55**)[94] and $[(Ph_3PAu)_3O]BF_4$[95] catalysts (Scheme 25), capable to cyclize *N*-alkenyl-ureas at room temperature and short reaction times.



Scheme 25

Hydroaminations of substrates with electron-donating substituent at nitrogen were unknown up until 2008, probably because of non-productive substitution of coordinated olefin with free amine and/or because of ineffective protonolysis of weakly acidic ammonium salt.[96] The idea was to introduce substrates in their protonated form in order to lower their basicity to a level where it would no longer preclude protonolysis, without causing significant drop in its nucleophilicity, which would inhibit the nucleophilic attack at the double bond. Even the most active, so far found Au-complexes, were not active enough for hydroaminations of thus protected aminoalkenes, by screening the reaction conditions, the authors could nevertheless find optimal combination of the Au salt, ligand and solvent (Scheme 17). The monodentate, sterically demanding phosphine ligand (**L15**) and AuCl in toluene catalyze hydroamination of substituted ammonium salts at 60–80 °C in 18–24 hours (Table 1, entries 232, 233, 405–412). The mechanism of Au-catalyzed

hydroamination of alkenyl-ammonium salts involves in its first step coordination of olefin with electrophilic central metal, followed by dissociation of ammonium salt and nucleophilic attack of amine at β-carbon of olefin. The thus formed Au-alkyl complex is then protodeaurated to furnish protonated cyclic amine and at the same regenerating the gold catalyst (Scheme 26).

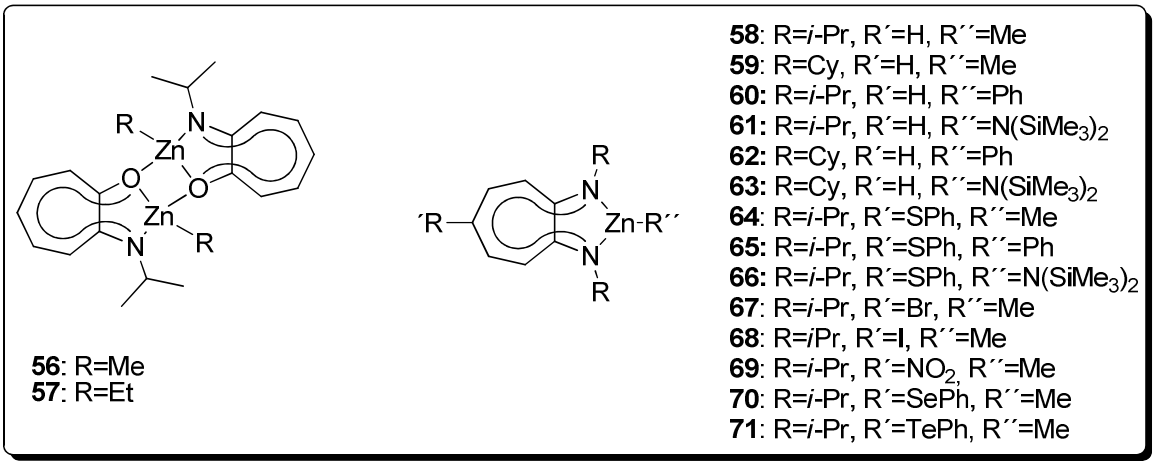


Scheme 26

In this proposal too Widenhoefer is being somewhat inaccurate:

- He assumes protonation of ammonium salt, ignoring the electrostatic repulsion of postulated cations,
- He fails to identify the base, which deprotonates the ammonium salt – the reaction medium contains only non-basic $[BF_4]^-$ and TfO^- anions; and since the entire substrate has already been protonated, it too can no longer play the role of base;
- Once again an improbable interaction of H^- and the cyclic ammonium salt during protodeauration gets postulated.

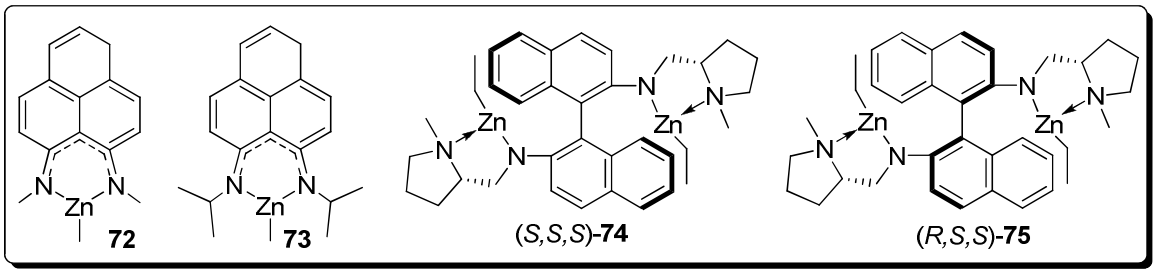
The zinc aminotroponiminate[97–100] and aminotroponate[101] complexes (Scheme 27) with their immobilized analogues[102,103] close the *d*-group of elements. They belong to complexes with weak catalytic activity.



Scheme 27

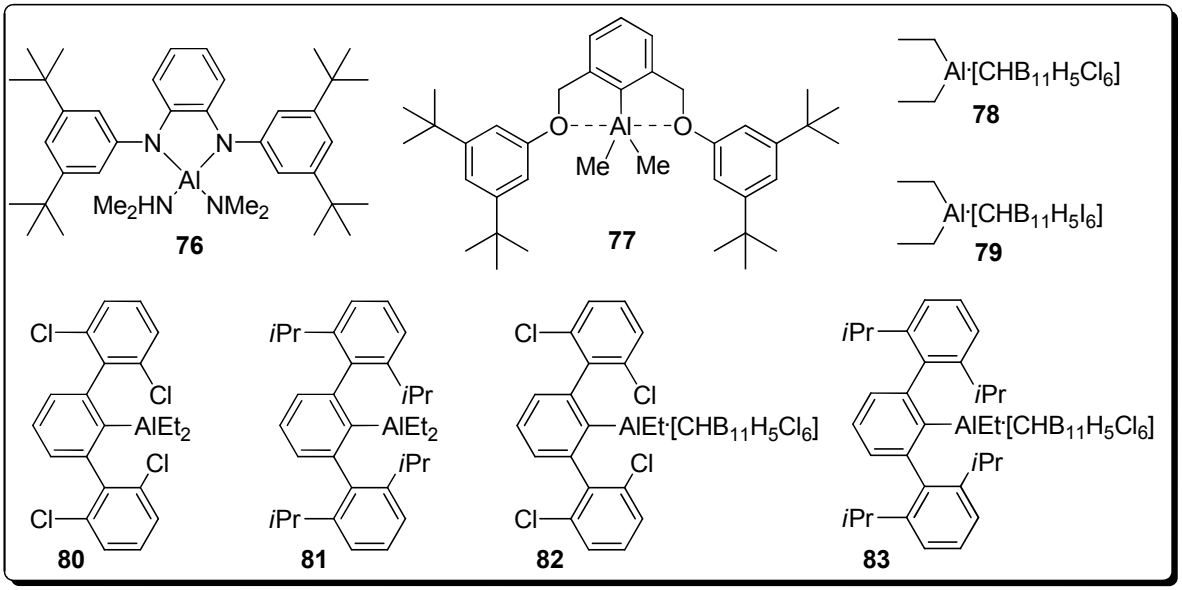
They are capable of catalyzing hydroamination of primary and secondary aminoalkenes with the Thorpe-Ingold effect in benzene at temperatures of 60–120 °C (Table 1, entries 126–129, 134, 135, 162, 163, 211–214, 257, 258, 367–370). They require higher catalyst charges and longer reaction times. Their biggest asset, improving their chances of industrial deployment, is their lack of toxicity and stability on air. Unfortunately, their preparation is all the more complicated, since $ZnMe_2$, the precursor of their preparation, is strongly pyrophoric.[97]

The pool of zinc-containing hydroamination catalysts was recently enriched by Zn-amides,[104,105] alkylzinc complexes[106,107] and also by rather less reactive complex of ZnI_2 with 8-hydroxychinoline.[108] However, the major drawback of these catalysts is their limitation to cyclize only activated substrates displaying Thorpe-Ingold effect, a feature that significantly reduces their synthetic utility (Scheme 28).



Scheme 28

The employment of post transition metals as hydroamination catalysts has been introduced only recently. In 2010, Bergmann described the catalytic activity of tetra- and penta-coordinated aluminium complexes as Al-amides[109] (**76**) and/or organoaluminium compounds with OCO-ligands (**77**).[110] Slightly more active cationic organoaluminium complexes (**78**, **79**, **82**, **83**) followed later (Scheme 29).[111] Generally, Al-containing complexes are less reactive hydroamination catalysts. They usually require activated substrates displaying Thorpe-Ingold effect, higher reaction temperatures (135–150 °C), prolonged reaction times (typically tens of hours) and often promote the undesired isomerization of terminal C=C double bond.



Scheme 29

So far, the latest post transition metal capable of (cyclizative) hydroamination is bismuth in the form of its hydrated triflate ($Bi(OTf)_3 \cdot nH_2O$) as an air and water tolerant Lewis acid. In 2011, Takaki performed the

tandem ene-reaction/hydroamination of reactive aminoalkenes and aminoallenes having Thorpe-Ingold activators using bismuth(III) triflate.[112] A year later, Mathia showed the successful cyclizative hydroamination of non-activated *N*-alkenyl-sulfonamides using the same catalyst, giving rise to 2-methyl pyrrolidines in good to excellent yields (up to 95%).[113] Based on extensive reaction screening and control experiments, the authors suggest that either a joint Lewis acid-Brønsted acid catalysis might be in operation, or triflic acid itself, generated *in situ* by hydrolysis of metal triflate, could be the true hydroamination catalyst (*cfr*. Chapter 2). However, since TfOH is extremely corrosive and difficult to handle, the practical use of $Bi(OTf)_3 \cdot nH_2O$ makes this methodology particularly valuable.

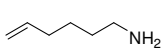
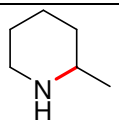
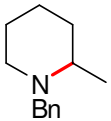
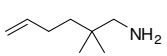
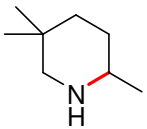
1.2. Synthesis of piperidines

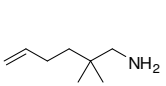
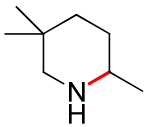
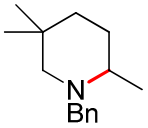
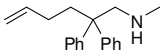
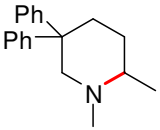
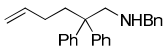
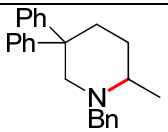
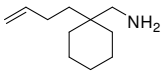
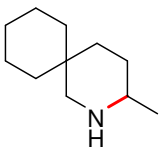
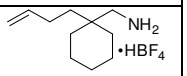
As it has been previously demonstrated (see Chapters 2.1. and 2.2. in Part 1), among the hydroaminations described in the literature strongly prevail those giving pyrrolidines over those leading to 6- or 7-membered cyclic amines – piperidines or azepanes. This imbalance is quite marked among the *d*-group metals.

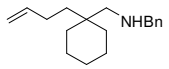
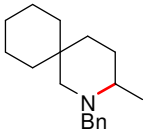
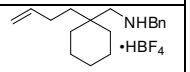
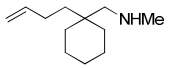
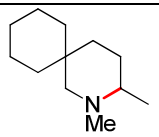
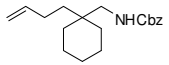
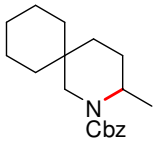
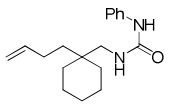
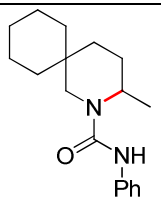
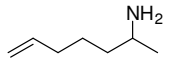
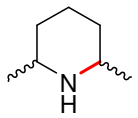
The hydroamination of 1-amino-hex-5-enes requires highly active catalytic complexes. To the most potent belong Y-thiolates **1**, **2** and **3** (Table 2, entries 8−10), affording piperidines with *ee* values of up to 80% at 60−75 °C (conditions comparable with pyrrolidines), but requiring a *gem*-dialkyl substitution on the their chain. Potent "half-sandwich" Zr-catalysts allow for fast hydroamination of sterically encumbered aminoalkenes with *ee* 58% (Table 2, entries 13 and 14), but their action is limited to primary amines only. Disubstituted amines do not undergo hydroaminations catalyzed by these metals and require reaction temperature over 100 °C. Out of all *d*-group metals the most outstanding catalysts are those sporting Pd(II) and Au(I) as central metals. They make hydroamination of alkenylcarbamates and alkenylureas at ambient temperature possible (NHC-Au-complex), in contrast to Y and Zr are much less oxophilic – they tolerate oxygenated substrates and solvents and the reaction is simple to conduct. What is more significant however, the $(PNP)PdCl_2$ complex **53** does not require activation by the Thorpe-Ingold effect at all (Table 3, entries 2 and 3). Au-complexes with sterically demanding, electron-rich, monodentate phosphine ligand too are suitable for preparation of piperidines by hydroamination of aminoalkenes, as they do not require strong acceptor at nitrogen, cyclize *N*-benzylated aminoalkenes in the form of ammonium salts, but require elevated reaction temperatures.

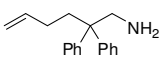
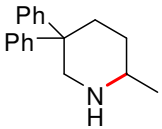
Because of limited number of the so far made reactions and variability of catalytic systems, it is very difficult to postulate general trends and tendencies for hydroaminations of aminoalkenes, leading to piperidines. The single most significant factor is probably the Thorpe-Ingo*ld* effect, introduction of *gem*-dimethyl in case of Zr-catalyst to use lower reaction temperature and to increase the reaction yield, albeit at twice as long reaction time (Table 2, entry 1 *vs.* 12). Likewise, *gem*-cyclohexyl chain on the substrate in a Pt(II)-complex catalyzed reaction gave markedly higher yields at ¼ of reaction time (Table 2, entry 5 *vs.* 28).

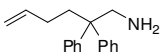
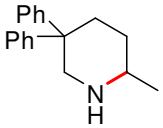
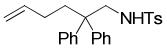
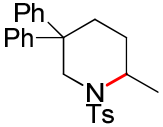
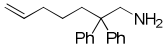
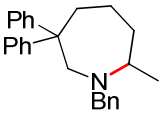
Table 2.

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
1	**L12**+$Zr(NMe_2)_4$/10			79[b,c]	toluene		135	24	*ee*=33	56
2	**45**-Zr/10			86[a]	C_6D_6		145	16		51
3	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			92	DCM		r.t.			77
4	2x$AgBF_4$+**53**-Pd+2x$Cu(OTf)_2$/5			76	DCM		r.t.			77
5	**L20**+$PtCl_2$/5			66	diglyme		80	96		78
6	**50**-Ir/2.5			0[a]	C_6D_6		110	16	complete substrate isomerization	73
7	1.2x**L11**+$[Rh(COD)_2]BF_4$/5			74	dioxane		70	7		65
8	(*R*)-**1**-Y/5			>95[a]	C_6D_6		60	18	*ee*=65 (*S*)	24
9	(*R*)-**2**-Y/5							10	*ee*=75 (*S*)	
10	(*R*)-**3**-Y/5						75	3	*ee*=80 (*R*)	
11	**39**-Zr/5			99[a]	C_6D_6		120	9		57
12	**L12**+$Zr(NMe_2)_4$/10			91[b,c]	toluene		85	48	*ee*=51	56
13	**30**-Zr/10			95[a]	toluene		110	1	*ee*=58	36
14	**31**-Zr/10			95[a]				0.5	*ee*=14	
15	**76**-Al/10			58[a]	C_6D_6		150	123		109

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
16	**72**-Zn+[PhNMe$_2$H][B(C$_6$F$_5$)$_4$]/5			2[a]	C_6D_6		120	24		105
17	**73**-Zn+[PhNMe$_2$H][B(C$_6$F$_5$)$_4$]/5			97[a]	C_6D_6		120	24		105
18	**47**-V/10			96[a]	C_6D_6		140	48	*ee*=32	63
19	**48**-V/10			90[a]	C_6D_6		140	48	*ee*=31	63
20	**25**-Y/2			>98[a]	C_6D_6	12.3	60	4		3
21	**52**-Pt+2xAgBF$_4$/3			90	benzene		80	48		80
22	Ti(NMe$_2$)$_4$/5			0	toluene		110	96		42
23	Ind$_2$TiMe$_2$/5			13[b]	toluene		105	24		28
24	**38**-Zr/10			96	C_6D_5Br		80	36		41
25	[Ir(COD)Cl]$_2$/5			72	dioxane		80	24		67
26	(*R*)-**L10**/YCl$_3$/4*n*-BuLi/6			84[a]	THF		r.t.	139	*ee*=36	8
27	(*R*)-**L10**/YCl$_3$/4*n*-BuLi/6			89[a]	C_6D_6			96	*ee*=38	
28	**L15**+AuCl+AgOTf/5			91	toluene		80	24		92

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
29	2xPPh_3+[$PtCl_2(CH_2{=}CH_2)$]/2.5			57	dioxane		120	6	slow addition of substrate	76
30	**L20**+$PtCl_2$/5			76	diglyme		60	9		78
31	**52**-Pt+2x$AgBF_4$/3			90	benzene		80	48		80
32	**L15**+AuCl+AgOTf/5			21[b]	toluene		80	24		33
33	Cu(O*t*-Bu)(Xantphos)/10			94	toluene/MeOH		100	24		85
34	[Au(P*t*-Bu_2(*o*-biphenyl)Cl] +AgOTf/5			84	dioxane		100	26		91
35	[Au(**L13**)Cl]+AgOTf/5			98	MeOH		r.t.	24		92
36	**55**-Au+AgOTf/5			94	dioxane		r.t.	48		94
37	**7**-Y/5			>95[a]	toluene-d_8		120	0.75	*cis*:*trans*=4:1	9
38	**8**-Y/5							1.5	*cis*:*trans*=5:1	
39	**9**-Y/5							0.25	*cis*:*trans*=4:1	

E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
40	$Ti(NMe_2)_4$/5			80	toluene		110	24		42
41	$Ti(NMe_2)_4$/5			76	toluene		105	24		27
42	Ind_2TiMe_2/5			89						
43	Cp_2TiMe_2/5			78						
44	$[Me_2Si(Cp)(t\text{-}BuN)]Ti(NMe_2)_2$/5			75						
45	$Ti(NMe_2)_4$/5			76[b]	toluene		105	24		28
46	Ind_2TiMe_2/5			89[b]						
47	Ind_2ZrMe_2/5			95[b]						
48	Ind_2HfMe_2/5			98[b]						
49	**32**-Zr/5			90	toluene-d_8		160	2		38
50	$[Zr(dpm)(NMe_2)_2]_2$/2.5			100[a]	toluene		100	15		36
51	$Zr(NMe_2)_4$/5			83				3		
52	**25**-Y/1			98[a]	C_6D_6	21.8	60	4.5		3
53	**49**-Ta/5			>95[a]	C_6D_6		120	36	*ee*=17	62
54	**33**-Ti/5			80[a]	toluene-d_8		160	93		38
55	**34**-Ti/5			4[a]	toluene-d_8		160	72		38
56	**38**-Zr/10			97	C_6D_5Br		100	17		41
57	**20**-Y/10			>95[a]	C_6D_6		65	1.8		20
58	**21**-Y/10			>95[a]	C_6D_6		65	0.8		20

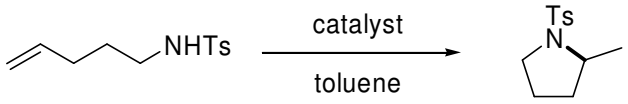
E	Catalyst/mol%	Substrate	Product	Y (%)	Solvent	N_t [h^{-1}]	T [°C]	t [h]	Comment	Ref.
59	**22**-Y/10			>95[a]	C_6D_6		65	0.8		20
60	**16**-Y/5			100[a]	C_6D_6		120	0.5		21
61	Au:PVP/5			99	EtOH		50	19	3 eq. Cs_2CO_3, air	90
62	**45**-Zr/10			90[a]	C_6D_6		145	20		51
63	**20**-Y/10			81[a]	C_6D_6		110	30		20
64	**21**-Y/10			85[a]	C_6D_6		110	21		20
65	**22**-Y/10			82[a]	C_6D_6		110	19		20

[a]Conversion determined by NMR. [b]Conversion determined by GC. [c]Isolated as *N*-trifluoroacetamide. [d]Isolated as 2-naphtoylamide. [e]Isolated as benzylcarbamate.

2. Catalysis by Brønsted acids – the future of intramolecular hydroaminations?

In the course of studies of Pd(II)-catalyzed hydroaminations of styrene tosylamides by the system 5% $Pd(PPh_3)_4$/20% TfOH, Hartwig observed in a control experiment without Pd-complex an intramolecular hydroamination catalyzed by Brønsted acid.[114] He expanded the scope of reaction to aminoalkenes with non-activated terminal double bond and achieved remarkable results. To his surprise, 20 molar % of trifluoro-methanesulphonic acid were capable of catalyzing hydroamination/cyclization of the above-mentioned substrates at temperatures up to 100 °C during 24 hours (Table 3).

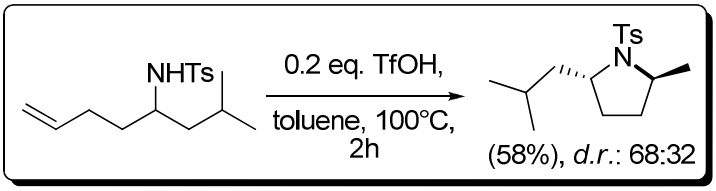
Table 3.



Catalyst/(%)	t [h]	T [°C]	Y [%]
TfOH/20	2	100	98[a]
TfOH/20	48	r.t.	75[a]
TFA/20	24	100	0[a]
AcOH/20	24	100	0[a]
C_6F_5COOH/20	24	100	0[a]
Tf_2O/20	2	100	95[b]
H_2SO_4/20	4	100	77[b]

[a]Conversion determined by ^1H NMR. [b]Yield after FLC.

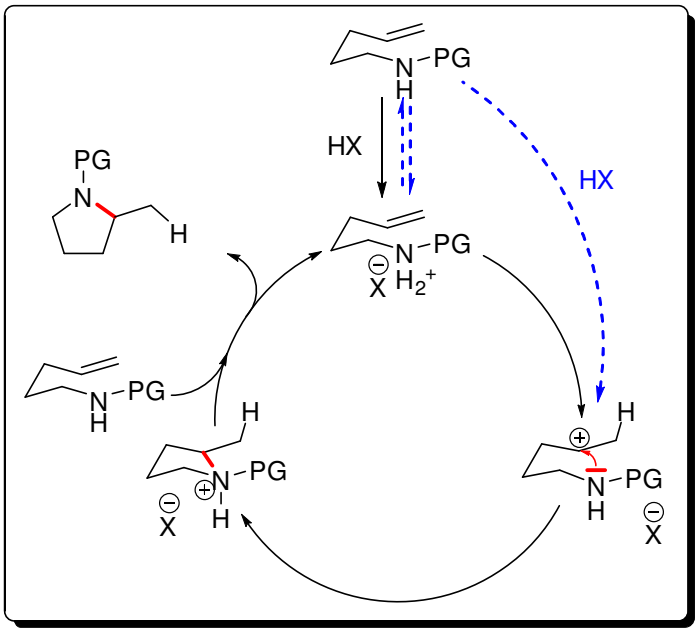
Under analogous conditions, Hartwig carried out also hydroamination of secondary alkenylamine; the furnished 2,5-*cis* and 2,5-*trans* pyrrolidines were present in the 32:68 ratio (Scheme 30).



Scheme 30

He also succeeded in cyclizing *N*-arylated amines to cyclic lactames and carried out screening of protecting groups at nitrogen of aminoalkenes with activated double bond. After comparing various reaction rates of formation of 5- and 6-memebered rings and total protonation of *N*-methylsulphonamide by one equivalent of TfOH, Hartwig suggested the intramolecular attack of protonated sulphonamide as the rate determining step. The mechanism postulated by him involves as its first step protonation of alkenyl tosylamide at nitrogen (or oxygen) of the protecting group, followed by the rate determining intramolecular proton attack on olefin, creating a carbocation trapped by the electron pair of nitrogen under formation of new C–N bond. By deprotonation of cyclic sulphonamide by another molecule of substrate, a product is formed and the catalytic cycle closed (Scheme 31). In view of the relatively low basicity of sulphonamide nitrogen, we consider protonation of substrate to be in a thermodynamic equilibrium. In other words, a

proportional representation of protonated sulphonamide and olefin cannot be excluded. A similar degree of plausibility possesses the attack of electron-rich olefin at proton without inevitable cooperation of substrate nitrogen (Scheme 31 – ***alternative version***).



Scheme 31

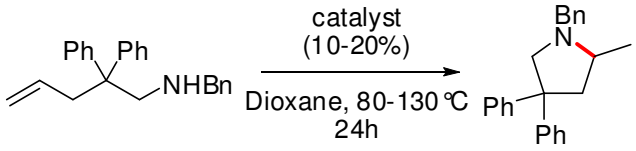
In 2007, Althammer and co-workers tested the ability of several Brønsted acids to catalyze hydroamination of aminoalkenes (Table 4).[57b] Out of the group of tested ammonium salts of organic and inorganic acids, [$PhMe_2NH^+$ $^-B(C_6F_5)_4$] and [NH_4^+ $^-O_2CCF_3$] stand out as the most potent ones. Under relatively hard reaction conditions (80–130 °C, 1,4-dioxane, 24 hours), they can transform a sterically highly encumbered substrate to the desired cyclic amine in good yields (Table 4).

The answer to the question put in the chapter title is obvious at the moment. The so far known hydroaminations catalyzed by Brønsted acids do not give much hope for their future use in the synthesis. Their probably only strong point is the price of catalyst and solubility in commonly used solvents. Their drawbacks on the other hand are higher catalysts charges needed, high reaction temperatures and relatively long reaction times, acidity of the medium and the corresponding limitations in the choice of substrate. There is also the fact that known examples of such hydroaminations have been limited to simple, unsubstituted aminoalkenes, made worse by the absence of any system for enantiomeric enrichment of products. Although plagued by various limitations, in special cases they may be useful in laboratory. However, if the reader – organic synthetic chemist – can find a way around those limitations, he may be awarded with an interesting and cheap method for preparation of unsubstituted pyrrolidines.

3. Summary and conclusions

Intramolecular hydroamination as synthetic methodology leading to saturated nitrogen heterocycles represents an extraordinarily attractive concept with enormous synthetic potential. It is a modern approach, as testified by the currency of papers dealing with this topic. Among its biggest assets must be counted its atom economy – the ability to effectively generate cyclic amine from acyclic substrate in a single step under preservation of molecular formula.

Table 4.



Catalyst/(%)	T [°C]	Y [%]
$NH_4^+ {}^-O_2CCH_3$/20	120	7[a]
NH_4F/20	120	<5[a]
NH_4Cl/20	120	5[a]
NH_4Br/20	120	5[a]
NH_4I/20	120	10[a]
$NH_4^+ {}^-O_3SCF_3$/20	130	20[a]
$(NH_4)BF_4$/20	120	25[a]
BINOLP(O)OH/20	130	33
NH_4PF_6/20	120	39
NH_4PF_6/20	130	44
$PhMe_2NH^+ {}^-B(C_6F_5)_4$/10	120	83
$PhMe_2NH^+ {}^-B(C_6F_5)_4$/20	80	76
$NH_4^+ {}^-O_2CCF_3$/20	120	56
$NH_4^+ {}^-O_2CCF_3$/20	130	74

[a]GC conversions.

The key feature of course is the possible control over generation of stereogenic centre, even in catalytic regimen. Consequently, there is no need for multiple reactants in suitable ratios, which inevitably wastes the above-stoichiometric reagent; moreover the catalyst can in principle be recycled. In an ideal case hydroamination proceeds fast, stereoselectively, with lowest possible amount of active catalyst, without substrate or solvents needing any special treatment. As is generally the case in practical synthesis hydroamination in its current state of elaboration does represent an ideal methodology. Let us review its (current) biggest assets:

- Catalysts are not active enough, a high charge of pre-catalysts, obtained by technically or economically demanding methods is necessary, possibly using high temperatures.
- Catalysts are often sensitive to water and air oxygen, thus requiring rigorous drying and deoxygenating of solvents, or even carrying out the experiment in a "dry-box".
- Often catalysts are quite expensive.
- The majority of reported experiments gives only GC or NMR conversions of substrates, very few real work up methods have been described and isolated yields given.
- The intolerance of catalysts of functionalized substrate is another problem, concerning mainly polar substituents (–OH, –CHO, etc.).

- For cyclization to be successful often Thorpe-Ingold activating substituents must be incorporated in the chain. Their introduction and subsequent removal reduces the potential of this methodology, requiring more steps to the desired synthetic target.

Walking through the periodic table, one can summarize the properties of catalytic complexes as follows:

Alkaline and alkaline earth metals

Complexes centred on these metals belong to potent catalysts of cyclization hydroamination, capable of catalyzing transformation of primary and secondary alkenylamines. They do not require steric effects facilitating ring formation, but if present, they allow for lower reaction temperature and/or shorter reaction times. The great advantage of BuLi is its low price, commercial availability and high activity in cyclizations of *gem*-disubstituted substrates even at laboratory temperature. Conversely, *n*-BuLi has marked tendency to isomerize olefins and does not allow incorporation of labile basic groups on the substrate chain. In addition, unlike in case of pyrrolidines, the preparation of piperidines requires the presence of Thorpe-Ingold activation substituents and increased reaction temperature.

Lanthanides and actinides

Lanthanides and actinides are currently the best known and most active catalytic system for hydroamination. Their biggest advantage is in some cases truly high activity and ability to cyclize both primary and secondary aminoalkenes and capability to achieve a tandem formation of C–N and C–C bond. Also, lanthanides and actinides achieved the highest enantioselectivity of this transformation with *ee* as high as 93% (see Part 1, Table 4, entry 127).

Its single biggest drawback remains the very high oxophility of catalysts and the related sensitivity to water and air oxygen. Standard experimental procedure of hydroamination catalyzed by these metals thus includes not only thorough drying and deoxygenation of solvents, but working in "dry-box", in the atmosphere of dry Ar or N_2. Oxophility of course governs the selection of solvents as well, the most common are hydrocarbons, rarely even THF. Finally the not to be underestimated factors include the price of catalysts – lanthanides and actinides and their salts cannot be counted among cheap catalysts. In addition the practical application of these reactions is handicapped by several synthetic steps needed to prepare the pre-catalysts and/or prices of enantiomerically pure ligands required for its synthesis.

Transition metals

Owing to the variability of properties of the *d*-group complexes, they spread over the entire virtual scale of activity. Y and Sc copy the properties as well as strong points of lanthanides and actinides (high enantiomeric enrichment of products), together with their disadvantages (mainly undesirable oxophility). Zr, Ti and Hf react with the intermediacy of a so-called metal-imide complex, thus excluding the use of secondary amines. Unfortunately they are just as oxophilic as Y, Sc and lanthanide and actinides. On the other hand, it was the zirconium complex that gave the *ee*=93%, thus enantioselectivity akin to that of lanthanides (Table 1, entries 96 and 97).

Complexes of Rh and Ir (**50**-Ir and **51**-Rh) stand out by their ability to catalyze hydroamination in water (albeit at fairly high temperatures) – sort of antipole to lanthanides and actinides. They are best suited

for preparation of pyrrolidines; hexenylamine cannot be transformed to the corresponding piperidine, rather the terminal double bond isomerizes to an internal alkene.

The dominant representatives of this group are catalytic systems [Pd(PNP)Cl_2/$AgBF_4$/$Cu(OTf)_2$], [Au(**L13**)Cl/AgOTf] and [AuCl/**L15**/AgOTf]. NHC complex Au(I) [Au(**L13**)Cl/AgOTf] proved to be a potent catalyst for cyclization of *N*-alkenylureas and amides, preferably activated by Thorpe-Ingold substituents; it does not require high reaction temperatures and/or too long reaction times. The reaction can be conducted both in dioxane and in protic solvents (MeOH) and even with the over-equivalent amount of water.

Hexenyl- or pentenylamines with/without electron-donating substituents at nitrogen are successfully cyclized by the [AuCl/**L15**/AgOTf] complex at elevated temperatures up to 80 °C in toluene.

Pd(PNP)Cl_2 appears to be the most universal catalyst both for pyrrolidines and piperidines. It allows cyclization of *N*-alkenylcarbamates in dichloromethane already at laboratory temperature, requires neither steric activators nor elevated reaction temperature for making piperidines (!) and even tolerates free hydroxyl group on the substrate chain. Its disadvantages at present is the inability to hydroaminate 2,2-disubstituted olefins and sensitivity of the PNP-ligand to oxygen. As soon as one has come to terms with its effective preparation and technical requirements of the procedure an attractive possibility for designing a universal and highly valuable synthetic methodology of cyclization hydroamination opens up.

Acknowledgments

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