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Preface

This book is dedicated to the memory of our friend Angelo Mugnoli

(Ω September 20, 2004)

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

Volume 8 (2004) keeps the international standard of THS series and contains fifteen chapters, covering the synthesis, reactivity, activity (including medicinal) and mass spectrometry of different heterorings. Reviews from France, Germany, Italy, Poland, Russia, Spain and Switzerland are present in this book.

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

Table of Contents

(for the contents of Volumes 1-8 please visit: http://www.soc.chim.it)

CYCLODEXTRINS: HETEROCYCLIC MOLECULES ABLE TO PERFORM CHIRAL RECOGNITION (PART I)

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In memory of Professor Marino Novi and Professor Angelo Mugnoli

Abstract. *The present paper collects the most significant advances appeared since late 1998 up to June 2005 in the field of chiral recognition performed by natural and modified cyclodextrins.*

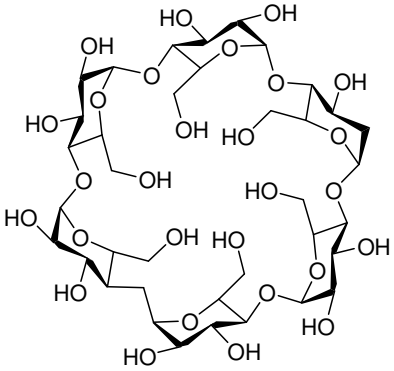
Contents

1. Introduction

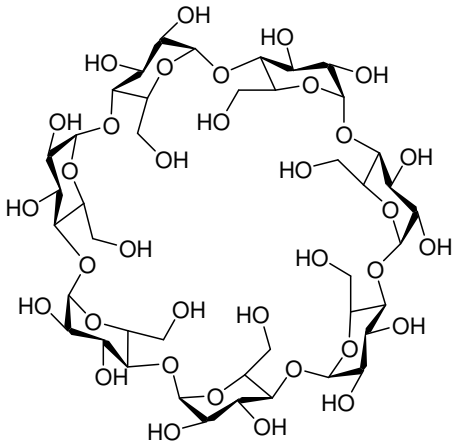
Enantiomeric discrimination/recognition is a topic of major importance in current supramolecular chemistry. It is a fundamental issue in biotransformations and enzyme catalysis, as well as a key step in stereocontrolled processes *in vitro* and in separation technologies.[1] Under this perspective, both natural and modified cyclodextrins have been object of an enormous interest,[2] as witnessed by the huge amount of work carried out during the last decades. Native cyclodextrins (Scheme 1), as cyclic oligosaccharides, are at the same time hetero-, poly- and macro-cycle hydrophilic molecules. Their bucket shaped and fairly flexible overall structure makes them able to form inclusion complexes with a very large number of suitably sized and structured organic species.[3] Because of the intrinsical chirality of their constituting sugar units, they are chiral molecules, and are consequently ideal candidates for performing supramolecular chiral recognition.

Indeed, the former examples reported in literature date up to the late 50's.[4] Moreover, it has been widely shown that inclusion and discrimination abilities[5] of cyclodextrins can be largely varied and tuned[6] by means of their chemical derivatization, *i.e.* by substitution of one or more (or even all) -OH groups, on either

the primary or the secondary cavity rim, with suitable pendant groups. Properties, transformations and utilizations of cyclodextrins are the subject of an immense literature. Papers on these topics appear at the rhythm of thousands every year, and are virtually countless. Reviews are periodically published. In particular, a volume of *Comprehensive Supramolecular Chemistry* (1996)[7] and an entire issue of *Chemical Reviews* in 1998 have been devoted to them. A specific review on enantiomeric recognition by cyclodextrins already appeared in 1996 too.[8] These publications constitute a sort of milestone in cyclodextrin literature. Since then, other minor reviews on particular topics have been published.[9-15]



α-Cyclodextrin (αCD)



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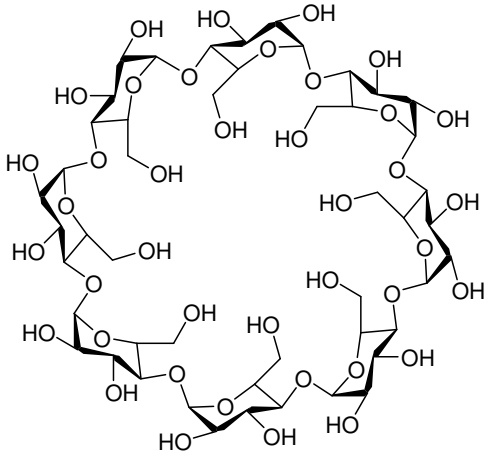
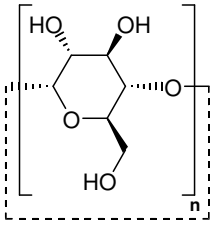


γ-Cyclodextrin (γCD)



αCD : n = 6
βCD : n = 7
γCD : n = 8

Scheme 1

Structures of native cyclodextrins.

The present paper is aimed to collect the most significant advances appeared during the last years (namely since late 1998 up to June 2005) in the field of chiral recognition performed by natural and modified cyclodextrins. In particular, we will focus mainly on the "conceptual" aspects of the recognition phenomenon, on its origin, characteristics and on investigation methodologies. Reviewing of particularly significant advances in "applicative" fields (recognition of pharmaceuticals and natural products, microanalysis, separation, asymmetric catalysis) will not be treated herein, but will be object of a future publication.

2. General features and concepts on chiral recognition by cyclodextrins

2.1. General concepts

Chiral discrimination ability is primarily related to the difference between the binding constants, K_R and K_S, towards the enantiomers of the same guest chemical species. Such a difference is the obvious consequence of the formation of two distinct diastereomeric complexes by the intrinsically chiral host, having different stabilities. Thus, an "enantioselectivity factor" α can be easily defined, as the ratio:

$$\alpha = K_R/K_S$$

which represents a quantitative measure of the discrimination effectiveness. Binding constants are usually measured by means of any suitable physico-chemical technique,[16] such as UV-vis spectrophotometry, circular dichroism (CD), NMR, potentiometric titration and, of course, microcalorimetry (data up to 1998 are collected in a review by Rekharsky and Inoue;[5] subsequent available data are collected and tabulated in appendix to the present paper). Fluorescence anisotropy[17-19] has been recently proposed as a useful technique in order to obtain thermodynamic information. Analytical techniques (HPLC,[20,21] GC,[22-24] CE[25]) may also be used for an evaluation of absolute binding constants. However for applications such as chromatography or electrophoresis, a selectivity factor is rather defined in terms of the different retention times of the enantiomers, which is matter-of-factly equivalent. It should also be mentioned that, from analysis viewpoint, the enantiodiscrimination might not be regarded as a strictly "thermodynamic" fact, but operationally as the actual possibility to detect distinct peaks on a chromatogram for the enantiomers. In a similar way, NMR discrimination may be simply considered as the ability for the chiral host to perform an effective signal splitting for the guest enantiomers. In this sense, evidence for enantiodiscrimination may also be obtained by FAB mass spectrometry.[26,27] Nonetheless, Near-Infrared spectrometry[28,29] and chemometric analysis of UV-vis spectra[30,31] have been recently proposed as useful methods for the determination of enantiomeric composition of mixtures.

Aminoacids, dipeptides, and their simple derivatives have been by far the substrates of choice in order to perform systematic studies on the discrimination abilities of cyclodextrins towards "central" chirality (see sections 3.1.-3.), because of their importance, easy availability, and particularly because of the possibility to explore the effects of large variations in guest molecular properties, such as hydrophobicity, polarity, steric hindrance, conformational freedom and charge (as a function of the pH value of the solvent medium). For the same purpose other simple classes of molecules, such as aromatic and aliphatic alcohols, amines and acids (section 3.4.), have been used too. Natural products (for instance camphor and related molecules, other simple terpene derivatives or alkaloids) have also been object of interest, particularly in the analysis field. However the structural complexity of this class of guests makes difficult to state any structure-discrimination correlation. Anyway these guests will not be considered in the present paper. Examples of discrimination towards axial or helical chirality have been occasionally reported (section 3.5.).

Despite any reasonable expectation, native cyclodextrins do not show outstanding discrimination properties.[5,32,33] Indeed, from data reported, calculated or measured selectivity factors rarely exceed the value of 1.25.[34] Much better results have been rather obtained with either chemically modified cyclodextrins (particularly with "non-symmetrically" substituted ones) and in more organized or sterically restricted or constrained systems, such as in ternary complexes. For instance, selectivity is usually poor for non-rigid guests experiencing sufficient conformational freedom within the host cavity.[32,33,35] In general, it is hardly possible to predict *a priori* the preference for a given stereoisomer. However it can be presumed that

selectivity does not change along a series of homologous chiral guests, provided that the hydrophobicity order of the groups around the stereogenic center does not change.[32] As it will be illustrated in detail afterwards, discrimination properties of cyclodextrins - as well as binding ability itself - are the result of a very fine balance between several (and often contrasting) interactions at a molecular level, so assessing any general rule is usually difficult. The general application of well assessed ideas, such as the "lock & key" or the "three point attachment" models,[36-41] has been variously discussed and sometimes questioned. Nonetheless, it has been proposed that appreciable recognition requires a sort of "structural cooperativity", irrespective of the overall binding strength. As a matter of fact, an enhancement in binding affinity, along a homologous series, frequently results in a reduction of chiral discrimination (in agreement with the reactivity-selectivity principle), owing to a "non-specificity" of the interaction forces.[33]

2.2. Thermodynamics of chiral recognition

Since K_R, K_S and α are only phenomenological parameters, their crude evaluation is not sufficient in order to gain a deep understanding of the intimate mechanisms involved in the discrimination process. Therefore, two complementary ways should be followed. The first one is the evaluation and discussion of the complete set of macroscopic thermodynamic parameters $\Delta G°$, $\Delta H°$, $\Delta S°$, Δc_P for the inclusion processes and of the differential enantioselectivity parameters $\Delta_{R,S}\Delta G°$, $\Delta_{R,S}\Delta H°$, $\Delta_{R,S}\Delta S°$. The second way is an investigation of the microscopic structural characteristic of the host-guest complexes, by means of experimental (NMR, crystallography) or computational tools.

Thermodynamic parameters can be obtained directly from calorimetric measurements or alternatively by application of van t'Hoff equation to binding constants. Moreover, it is also possible to obtain directly the differential parameters from selectivity factors measured by chromatography,[21-23] electrophoresis[42] or fluorescence anisotropy[17-19] at different temperatures, by means of a suitable data processing. The selectivity factor α is bound to $\Delta_{R,S}\Delta G°$, $\Delta_{R,S}\Delta H°$ and $\Delta_{R,S}\Delta S°$ by the relationship:

$$R\ \mathrm{T}\ \ln\alpha = -\ \Delta_{R,S}\Delta G° = -\ \Delta_{R,S}\Delta H° + \mathrm{T}\ \Delta_{R,S}\Delta S°$$

As well as inclusion itself, recognition may be either enthalpically or entropically driven or both. As a general guideline large negative enthalpy variations are usually attributed to the occurrence of strong van der Waals or hydrogen bonding, rather than electrostatic (ionic, dipolar), host-guest interactions.[32,43,44] Negative entropy variations are related to severe loss of conformational freedom for both host and guest on inclusion,[44] while positive entropy variations are rather attributed to desolvation phenomena, in particular when charged species interact.[37,45] At this regard, Rekharsky and Inoue introduced the interesting concept of "ordering entropy".[33]

In principle, we can properly speak of chiral discrimination only if $\Delta_{R,S}\Delta G°$ is significantly larger than its own indetermination. However, cases of scarce or no discrimination are not devoid of interest. As a matter of fact, we can properly claim for absolute lack of selectivity, indeed, only if also $\Delta_{R,S}\Delta H°$ and $\Delta_{R,S}\Delta S°$ values are negligible.[32] Nevertheless, it is not uncommon to find examples of no apparent selectivity to whom correspond significant $\Delta_{R,S}\Delta H°$ and $\Delta_{R,S}\Delta S°$ values. This implies an almost "perfect" compensation between inclusion enthalpies and entropies on passing from one enantiomer to the other, *i.e.* $\Delta_{R,S}\Delta H° = \mathrm{T}\Delta_{R,S}\Delta S°$. Enthalpy-entropy linear correlations for a series of homologous processes[46] ("isokinetic" or "isoequilibrium" compensation correlations), according to the general relationship:

$$\mathrm{T}\Delta S°_{\mathrm{i}} = \mathrm{T}\Delta \mathrm{S}°_{\mathrm{o}} + (\mathrm{T}/\Theta)\ \Delta H°_{\mathrm{i}}$$

are a well assessed topic in supramolecular chemistry that is very frequently discussed in the present context. Therefore, "perfect" compensation and lack of selectivity at room temperature implies that $\Delta_{R,S}\Delta S^{\circ}_{o} = 0$ J mol^{-1} K^{-1} and $(T/\Theta) = 1$. Differently, we could observe at the same time both compensation and selectivity. The occurrence of compensation accounts for a situation where, on increasing host-guest interactions along a series of guests, at the same time both a more exothermic process (*i.e.* a larger enthalpic gain) and a more severe loss of conformational freedom (*i.e.* a less favourable entropy variation) are involved. However, the actual origin of the compensation effect is still matter of debate,[44,46,47] owing to its extra-thermodynamic nature, and because it could sometimes be an artifact of the measurement method. Its correct interpretation has been variously questioned too, and there is yet no general agreement about some of its aspects. Thus, particular caution is needed when its occurrence in chiral recognition is taken into account in order to achieve any structural/microscopic information.

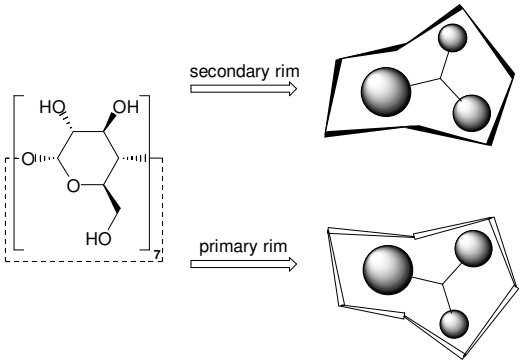
2.3. Molecular models…

The possible occurrence of the compensation effect, within a general overview of all available data, suggested that any lack in selectivity may be somehow related to the ability of both the cyclodextrin and the chiral guest to apt themselves onto each other, in order to gain the best reciprocal fit.[48] This, in turn, supports the idea of a quite flexible and "adjustable" host, contrasting with the familiar picture of cyclodextrins as rigid buckets. However, this obsolete image should be now definitively abandoned,[49] thus some words have to be spent about the point. Despite any common thinking, the formal C_n axial symmetry of natural cyclodextrins is a mere pictorial artifact, based on the assumption of an essential conformational steadiness. However, it has been largely demonstrated since the early'90s[50] that cyclodextrins may experience a quite fair conformational freedom, with consequent loss of the axial symmetry, owing to both the free rotation of the -C(6)H_2-OH units and the partially free rotation around the glycosidic bonds. This dynamic behaviour occurs not only in the gas phase or in solution, but to some extent also in the solid phase, as recently reviewed.[49]

Now, the question is whether and how we can draw up any suitable microscopic model able to account for the interactions working at molecular level, when the recognition phenomenon occurs, and thus correlating the structural features of the host, the chiral guest and their complex. As it will be illustrated in the following sections, the general idea is now currently agreed that recognition may be somehow related to the interaction of the stereogenic unit of the guest with either rim of the cyclodextrin, rather than with its inner cavity. This idea has been supported by Rekharsky and Inoue[32] and by Liu,[51] and has been particularly developed by Kano,[52,53] who used it in order to explain the reverted selection of different modified cyclodextrins towards some helical transition metal complexes (see section 3.5.). Kano's model considers that the two cyclodextrin rims possess a somewhat specular helicity, due to both the intrinsical chirality of the sugar units and a suitable distortion of the cavity itself, as shown in Scheme 2. It is worth noting that the loss of C_n symmetry for the host is consequently a key point in discrimination ability. The latter statement easily explains the observation that partly modified (and low symmetry) cyclodextrins usually show much better selection abilities than natural or symmetrically modified ones.

Investigation on the microscopic structural features of cyclodextrin complexes may be carried out with either experimental or computational techniques. Among the former ones, NMR[10] has by far played the most important role. ROESY experiments, in particular, allow to individuate the correct mode of penetration and

to get a reasonable picture of the mean behaviour of the guest within the host cavity. It should be remembered that NMR is a "slow response" technique, and therefore it allows to get time-mediated information. NMR results have been object of a very recent review by Dodziuk,[10] so we will not discuss them in detail herein, but we will occasionally cite some particular result in the following sections when needed. Nevertheless, it is worth just mentioning here that modified cyclodextrins able to act as ligands towards lanthanide ions, have been used as supramolecular shift reagents.[54-56] Microscopic information have been also occasionally obtained by UV-vis, CD[57,58] and, of course, by crystallography for the solid phase. The latter technique has been used only occasionally, in particular as support in studies on the bulk-scale enantioseparation by differential precipitation of the two different complexes.



Scheme 2

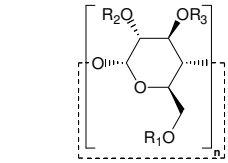
Kano's model for cyclodextrin inclusion complexes (each bold or empty triangle represents a glucose unit).

2.4. …and Molecular Modeling

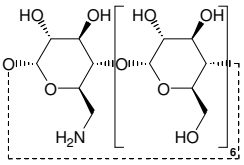
Proceeding with the previous discussion, in the present section we will briefly report on the most recent computational studies. Molecular Modeling techniques have been occasionally used in chiral discrimination studies; three reviews by Lipkowits cover the subject up to 2000.[59-61] In principle, computation offers the fascinating perspective to provide us with an easy way to get insights into the intimate life of host-guest complexes. However, there are also some serious difficulties to face. Indeed, systems involving cyclodextrins are "large" for a quantum-mechanical approach, and plenty of conformational freedom degrees makes the corresponding potential energy surfaces extremely complex.[59] Thus, very large cpu time and hardware resources are needed to accomplish a reliable computation, in particular if also an explicit solvent environment has to be taken into account. As a consequence, conformational searches and sampling of the potential surfaces become a hard work, and searching for full geometry optimized minima can easily afford artifact results. Moreover, these systems usually have several different conformations very close in energy, so that searching only for a full-optimized absolute minimum energy structure could be somewhat pointless.

In order to cope with these problems, Molecular Dynamics (MM-MD)[45] or Monte Carlo (MC)[62] calculations have usually been the approach of choice; different force fields (MM2, MM+, MMX, AMBER, CHARMM, CVFF, CFF91, Tripos) have been used for this purpose. It is worth noting that, as well as NMR, these kinds of calculations provide with a time-mediated picture of the inclusion complex. However, computations are frequently used only for qualitative comparisons with experimental findings, so several papers report only some suitable optimized minimum energy models. Such models can be obtained starting

from the dynamic simulation pool or from a sort of "hand made" docking sampling. Energy minimizations and geometry optimizations are sometimes accomplished dynamically by Simulated Annealing techniques. A recent example is provided in an investigation by Lebrilla on the structure of inclusion complexes formed by heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin **1** (Scheme 3) with some aminoacids.[63] Recently Cai introduced a particular Fast Annealing Evolutionary Algorithm (FAEA) for the same purpose;[64] this technique was used for instance to study the inclusion of a group of aminoacids with αCD. For the sake of completeness, it has to be mentioned that in a few occasions a semi-empirical (AM1) quantum mechanics approach has been attempted for similar systems,[65-67] despite Lipkowitz advised against this.[59]



	n	R_1	R_2	R_3
1	7	Me	Me	Me
10	7	H	Ac	Ac
11	7	SO_3H	H	H
12	7	SO_3H	Ac	Ac
13	7	H	Me	Me
22	8	(^{t}Hex-Me_2)Si	Me	Ac
23	8	(^{t}Hex-Me_2)Si	Ac	Me
25	7	(^{t}Bu-Me_2)Si	Me	Me



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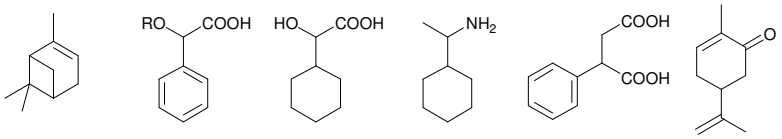
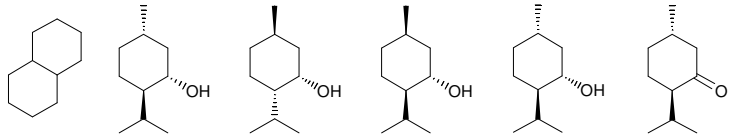
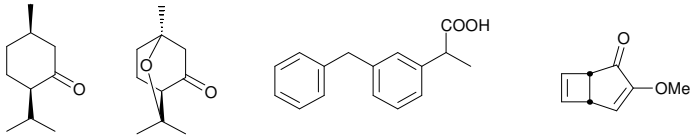


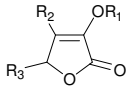
2 **3** : R=H, **6** : R=Ac **4** **5** **7** **9**



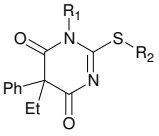
14 **15** **16** **17** **18** **19**



20 **21** **24** **34**



	R_1	R_2	R_3
26	H	Me	Me
27	Me	Me	Me
28	H	Et	Me
29	H	Me	Et



	R_1	R_2
30	Me	H
31	H	Me
32	Me	Me
33	Et	H

Scheme 3

The joint use of NMR and computational studies may constitute a powerful tool for structural elucidation studies. Recent examples are reported concerning the study of the interaction between α-pinenes **2** and αCD,[68,69] enantiodiscrimination of mandelic acid **3**, hexahydromandelic acid **4** and 1-cyclohexyl-ethylamine **5** by βCD,[70] enantiodiscrimination of acetylmandelic acid **6** and phenyl-succinic acid **7** in their anionic forms with mono-(6-amino)-(6-deoxy)-βCD **8**,[71] inclusion of carvone **9** enantiomers in βCD[65] or the inclusion of Ala-Phe and Ala-Tyr dipeptides in βCD, heptakis-(2,3-*O*-diacetyl)-βCD **10**, heptakis-(6-*O*-sulfate)-βCD **11** and heptakis-(2,3-*O*-diacetyl-6-*O*-sulfate)-βCD **12**.[72] A nice example of a joint use of NMR, EPR, ESI-MS and MD calculations on the inclusion of several chiral nitroxydes and amines in heptakis-(2,6-*O*-dimethyl)-βCD **13** was recently provided by Lucarini and Mezzina[73] (see section 3.4.).

Beside structural elucidation problems, computational information has been used to support investigations on analytical separations. This means to predict or rationalize the correct preference for one stereoisomer and, in particular, the difference in energy among the inclusion complexes. In these cases it may be particularly interesting to explore interactions acting at a molecular level. Unfortunately, the validity of quantitative computational results has been recently questioned.[68,74] One major point is the fact that usually the two different complexes are very close in energy (a difference of 0.2 kJ mol^{-1} is often sufficient in order to observe chromatographic or electrophoretic peak resolution).[49] The second, more important point is the simulation time, that can hardly exceed few ns. It has been shown that a wrong choice could affect the final result, if one is not sure that convergence has been really achieved.[68] There is a recent example of comparison between different force fields in predicting the affinity of βCD for the stereoisomers of decalin **14**.[74] It was found that reliability of results is only qualitative. Although this is only a very particular system (it should be taken into account that no specific interaction could be ascribed to the simple aliphatic guest), nonetheless it shows that particular caution is needed in evaluating computational results.

Mendicuti[75] analyzed the components of the binding energetics between a group of mentane terpenoids (menthol **15**, *neo*-menthol **16**, *i*-menthol **17**, *neo*-*i*-menthol **18**, menthone **19**, *i*-menthone **20** and 3-oxo-1,8-cineole **21**) and octakis-(2-*O*-methyl-3-acetyl-6-*O*-(*t*-hexyl-dimethyl)silyl)-γCD **22** or octakis-(2-acetyl-3-*O*-methyl-6-*O*-(*t*-hexyl-dimethyl)silyl)-γCD **23**. Jung[62] discussed more simply the chiral recognition of Fenoprofen **24** in terms of total interaction energies and structural parameters. Study of potential surfaces was exploited by Höltje[76] to investigate the interaction between heptakis-(2,3-*O*-dimethyl)-(6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **25** and four dihydrofuranones **26**-**29**. The methodology adopted allows simulating the multiple contacts between host and guest, and in particular outlines the importance of hydrogen bond in both binding and enantiorecognition. Similarly, Jung[45] investigated the interaction of *N*-acetyl-Phe with βCD, by means of Poisson-Boltzmann surface area approach (for discussion see section 3.1.). More trivially, AM1 semiempirical calculations were used by Zborowsky[66] to predict the correct order of elution of the enantiomers of four thiobarbituric **30**-**33** acid derivatives in reversed-phase HPLC in the presence of βCD as chiral additive. The Author used an arbitrary docking procedure to obtain only suitable minimum energy fully optimized structures. Sohlberg[67] also studied the interaction of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one **34** with βCD by means of AM1 calculations to predict the order of elution of the enantiomers in GC. In this case the Author used a docking procedure to generate a set of starting structures, which were optimized and whose energies were submitted to statistical analysis.

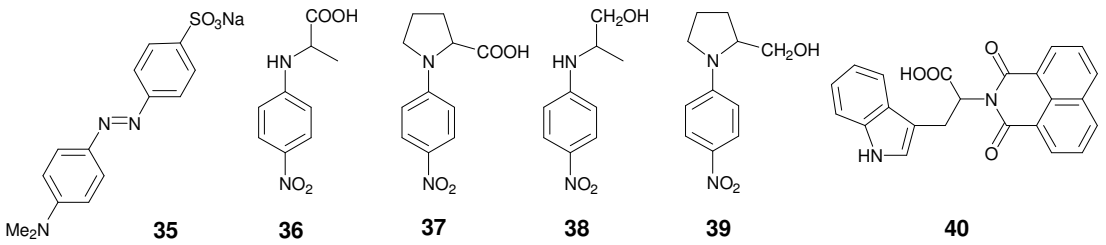
3. Chiral recognition on stage

In the following sections we will present the latest acquisitions on chiral discrimination properties of cyclodextrins by the "conceptual" viewpoint. Applications or uses in analytical context are not considered here, however we will cover also some paper dealing with analysis techniques when pertaining to the present subject.

3.1. Recognition of aminoacids, peptides and their derivatives (1): native cyclodextrins

Affinity of native cyclodextrins towards non-derivatized aminoacids is generally poor, with most of the binding constants reported having values below 100.[5,64,77] Therefore, calculated enantioselectivity ratios seem sometimes excellent, but caution is needed in order to evaluate any report, because of high

experimental indeterminations. Most of earlier data have been obtained by calorimetric measurements. More recently other experimental approaches have been tried.



Scheme 4

Shaomin[78] for instance used competitive spectrophotometric titration in order to evaluate the binding constants between some α-aminoacids and αCD in acidic medium. Methylorange **35** (Scheme 4) was used as molecular probe. A good chiral selection between the enantiomers of leucine (α=1.35) was found; however, lack of any information on experimental indetermination, within a general overview of the work, makes the finding questionable. Holzgrabe[79] used potentiometric titrations to study the behavior of αCD and βCD towards several aliphatic and aromatic aminoacids and dipeptides. His approach allows to obtain the binding constants of both the zwitterionic and anionic forms of the guests, but suffers for the fact that determinations are carried out in not-buffered systems at continuously varying pH values. Under these circumstances, binding constants significantly different from other literature reports are found, and experimental indeterminations are often high, in particular when complexes with a 2:1 stoichiometry may be formed together with the expected 1:1 complexes. Apparently very good selectivities are found for bulky aminoacids (α up to 7.0), which may afford also good separations in capillary electrophoresis, but data are not further discussed. Capillary electrokinetic chromatography was used by Waldron[80] to obtain the binding constants with βCD for the stereisomers of Ala-Phe and Leu-Phe in acidic buffered media and in presence of urea as additive; also in this case selectivities were poor (α up to 1.1).[81]

Much more attention has been devoted in the last years to derivatives of aminoacids and peptides. Rekharsaky and Inoue have examined in several occasions the thermodynamic behaviour of native (as well as variously modified, see below) cyclodextrins towards several classes of guests, including aminoacids and related molecules. Examination of a series of Phe derivatives,[32] in comparison with some suitable derivatives of Ala, Tyr, and Trp, led the Authors to the conclusion that an effective enantioselection (up to α=1.35) in favour of the *S* (*L*) isomer can be achieved when the stereogenic center is held near the secondary host rim, irrespective of the actual binding affinity (which is in turn influenced by several different factors, such as the hydrophobicity of the guest, its charge and the actual distance between the cavity and any occurring charged group). It is worth noting that selection can be inverted in favour of the *R* (*D*) isomer by *N*-derivatization of the guest with a highly hydrophobic group (α values up to 1.14). In this case it may be presumed that the latter group is the one actually included into the cavity. Selectivity is entropy-driven in some cases, enthalpy-driven in others, with no satisfactory rationale. These conclusions are partly in disagreement with the data reported by us,[44] on examining a series of *N*-(*p*-nitrophenyl)-amines, including the derivatives of Ala **36** and Pro **37** and the related alcohols alaninole **38** and prolinole **39**. Indeed, the *S* isomer of all these derivatives is preferred by βCD. Selection is enthalpy-driven for **37** and **39**, but entropy-driven for **36** and **38**, as a function

of the number of hydrogen bonds allowed for the "ancillary chain" of the guest. In fact, these guests have to be included in two different enthalpy-entropy compensation plots, having different Θ values. It is interesting to notice that no significant selection towards the aminoalcohols is shown by αCD, while a modest selection is found for the aminoacid derivatives, that is inverted on passing from pH=2.5 (α up to 1.23) to pH=6.0 (α up to 1.11). The latter finding is in agreement with some similar observations by Waldron.[80] For the sake of completeness, it is worth mentioning that computational results by Jung suggest the occurrence of different conformational population distribution induced by the host on the guest enantiomers, which may justify the fair enantiodiscrimination of *N*-acetyl-Phe by native βCD.[45]

Rekharsky and Inoue also examined the behaviour of some derivatives bearing two aromatic rings.[48,82] These guests can selectively insert one of their aryl groups into the relatively small αCD or βCD cavities, but they are able to introduce both rings in the widest γCD. In this context, NMR has been an effective tool in order to individuate the correct inclusion mode. With *N*-Cbz-Glu-Tyr, for instance, αCD and βCD include preferentially the more hydrophobic carbobenzyloxy moiety. With γCD the two aromatic groups are co-included, but they can surprisingly assume at least two different arrangements within the host cavity. Rings co-inclusion is interesting, on the assumption that non-covalent stacking interactions could be able to induce significant enantioselectivity, due to steric and conformational requirements. Under this perspective the characteristics of the chain tether linking the rings can constitute very important factors. The Authors found in general relatively modest affinities and enantioselectivities for these derivatives (up to α=1.6), which become lower on increasing the tether length and conformational freedom, but also excellent diastereoselectivities (up to α=7). These effects are generally entropic in origin, and depend also on the solvation of the tether, so that interesting consideration on conformational equilibria for proteins could be inferred. The same Authors examined also the binding properties of βCD and γCD towards *N*-dansyl-Phe and *N*-naphtyl-Phe.[83] Owing to the bulky *N*-derivatizing group, γCD was found to be a better ligand, and inclusion is enthalpy-driven due to the occurrence of large van der Waals interactions. Curiously the *S* isomer of *N*-naphtyl-Phe is preferred by βCD (α=1.72), whereas in the other three cases the *R* isomer is preferred, as expected (α up to 1.6). On the basis both thermodynamic and NMR data, the finding was explained admitting the occurrence of a peculiar "perpendicular" penetration mode into the host in the former case. Data, in general, suggested that chiral selection increases on increasing the depth of guest penetration.

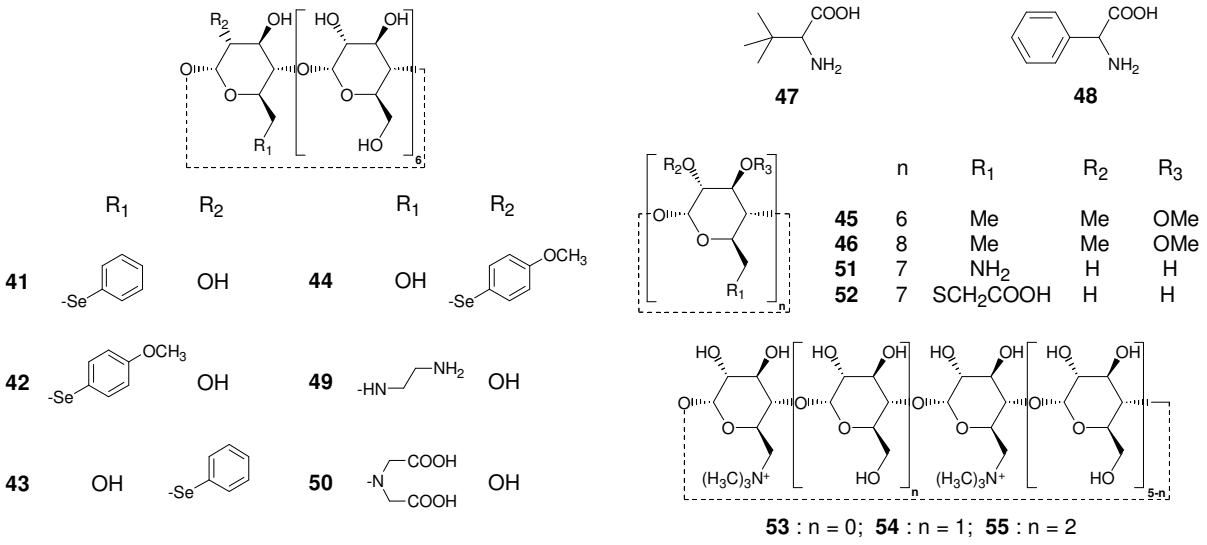
Co-inclusion of different aromatic groups has been exploited also by Jursic[84] for a curious recognition experiment on benzo[*de*]isoquinoline aminoacid derivatives. On the basis of NMR and MS evidences, the Author found that the tryptophane derivative **40** may form polymeric assemblies in the presence of γCD due to the favourable π-π stacking of the electronically complementary rings of subsequent guest molecules, held together by the γCD units. Similar assemblies are not formed by the alanine or phenylalanine derivatives, or in the presence of αCD or βCD. As a consequence, outstanding NMR signal splitting is observed for the racemate in the presence of γCD; partial splitting is observed also for βCD, due to the formation of the usual 1:1 complex. However, apparent thermodynamic parameters indicate βCD as the best selector.

3.2. Recognition of aminoacids, peptides and their derivatives (2): modified cyclodextrins

Chemical modification of cyclodextrins[85,86] can deeply change their physico-chemical properties and affects the microscopic interactions with a given guest. Modification may be accomplished on either the

primary (narrow) or secondary (wide) host rim, may regard one or more or even all the hydroxyl groups on a rim, with the introduction of neutral, anionic or cationic (stably charged or ionizable) pendant groups.

Studies on chiral recognition of aminoacids and their derivatives have rarely dealt with hosts bearing neutral pendant groups, because their presence only affects hydrophobic interactions. Liu recently synthesized a series of mono-(phenylseleno)-βCD **41**-**44** (Scheme 5), and studied their selection properties towards some aminoacids.[87] Aromatic pendant group are well known to give usually self-inclusion, as demonstrated in this case by CD spectra. Discrimination properties of these cyclodextrins seem excellent, with selectivity values up to 8.4 for Leu; however there is no neat preference for one enantiomer over the other (the *S* isomer is preferred in 10 cases on 15). Unfortunately, evaluation of the differential thermodynamic parameters was not performed. Inclusion complexes of Leu enantiomers were also studied by means of NOESY NMR. Surprisingly, completely different interaction modes were found for the two enantiomers: the *S* form is completely embedded within the host cavity, together with the co-included pendant group; differently the *R* enantiomer partly protrudes with its zwitterionic head out of the primary rim, whereas the pendant group is outside the cavity. Liu's work is one of the rare examples of the use of a 2-substituted-cyclodextrin (it is well known, indeed, that chemical modification of the primary hydroxyl groups of a cyclodextrin is by far easier to accomplish!).



Scheme 5

Liu and Inoue recently synthesized a series of phosphoryl-tethered βCDs,[35] and used them in particular to study their inclusion thermodynamic properties towards *N*-Cbz-Ala. The *R* enantiomer is generally preferred, with good selectivities (up to α=2.2), probably owing to ineffective enthalpy-entropy compensation due to the particular tether groups. Discrimination abilities of permethylated αCD **45**, βCD **1** and γCD **46** towards some aminoacid 2-propyl esters (Ala, Val, *t*-leucine **47**, Trp, Phe, phenylglycine **48**, Pro, Ser, Met) was also evaluated by Shizuma using FAB-MS techniques.[27] Discrimination ratios do not exceed the value of 1.3, but seem in fair agreement with values measured in solution. The gas-phase behaviour of **1** and **46** towards simple aminoacids has been thoroughly investigated by means of MS techniques also by Lebrilla.[36,63,88] In particular, he studied the guest exchange reaction between the protonated cyclodextrin-aminoacid complexes and suitable alkylamines. Kinetic enantioselectivities (k_S/k_R)

can vary from 3.8 (exchange Ile – *n*-propylamine) to 0.67 (exchange Tyr – *n*-propylamine) in the presence of **1**. Data suggest that a good dimensional host-guest fit is a crucial factor in determining a good enantioselectivity, which seems to pass trough a maximum on increasing guest dimensions. Computational models[63] seem to suggest that different interaction modes occur for the inclusion of Val enantiomers (resulting in a high k_S/k_R ratio), whereas enantiomers of Phe or Tyr (low k_S/k_R ratio) are forced to interact similarly. Experimental results are also discussed under the perspective of the "three point attachment" model,[36] suggesting that the occurrence of two attractive and one repulsive interactions constitute the optimum condition to observe high enantioselectivity. As a further development, such guest exchange reactions have been exploited as a suitable methodology for enantiomeric excess determination,[36,88] by the use of both Fourier-transform (FTMS) and quadrupole ion trap (ITMS) mass instruments. It is worth noting that in the latter case lower selectivity ratios are observed, owing to the peculiar operational conditions.

Most of the works dealing with modified cyclodextrins and aminoacid derivatives use charged or easily ionizable hosts as selectors. As a matter of fact, this allows to study how the occurrence of electrostatic interactions, along with the other usual interactions, may affect both binding abilities and chiral recognition properties of the host - considered that also the guests may be charged, depending on the pH value of the aqueous medium. Lincoln, for instance, studied the interaction of Trp and Phe with mono-(6-(2-amino)ethylamino)-(6-deoxy)-βCD **49** and mono-(6-bis-(carboxymethyl)-amino)-(6-deoxy)-βCD **50** by means of pH titration and ROESY NMR;[89] unfortunately poor or no discrimination was found. Kano has investigated both cationic and anionic cyclodextrins.[37,90] By means of NMR titration, he found that heptakis-(6-amino)-(6-deoxy)-βCD **51** at pH=6.0 (the host is supposed to be in the hepta-cationic form) shows high binding affinities towards acetyl derivatives of Trp, Val, Phe and Leu, with good discrimination for the former two derivatives (α up to 1.6). The *S* isomer is always preferred. NMR spectra suggest that the anionic head group of the included guests protrudes out of the primary host rim. Computational studies also indicate that the host is distorted in such a way to minimize the interactions among the charged groups, making the primary rim as the wider one. Interestingly, inclusion in these cases is almost exclusively entropy-driven. Mono-(6-amino)-(6-deoxy)-βCD **8** at pH=6.0 shows worse binding and selection abilities. On the other hand, anionic heptakis-(6-carboxymethyltio-6-deoxy)-βCD[90] **52** showed only fair binding abilities towards a series of cationic aminoacid and dipeptide methyl esters (it is noteworthy that binding constants depend also on the buffer concentration). Significant enantioselectivities are found in particular for tryptophane derivatives (α values up to 1.8), and this time *R* enantiomers are always found to be preferred.

The behaviour of aminated cyclodextrins has been thoroughly examined also by Rekharsky and Inoue.[33,43,91,92] Mono-(6-amino)-(6-deoxy)-βCD **8** at pH=6.9, for instance, was compared with βCD.[33,91] The cationic host shows fair selectivities (slightly better with respect to βCD) towards some aminoacid derivatives, in favour of the *S* isomer for *N*-acetyl derivatives of Phe, Tyr and Trp (all monoanions) and for Gly-Phe (zwitterion), in favour of the *R* isomer for *N*-^{t}Boc-Ala, *N*-Cbz-Ala and *N*-Cbz-Asp (monoanions) and *N*-Cbz-Ala-methyl ester (neutral); α values range up to 1.7 in the former case, up to 1.17 in the latter one. Binding enthalpies and entropies are less negative (or more positive) than those found for βCD. Considering that electrostatic interactions should make binding enthalpies and entropies *more* negative, experimental findings have been interpreted assuming that desolvation of the charged interacting groups of both host and guest should be the actual inclusion driving force. Enantioselectivity seems in most cases slightly enthalpy-driven. Better discrimination performances of **8** with respect to βCD have been also

interpreted in terms of the lesser symmetry of the substituted host. Therefore the even less symmetrical *AB*-, *AC*- and *AD*-bis-(6-trimethylammonium)-(6-deoxy)-βCDs[91,43] **53**-**55** were tested by the same Authors towards *N*-Cbz-Glu and *N*-Cbz-Asp, *N*-acetyl-Tyr and *N*-Cbz-Glu-Tyr. NMR ROESY spectra showed that the presence of the charged groups is able to revert the penetration mode of *N*-Cbz-Glu and *N*-Cbz-Asp with respect to βCD, in such a way to achieve the best electrostatic interaction between the charged groups of both host and guest. Dicationic hosts show fair selectivity for the *S* isomer of *N*-Cbz-Glu and *N*-acetyl-Tyr (α up to 1.4), and a good diastereoselectivity for the *R,S* isomer of *N*-Cbz-Glu-Tyr over the *S,S* isomer, but nearly no selectivity with *N*-Cbz-Asp. Different selectivities are tentatively discussed in terms of the plausible structural features of the inclusion complexes. A detailed discussion of the NMR spectra of **53** with the enantiomers of *N*-Cbz-Glu has also been reported by Yamamura.[93] The same Author reported[94] appreciable selection properties for mono-(6-trimethylammonium)-(6-deoxy)-βCD cation towards *N*-acetyl-Phe enantiomers (α=1.24). Binding constants were measured by capillary zone electrophoresis (CZE); noticeably, constants were obtained applying a suitable data normalization processing, in order to correct errors due to variations of medium viscosity. Finally, Scriba reported a curious peak inversion in CE separations, on varying the pH value of the medium, for a series of dipeptides and tripeptides in the presence of several βCD derivatives as selectors.[95-99] This observation could be ascribed in some cases to different variations of the apparent binding constants for the enantiomers of the same species (leading to a reversal of their order) on changing the pH, but it is also due indeed to different variations of the mobility of the different complexes. Moreover, NMR studies suggested the occurrence of different host-guest interaction modes, depending on the substitution pattern on the secondary host rim.[96]

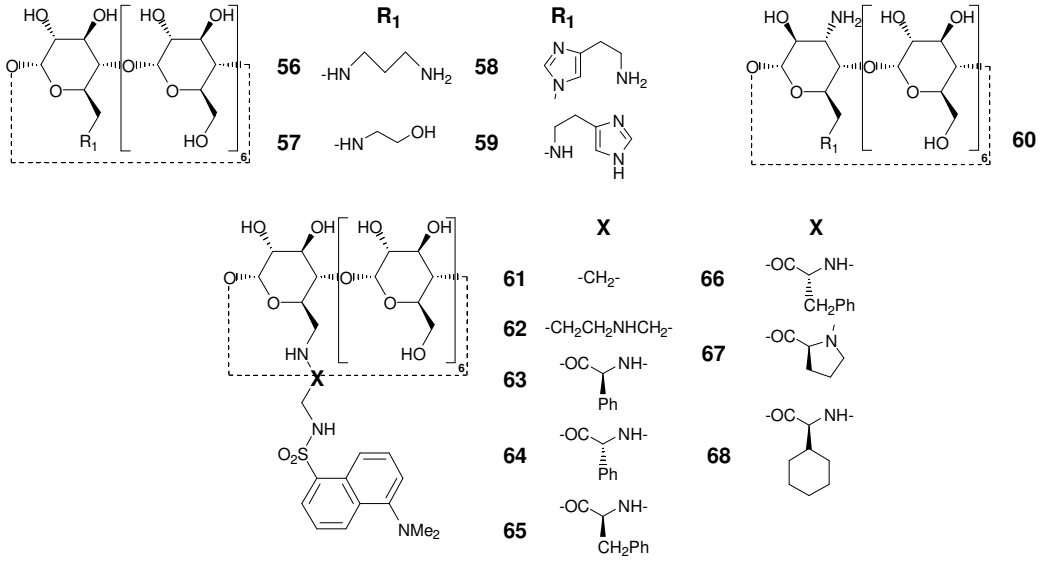
As a concluding remark, an interesting work by Holzgrabe on NMR and Molecular Modeling for cyclodextrin-dipeptide inclusion complexes have been already mentioned in section 2.4.[72]

3.3. Recognition of aminoacids, peptides and their derivatives (3): higher order systems

The examples reported above easily suggest that introduction of specific structural constraints or steric requirements may result in remarkable stereoselectivity. Such constraints/requirements have been achieved in more organized species, such as non-1:1 stoichiometry complexes or, better, in ternary or higher order complexes. More common examples involve complexes containing either metal cations or highly hydrophobic and rigid organic molecules as ternary agent.

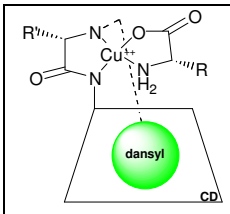
Cyclodextrins bearing pendant groups able to act as ligands towards metal ions have been used in chiral recognition studies by Lincoln[100] and by Rizzarelli[101] since the '90s. The fundamental idea is that the constraints due to the formation of a complex species, in which the metal centre links at the same time the pendant group and the aminoacid head, may induce an effective selection. In particular, Lincoln examined selection properties of Co^{++}, Ni^{++}, Cu^{++} and Zn^{++} complexes of mono-(6-(2-amino)-ethylamino)-(6-deoxy)-βCD **49** towards Trp by potentiometric titration.[102] Observed discrimination was good for the Cu^{++} complex (α=2.18) and fair for the Co^{++} complex, while scarce or no discrimination was found with Ni^{++} or Zn^{++} complexes. By contrast, complexes of mono-(6-(3-amino)-propylamino)-(6-deoxy)-βCD **56** (Scheme 6) with Co^{++}, Ni^{++} and Cu^{++} all showed good discrimination (α values up to 10). Selectivity of mono-(6-(2-hydroxy)-ethylamino)-(6-deoxy)-βCD **57** complexes with the same metal cations towards Phe, Trp and His was investigated by Russell.[103] Excellent selectivities were found in the presence of Ni^{++}, and quite good selectivities are shown also by Co^{++} and Cu^{++}, but not by Zn^{++}. As a tentative explanation, differences could

be attributed to geometric constraints arising from ligand field effects. It is worth noting that both the previous Authors found no correlation between enantioselections and absolute stability constants. Rizzarelli used mono-(6-(4-(2-aminoethyl)-imidazolyl))-(6-deoxy)-βCD **58** and mono-(6-(2-(4-imidazolyl)-aminoethyl))-(6-deoxy)-βCD **59** Cu^{++} complexes to discriminate the enantiomers of Ala and Trp.[104] By potentiometric titration, no chiral recognition was found for Ala. Host **58** showed good selection towards the *S* isomer of Trp, while a fair selection towards the *R* isomer was found for **59**. On the basis of ESR, UV-vis and CD evidences, these findings have been tentatively explained admitting a preference for a *cis* arrangement of the amino-groups belonging the aminoacid and the cyclodextrin; such an arrangement favours the inclusion of the side chain of the aminoacids into the host cavity for the *R* isomer in the former case, for the *S* isomer in the latter one. Mono-(3-amino)-(3-deoxy)-*A*(2*S*,3*R*)-βCD **60** was synthesized and used for electrophoresis enantiodiscrimination of aminoacids by Cucinotta.[105] Stability constants for the ternary complexes formed in the presence of Cu^{++} ions with Phe and Ala were obtained by potentiometric measurements, indicating excellent selection properties towards the former aminoacid (α up to 8.9).



Scheme 6

Fluorescent β-cyclodextrins **61**-**68** bearing suitable ligand pendant groups able to bind Cu^{++} ions, specifically designed for aminoacid detection, were recently synthesized and studied by Marchelli.[106-108] The pendant groups were constituted by an aminoacid residue (*R* or *S* phenylglycine and Phe, *S* Pro, *S* cyclohexylglycine) linked to a dansyl fluorophoric group.



cyclodextrin.H_2 (*fluorescent*) + Cu^{++} ⇌ cyclodextrin.Cu (*non fluorescent*) + 2 H^+

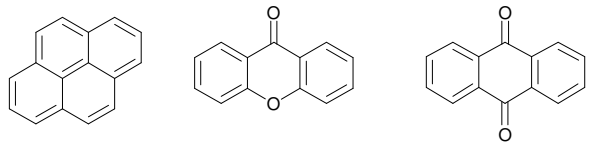
cyclodextrin.Cu (*non fluorescent*) + Aminoacid + H^+ ⇌ cyclodextrin.Cu.Aminoacid.H^+ (*non fluorescent*)

cyclodextrin.Cu.Aminoacid.H^+ (*non fluorescent*) + Aminoacid + H^+ ⇌ cyclodextrin.H_2 (*fluorescent*) + $Cu(aminoacid)_2$

Scheme 7 **Scheme 8**

Chiral selection was detected as different variation in fluorescence response consequent to binding. Data relevant to a series of analytes indicate that cyclodextrins derivatized with an *S* aminoacid show good selection properties; moreover, *N*-alkylation or α,α-disubstitution of the analyte molecule are factors enhancing chiral discrimination. A likely structure for the ternary complex is illustrated in Scheme 7. Nevertheless, further investigations[107] clarified that a multi-step equilibrium mechanism is involved in the enantioselective fluorescence "switching on" process (Scheme 8).

Yang and Bohne[109] had observed that the 2:1 inclusion complex between βCD and pyrene can be stabilized by the co-inclusion of a further organic molecule ("ternary agent"), able to be placed in the residual cavity let free by the pyrene. Starting from this finding, we investigated by spectrofluorimetric titration the interaction of some binary complexes, formed by βCD or heptakis-(6-amino)-(6-deoxy)-βCD **51** (at pH 8.0 and 9.0) and various fluorophoric guests (namely pyrene **69**, xantone **70**, anthraquinone **71**, Scheme 9), with several model aminoacids (Leu, Ile, Phe, Met, Pro, Val, His) and their methyl esters as ternary agents, in order to study chiral recognition abilities of these systems.[110,111] The chosen fluorophores may form with βCD and **51** either 1:1 or 1:2 binary complexes as a function of their symmetry and hydrophobicity; in the same way, ternary complexes may present either a 1:2:1 or a 1:2:2 stoichiometry. In general, good to excellent enantioselectivities are found in favour of either isomer (α values up to 7.4; it is worth noting that the dicationic **51** at pH 8.0 shows a neat preference for *S* isomers, and in general a stronger stabilizing effect by the ternary agent). Both stability and selectivity of the complexes depend on a fine balance between several factors (charge, polar, hydrophobic and solvation effects), which are complicated to discuss in detail. However, data seem to suggest that the hydrophobic character of the ternary agent may be the prevailing factor in controlling the interactions with neutral hosts, while electrostatic interactions predominate with the cationic host.



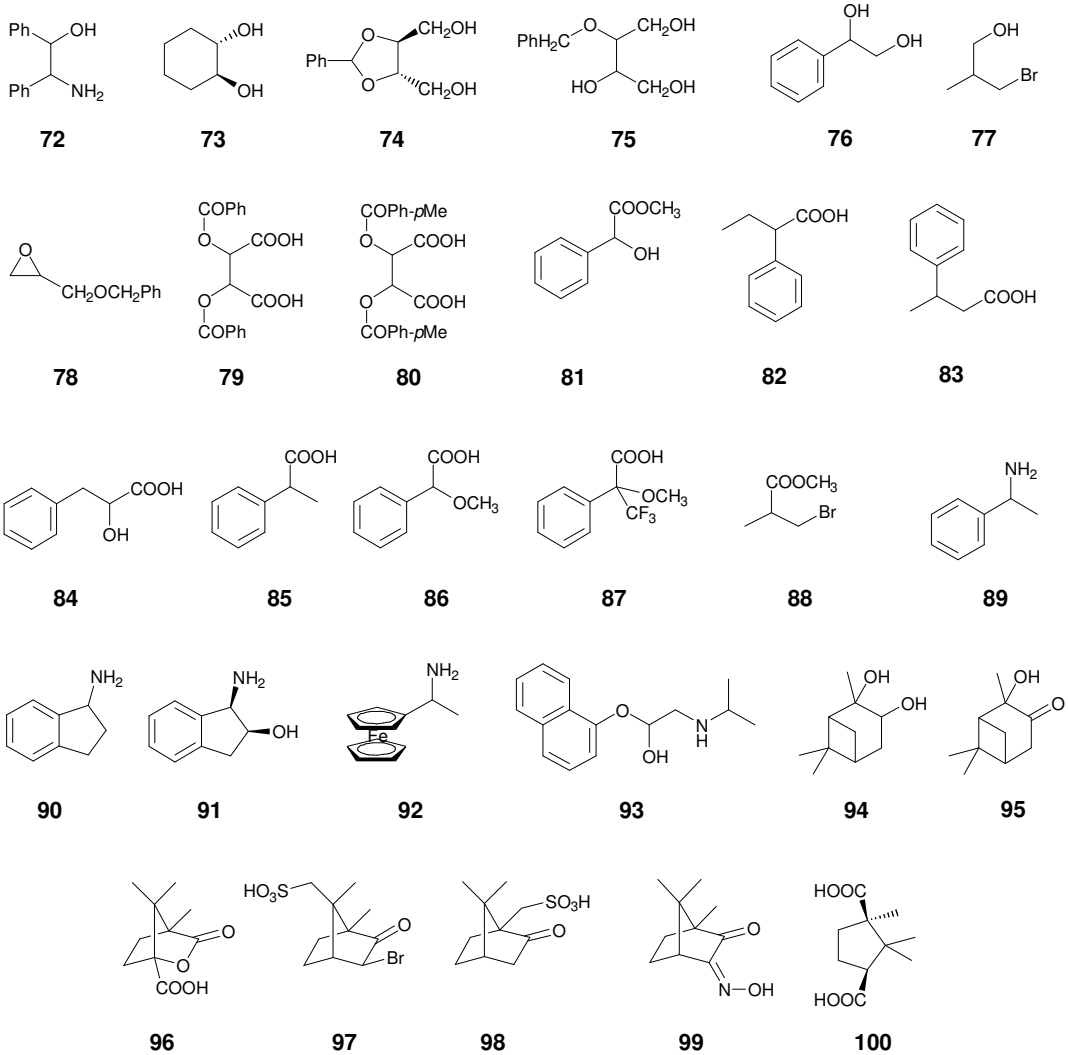
69 **70** **71**

Scheme 9

3.4. Recognition of simple alcohols, amines and acids

The study of the binding behaviour of cyclodextrins toward suitable classes of homogeneous simple derivatives (alcohols, acids, amines and so on) constitutes the natural complement to the studies on aminoacid derivatives illustrated in the previous sections. In fact, Rekharsky and Inoue have examined and compared at the same time aminoacids derivatives and other classes of compounds (including some monoterpene derivatives) in their investigations;[32,33] so, part of their work has been already described previously. Anyway, generally poor discrimination abilities by native βCD are confirmed by these Authors for non-aminoacid guests too.[32] Indeed, among 32 enantiomeric pairs **3-5**,**72**-**100** (terpene derivatives included, Scheme 10), no significant discrimination within experimental indeterminations is found in 21 cases; moreover, in 12 of these cases nor the selectivity thermodynamic parameters $\Delta_{R,S}\Delta H°$ and $\Delta_{R,S}\Delta S°$ are significantly non-zero, whereas in the other 9 ones nearly complete enthalpy-entropy compensation apparently takes place. About the remaining cases, which show actual discrimination, good α values are

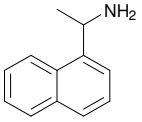
found indeed only for di-benzoyl-tartaric acid dianion (α=1.6), camphoric acid dianion (α=1.26) and α-trifluoromethyl-α-methoxy-phenylacetic acid anion (α=1.25), all other α values being smaller than 1.2. By comparison of all the results obtained, some general conclusions may be drawn. Native βCD seems to show a general preference for the *R* isomer of chiral compounds joining on the stereogenic center a hydroxyl group, a hydrogen atom, a charged (carboxylate) group, and a hydrophobic group for inclusion; this preference may be switched if the hydrophobicity order of the group is reverted (for instance by esterification). Enantioselectivity seems disfavoured on increasing the flexibility of the host and, in general, on increasing the overall binding affinity. The presence on the guest structure of a hydroxyl group alone on the alkyl framework does not seem able to influence effectively the occurrence of chiral recognition. Replacement of a hydroxyl group with a positively charged ammonium group on the host structure,[33] generally is found to improve chiral discrimination abilities, with only few exceptions (revert of enantioselection is seldom observed). For this host overall binding abilities may be either improved (anionic guests) or diminished (neutral or cationic guests) with respect to native βCD, and usually less negative inclusion enthalpies and entropies are observed. Enhancement of enantioselectivity may be ascribed in several cases to entropic factors ("ordering entropy").



Scheme 10

These findings may be partly explained in terms of less effective van der Waals interactions (because of the worst fit of the guest into the host cavity) and concomitant more favourable desolvation entropy, both due to the occurrence of the interactions between oppositely charged groups. However both binding affinities and chiral selectivities are so variously influenced by different structural factors, that an exaustive discussion of all effects involved is rather complicated (interested readers are adviced to refer to the original papers).

An interesting attempt to improve enantioselectivity for native cyclodextrins is due to Koide.[112] Starting from the observation that chiral crown ethers show good enantiodiscrimination abilities towards primary amines, by means of capillary electrophoresis the Author studied the complexation equilibria between the achiral 18-crown-6 ether, native βCD and the three chiral amines 1-aminoindane **90**, 1-(1-naphtyl)-ethylamine **101** and 1,2,3,4-tetrahydro-naphtylamine **102**, (Scheme 11). Unlike bare amines, the crown ether-amine complexes are effectively discriminated by βCD (with α values up to 1.5), as confirmed also by NMR measurements.



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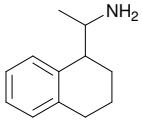
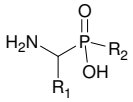


102

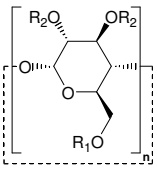


	R_1	R_2		R_1	R_2
103	Ph	OH	**114**	^{i}Pr	OH
104	$PhCH_2$	OH	**115**	^{i}Bu	OH
105	$Ph(CH_2)_2$	OH	**116**	Cyclopropyl	OH
106	2-Naphtyl	OH	**117**	Cyclopentyl-CH_2	OH
107	*o*-Cl-Ph	OH	**118**	Cyclohexyl-CH_2	OH
108	*m*-Cl-Ph	OH	**119**	Ph	H
109	*p*-Cl-Ph	OH	**120**	$PhCH_2$	H
110	1,3-Cl_2-Ph	OH	**121**	$PhCH_2CH_2$	H
111	*p*-NH_2-Ph	OH	**122**	Ph	CH_3
112	*p*-HO-Ph	OH	**123**	Ph	C_2H_5
113	*p*-CH_3-Ph	OH	**124**	^{i}Bu	H

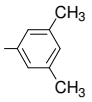
Scheme 11

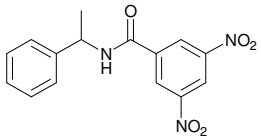
Kafarsky used ^{31}P NMR to detect, just qualitatively, the dicrimination properties of native αCD and βCD towards a series aminophosphonic and aminophosphinic acids **103**-**124**.[113] Neat splitting of the ^{31}P NMR signal for most of the probe compounds can be observed in the presence of αCD (up to $\Delta\delta$=0.63 ppm at a fixed 100 mM host concentration), whereas βCD is effective only in few cases. Better splitting is observed at lower pH values. The presence of strongly polar groups on the guest structure decreases its binding affinity and enantiodiscrimination. ^{1}H NMR for qualitative detection of enantioselectivity was exploited by Salvadori.[114,115] Variously benzoylated and benzylated α- and β-ciclodextrins **125**-**130** (Scheme 12) were found able to effectively perform signal splitting for a series of 3,5-dinitrophenyl derivatives **131**-**137**.[114] Such results suggest that these hosts can be interesting candidates as chiral solvating agents for NMR in non-polar solvents, provided that the guest to resolve could be derivatized with a 3,5-dinitrophenyl group. The same Author examined the behaviour of a series of (3,5-dimethyl)phenyl-carbamoylated cyclodextrins **138**-**144** towards very different aromatic (and some aliphatic) derivatives too.[115] ROESY data exclude that the aryl-carbamoyl groups on the secondary rim penetrate into the cyclodextrin cavity, thus they constitute a sort of extention of the host cone. Interestingly, host-guest interaction does not seem to involve directly the

very cyclodextrin cavity, but rather such an extended aryl cone; nonetheless, derivatization of the primary rim hydroxyl groups has a favourable effect on overall chiral discrimination abilities.

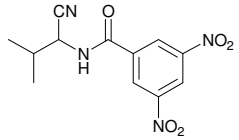


	n	R_1	R_2
125	6	H	PhCO
126	6	PhCO	PhCO
127	6	PhCO	H
128	7	PhCO	PhCO
129	6	H	$PhCH_2$
130	6	PhCO	$PhCH_2$
138	7	ArNHCO	ArNHCO
139	7	ArNHCO	ArNHCO
140	6	ArNHCO	ArNHCO
141	7	H	ArNHCO
142	6	H	ArNHCO
143	7	^{t}BuMe$_2$Si	ArNHCO
144	6	^{t}BuMe$_2$Si	ArNHCO

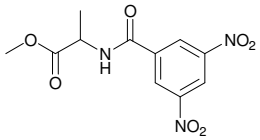
Ar = 



131



132



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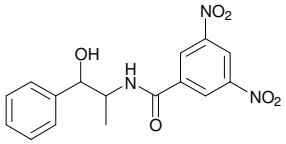

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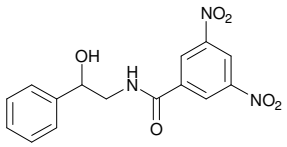

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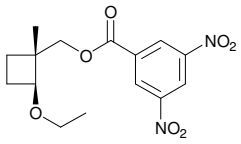

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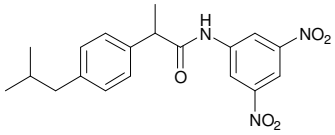


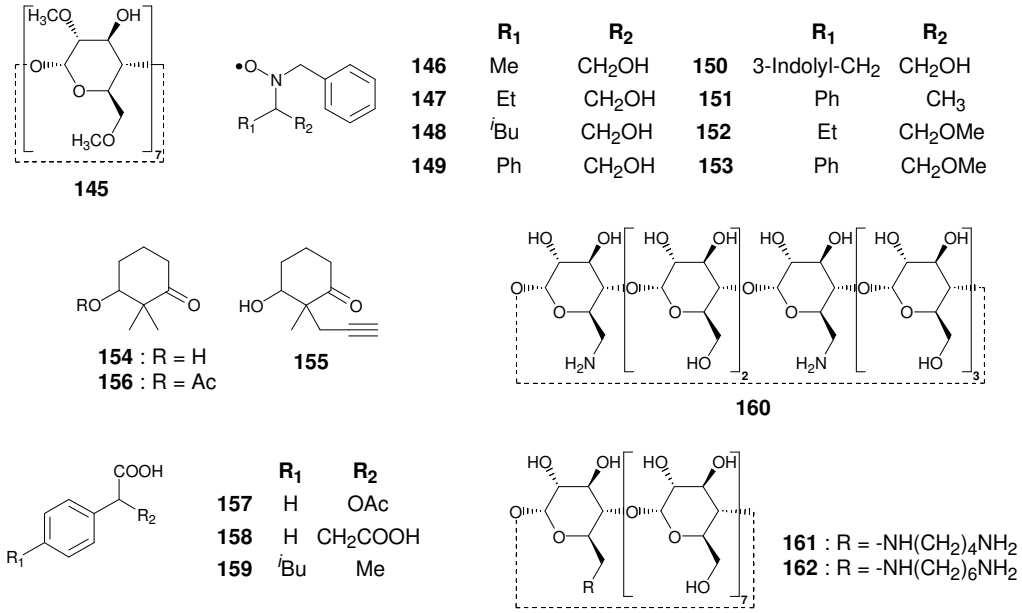
137

Scheme 12

Intriguing recent investigations involved the combined use of different experimental approachs. For instance, Lucarini and Mezzina used joint EPR, NMR, ESI-MS and Molecular Dynamics techniques in order to study the enantiorecognition properties of heptakis-(2,6-di-*O*-methyl)-βCD **145** towards a series of chiral *N*-benzyl-nitroxyde radicals **146**-**153** (Scheme 13) and their precursor amines.[73] Data indicate the occurrence of different behaviours depending on whether a further aryl group is linked to the stereogenic C atom or not. As a matter of fact, in the latter case the *N*-benzyl moiety is the one actually included into the host cavity, resulting in poor enantiodiscrimination; differently, in the former case penetration direction of the guest is reversed, resulting in direct interaction of the stereogenic center with the host and appreciable discrimination. Enantiodiscrimination ratios α range up to 1.31 (from binding constants measured by NMR).

NMR and HPLC techniques were used by Marsaioli[116] to study the interaction between three cyclohexanone derivatives **154**-**156** with αCD, βCD, γCD and their permethyl-derivatives **1**, **45** and **46**. Apparent binding constants and complexed populations, together with ^{13}C complexation and induced shifts diffusion coefficients measurements by pulsed field gradient spin-echo, are used in order to predict whether and to what extent it is possible to detect peak separation in HPLC experiments. The occurrence of both high complexed populations and ^{13}C complexation induced shifts is judged as an effective prediction criterion. However, the main drawback of the methodology used consist in the striking differences among the equilibrium constant values for the same system estimated in different ways. A joint capillary zone electrophoresis (CZE), ^{1}H NMR and MM-MD approach has been exploited also by Kano,[71] to study the interaction of some phenylacetic acid anion related guests **3**, **86**-**87**, **157**-**159** with βCD, permethyl-βCD **1**, mono-(6-amino)-(6-deoxy)-βCD **8** and *A,D*-di-(6-amino)-(6-deoxy)-βCD **160** (the latter hosts in their

cationic forms). This time, CZE trials were used to find out the best cases of enantioselection for undergoing further investigation. Good results were indeed obtained only with monoamino-βCD (CZE α values up to 1.20) and for the separation of 2-phenylsuccinic acid dianion with **160** (CZE α=1.65).

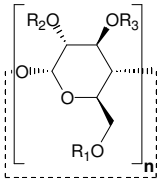


Scheme 13

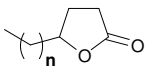
The behaviour of some 6-(ω-amino-alkylamino)-(6-deoxy)-βCDs **49**, **56**, **161**-**162** towards some carboxylic acids, including the enantiomers of 2-phenyl-propionic acid **85**, was examined by Lincoln using pH potentiometric titration.[117] In principle, for these systems four different complexes might be detected (namely dicationic host – neutral guest, dicationic host – anionic guest, monocationic host – anionic guest, neutral host – anionic guest), whose relative stabilities may be tentatively rationalized in terms of different solvation and hydrophobic character of both host and guest. However, for the complexation of the aforesaid chiral guest no systematic rationale for the observed enantioselectivities could be found, with α values randomly varying up to 2.46, and no neat preference for any configuration.

A concluding paragraph is deserved to thermodynamics investigations by the use of chromatographic tecniques. Indeed, as stationary phases or additives for stationary phases, polyalkylated/acylated cyclodextrins have been probably the most popular chiral selectors for GC. We already mentioned that in general it is possible to derive enantioselectivity differential thermodynamic parameters from chromatographic selectivity data at different temperatures. As we will discuss more in detail later, when GC is concerned two different methodologies should be used,[23,24] depending on the fact that the chiral selector is used either as pure stationary phase or diluted in a suitable support phase. In the second case suitable "retention increments" for the selectand enantiomers are measured with respect to an inert (achiral) reference standard substance. The latter method is probably the most used. As a matter of fact, although the introduction of a small systematic error in obtained data must be taken into account, overall results are considered more reliable, as shown by Schurig[23] in a comparative work relevant to the enantioseparation of methyl lactate enantiomers on two LIPODEX E (octakis-(3-*O*-butanoyl-2,6-*O*-pentyl)-γCD) **163** columns (Scheme 14). A comparison among the results obtained by means of the two different methods was carried

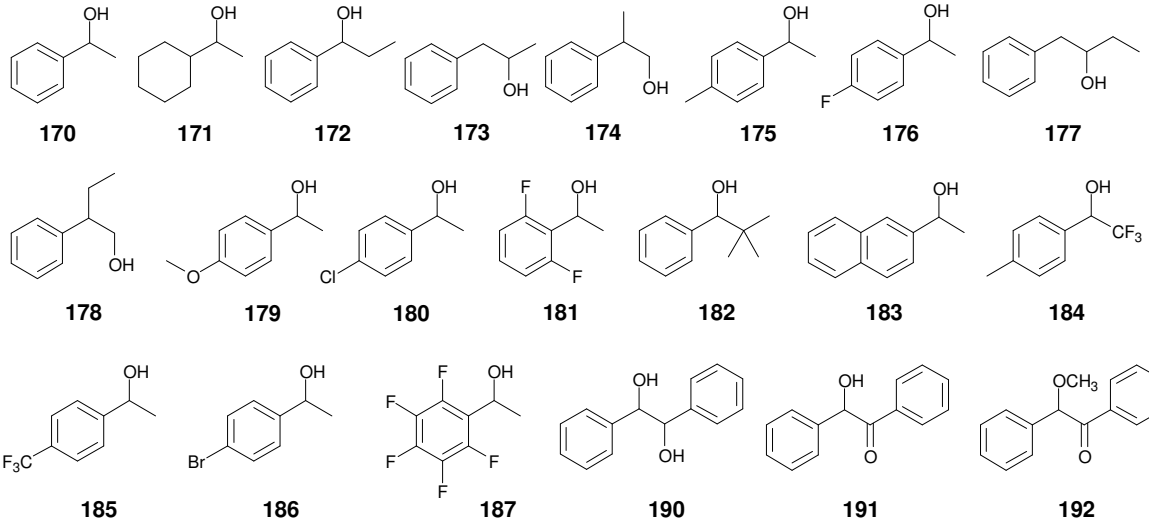
out also by Bicchi,[118] examining the selection performances of octakis-(2-*O*-methyl-3-*O*-acetyl-6-*O*-(*t*-hexyldimethyl)silyl)-γCD **22** and octakis-(2-*O*-acetyl-3-*O*-methyl-6-*O*-(*t*-hexyldimethyl)silyl)-γCD **23** towards a series of chiral γ-lactones **164**-**169** (toghether with some menthane-type monoterpenes **15**-**21**). Thermodynamic data indicate the former cyclodextrin as the most effective in performing enantioseparation, due to a sort of cooperativity between the substituent groups on the secondary host rim.



	n	R_1	R_2	R_3
163	8	^{n}Pent-	^{n}Pent-	^{n}PrCO-
188	7	^{t}BuMe$_2$Si-	Me-	Me-
189	7	^{n}Pent-	^{n}Pent-	Ac-



164 : n = 1 ; **165** : n = 2
166 : n = 3 ; **167** : n = 6
168 : n = 7 ; **169** : n = 8



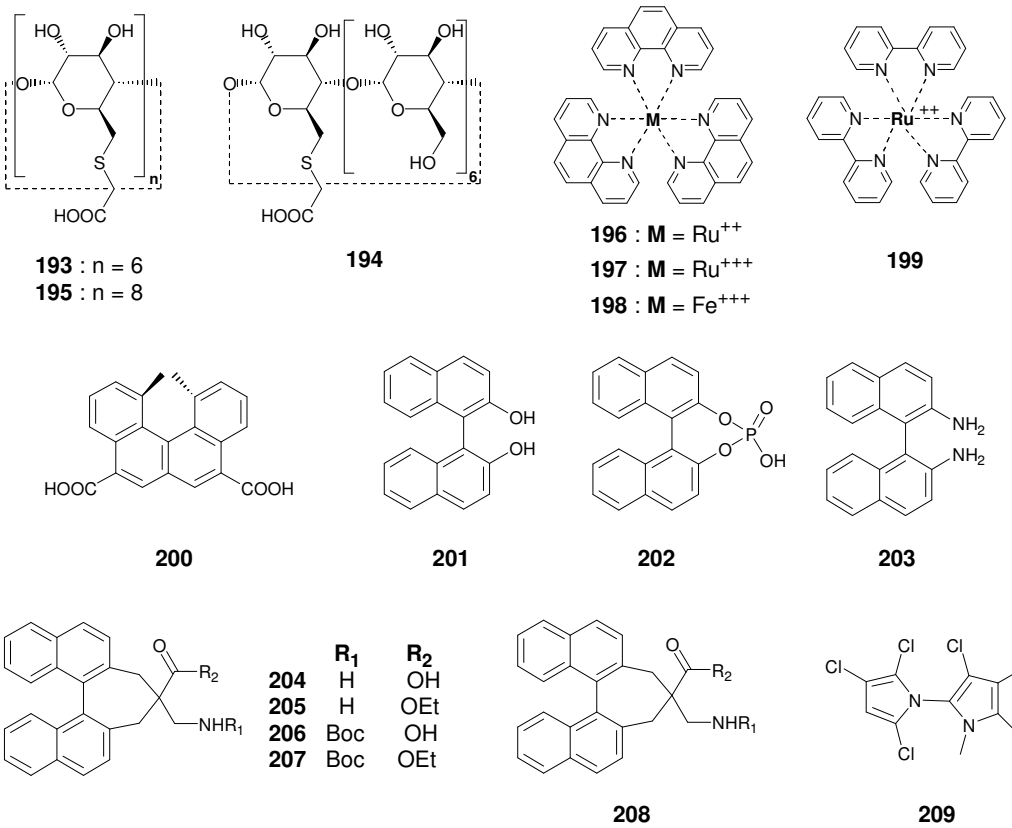
170 **171** **172** **173** **174** **175** **176** **177**
178 **179** **180** **181** **182** **183** **184**
185 **186** **187** **190** **191** **192**

Scheme 14

Sitangkoon[119] carried out a systematic thermodynamic study on the GC enantioseparation of a series of aromatic alcohols **81**, **170**-**187** using a heptakis-(2,3-di-*O*-methyl-6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **188** coated capillary column. The presence of hydrophobic substituents on the aromatic ring seems to favour chiral discrimination, enhancing $\Delta_{R,S}\Delta H°$ values observed, whereas the presence of a long, bulky or electronwithdrawing chain on the stereogenic centre has the opposite effect. Unfortunately, only graphical presentation of experimental data can be found in the paper. The interaction between LIPODEX-D (heptakis-(2,6-di-*O*-pentyl-3-*O*-acetyl)-βCD) **189** and a series of linear chain alkyl nitrates has been thoroughly investigated by Ballschmiter.[120] In particular, data suggest that the presence of an ethyl group on the asymmetric carbon atom gives a strong contribution to $\Delta_{R,S}\Delta H°$ values, which tend to decrease (at least for 3-substituted derivatives) on increasing the chain length. Enantioselection appears to be essentially entropy-driven. Finally, Lin[121,122] recently studied the CZE enantiodiscrimination of hydrobenzoin **190**, benzoin **191** and benzoin methyl ether **192** using a dual cyclodextrin system - sulfated βCD **11** together with either βCD or commercial hydroxypropyl-βCD (mixture of iosomers)[123] - as selector additive and in the presence of borate buffer. Reversal of enantiomer migration for hydrobenzoin could be observed on varying the experimental conditions; apparent binding constants are reported.

3.5. Recognition of axial and helical chiral molecules

Few but intriguing examples are reported in recent literature about the ability of cyclodextrins to recognize non-central chirality. Kano studied,[52] by means of capillary zone electrophoresis and NMR, the behaviour of permethyl-αCD **45**, βCD, hexakis-6-(carbomethoxymethylthio)-6-(deoxy)-αCD **193** (Scheme 15) hexaanion, mono-6-(carbomethoxymethylthio)-6-(deoxy)-βCD **194** monoanion, heptakis-6-(carbomethoxy-methylthio)-6-(deoxy)-βCD **52** heptaanion and octakis-6-(carbomethoxy-methylthio)-6-(deoxy)-γCD **195** octaanion towards the helical complexes $Ru(phen)_3^{++}$, $Ru(phen)_3^{+++}$, $Fe(phen)_3^{+++}$ and $Ru(bpy)_3^{++}$ **196**-**199**.



Scheme 15

In particular, the complete set of thermodynamic parameters for $Ru(phen)_3^{++}$ and $Ru(phen)_3^{+++}$ with **52** and **195** and for $Ru(phen)_3^{++}$ and $Ru(bpy)_3^{++}$ with **45** are reported. It is worth noting that the interaction with the anionic hosts present remarkably positive inclusion entropies, and that significant Δc_p values are found for the complex of the γCD derivatives. Thorough examination of the entire set of data showed that interaction of the metal complexes with the narrow αCD involves the secondary rim of the host, whereas for monoanionic βCD derivative interaction involves the derivatized primary rim, with consequent inversion of selection on passing from the former host to the latter one. This led to the structural hypothesis, already mentioned in section 2.3., claiming for a sort of specular helicity of the two host rims, which could be exalted by a suitable twisting of the host itself. The same Author reported also[124,125] that βCD and γCD are able to bind and effectively recognize the helicity of 1,12-dimethylbenzo[*c*]phenantrene-5,8-dicarboxylate **200** dianion in aqueous solution (α values are 8.5 and 4.5 respectively), probably due to hydrogen bonding assistance. As a matter of fact, binding constants are strongly reduced and selectivity is lost on passing to

DMSO solution. The *P* isomer presents less favourable binding constants and enthalpies than the *M* isomer, but NMR evidence shows the former one penetrates more deeply into the cavity. Therefore it may be concluded that penetration is an enthalpy-demanding process owing to the desolvation of the anionic carboxylate groups.

McCarroll[19] exploited fluorescence anisotropy in order to obtain the differential thermodynamic parameters for the interaction of the atropisomers of [1,1'-binaphtalene]-2,2'-diol **201**, binaphtyl-2,2'-dihyl-hydrogenophosphate **202** and [1,1'-binaphtalene]-2,2'-diamine **203** with βCD. Recognition in these cases is found to be entropy driven. The finding has been interpreted assuming that only one naphtyl moiety is actually inserted in the host cavity, which could result in significant interaction between the other naphtyl group and the host rim surface, with consequent disruption of the solvent shell environment. Zerbinati[126,127] investigated the possibility to separate the enantiomers of the same substrate in capillary electrophoresis in the presence of several hosts (αCD, βCD, γCD, methyl-βCD (s.d. 1.8), hydroxypropyl-βCD (s.d. 0.4), ethylcarbonate-βCD (s.d. 1), ethylcarbonate-γCD (s.d. 0.4), dimethylamino-ethylcarbonate-βCD (s.d. 1.2), mercaptosuccinic-βCD (s.d. 3), maleic-βCD (s.d. 3), heptakis-(6-amino)-(6-deoxy)-βCD) working out to find the best separation conditions. Warner studied the separation of the same substrates by micellar electrokinetic chromatography.[128] Similarly, Péter investigated the HPLC separation of the dinaphthyl derivatives **204**-**208** by means of four different β-cyclodextrin-bondend stationary phases.[129]

Finally, it is worth just mentioning that GC[130,131] or electrophoresis[132,133] separation of the atropisomers of several polychlorinated biphenyl pollutants has been recently reported, by the use of chiral stationary phases or media containing several cyclodextrin derivatives. In a similar way, GC separation of the atropisomers of 2,3,3',4',5,5'-hexachloro-1'-methyl-1,2'-bipyrrole **209** has helped to confirm the correct structural determination of the compound.[134]

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123. Several cyclodextrin derivatives are at present avaliable commercially, which are actually mixtures of compounds at different degree of substitution; the indication of the average substitution degree (s.d.) is frequently provided. In these cases we chose to give no pictorial rapresentation, because it could be somewhat misleading.
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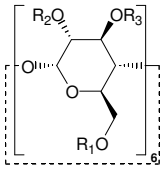
Appendix: Most recent thermodynamic data pertaining chiral discrimination by cyclodextrins

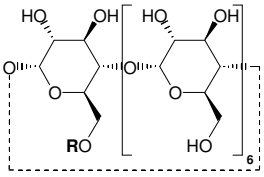
(Cyclodextrin structures have been re-numbered according to the following Scheme, in order to achieve a clearer and more recognizable data tabulation.)

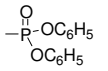
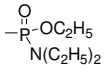
i) α-Cyclodextrins



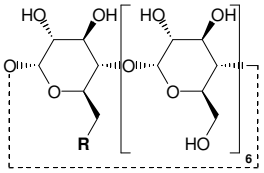
	R_1	R_2	R_3
1α	H	H	H
2α	CH_3	CH_3	CH_3

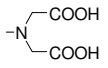
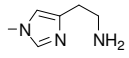
ii) Native and mono-functionalized β-cyclodextrins



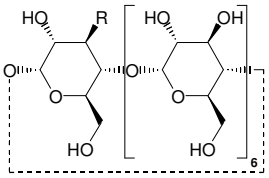
	R		R
1β	H	**3β**	
2β		**4β**	

iii) Mono-(6-deoxy)-functionalized β-cyclodextrins

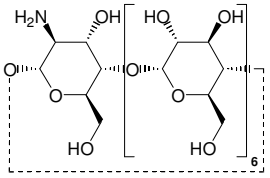


	R		R		R
5β	$-NH_2$	**9β**	$-NH(CH_2)_4NH_2$	**13β**	C_6H_5Se-
6β	$-N(CH_3)_3^+$	**10β**	$-NH(CH_2)_6NH_2$	**14β**	*p*-Me-C_6H_5Se-
7β	$-NH(CH_2)_2NH_2$	**11β**		**15β**	*p*-MeO-C_6H_5Se-
8β	$-NH(CH_2)_3NH_2$	**12β**			

iv) Mono-(2-deoxy)- or –(3-deoxy)-functionalized β-cyclodextrins

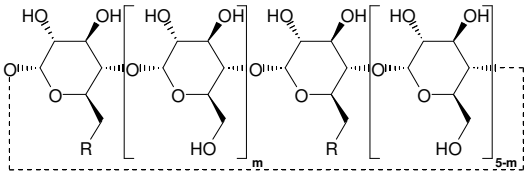


	R
16β	C_6H_5Se-
17β	*p*-$CH_3O-C_6H_4Se-$



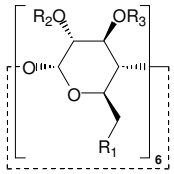
18β

v) Di-functionalized β-cyclodextrins

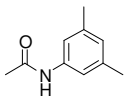
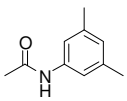
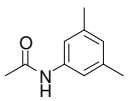
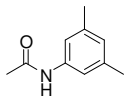
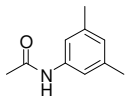


	m	R		m	R
19β	2	$-NH_2$	**21β**	1	$-N(CH_3)_3^+$
20β	0	$-N(CH_3)_3^+$	**22β**	2	$-N(CH_3)_3^+$

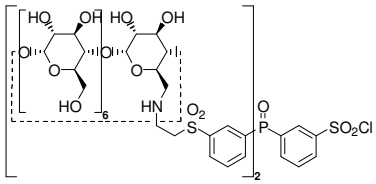
vi) Per-functionalized β-cyclodextrins



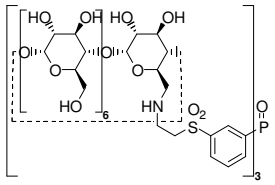
	R_1	R_2	R_3
23β	$-OSO_3H$	$-OSO_3H$	$-OSO_3H$
24β	$-NH_2$	H	H
25β	$-SCH_2COOH$	H	H
26β	$-OCH_3$	$-CH_3$	H
27β	$-OCH_3$	$-CH_3$	$-CH_3$

	R_1	R_2	R_3
28β			
29β	$-OSiMe_2{}^tBu$		

vii) Other β-cyclodextrin derivatives



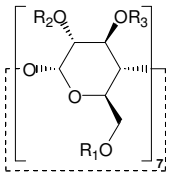
30β



31β

32β : Hydroxypropyl-βCD (average s.d. 3.5)
33β : Carboxymethyl-βCD (average s.d. 3.5)

viii) γ-Cyclodextrins



	R_1	R_2	R_3	
1γ	H	H	H	
2γ	$-SCH_2COOH$	$-CH_3$	$-CH_3$	
3γ	$-OC_5H_{11}$	$-C_5H_{11}$	$-COC_3H_7$	(Lipodex E)

Host (charge)	Guest (charge)	Log *K*	$\Delta H°$ (kJ mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	notes	method	ref.
1α	*N*-Ac-*(R)*-Tyr (-1)	0.95 ± 0.10	-16 ± 3	-11 ± 3	pH 6.9	cal.	43
1α	*N*-Ac-*(S)*-Tyr (-1)	0.85 ± 0.12	-24 ± 3	-19 ± 3	pH 6.9	cal.	43
1α	*N*-Cbz-*(R)*-Glu (-2)	1.18 ± 0.06	-19 ± 2	-12 ± 2	pH 6.9	cal.	43
1α	*N*-Cbz-*(S)*-Glu (-2)	1.15 ± 0.06	-21 ± 2	-15 ± 2	pH 6.9	cal.	43
1α	*N*-Cbz-*(R)*-Glu-*(S)*-Tyr (-2)	1.23 ± 0.05	-19 ± 2	-12 ± 2	pH 6.9	cal.	43
1α	*N*-Cbz-*(S)*-Glu-*(S)*-Tyr (-2)	1.24 ± 0.04	-18.4 ± 1.5	-11.3 ± 1.5	pH 6.9	cal.	43
1α	*(R)*-Leu	1.13	-61.29	-55.20		UV	78
1α	*(S)*-Leu	1.27	-62.03	-54.73		UV	78
1α	*(S)*-Met	1.26	-12.61	-5.94		UV	78
1α	*(RS)*-Met	1.26	-26.59	-20.01		UV	78
1α	*(R)*-*N*-(*p*-Nitrophenyl)-Ala	2.86 ± 0.03	-32.8 ± 0.7	-16.5 ± 0.7	pH 6.0	UV	44
1α	*(R)*-*N*-(*p*-Nitrophenyl)-Ala (-1)	3.05 ± 0.02	-35.4 ± 0.4	-18.6 ± 0.4	pH 6.0	UV	44
1α	*(S)*-*N*-(*p*-Nitrophenyl)-Ala	2.95 ± 0.02	-33.9 ± 0.6	-17.0 ± 0.6	pH 6.0	UV	44
1α	*(S)*-*N*-(*p*-Nitrophenyl)-Ala (-1)	3.00 ± 0.01	-34.8 ± 0.5	-17.6 ± 0.5	pH 6.0	UV	44
1α	*(R)*-2-(*p*-Nitrophenyl)-amino-propanol	3.09 ± 0.01	-36 ± 0.4	-18.4 ± 0.5	pH 6.0	UV	44
1α	*(S)*-2-(*p*-nitrophenyl)-amino-propanol	3.10 ± 0.02	-36.1 ± 0.4	-18.5 ± 0.5	pH 6.0	UV	44
1α	*(R)*-*N*-(*p*-Nitrophenyl)-pirrolidin-3-ol	3.11 ± 0.01	-36.5 ± 0.4	-18.7 ± 0.4	pH 6.0	UV	44
1α	*(S)*-*N*-(*p*-Nitrophenyl)-pirrolidin-3-ol	3.13 ± 0.03	-36.9 ± 0.4	-19.0 ± 0.4	pH 6.0	UV	44
1α	*(R)*-*N*-(*p*-Nitrophenyl)-prolinol	3.25 ± 0.01	-38.5 ± 0.6	-19.9 ± 0.6	pH 6.0	UV	44
1α	*(S)*-*N*-(*p*-Nitrophenyl)-prolinol	3.25 ± 0.01	-38.4 ± 0.6	-19.9 ± 0.6	pH 6.0	UV	44
1α	*(R)*-*N*-(*p*-Nitrophenyl)-Pro	2.97 ± 0.01	-34.3 ± 0.6	-17.4 ± 0.6	pH 6.0	UV	44

1α	*(R)*-*N*-(*p*-Nitrophenyl)-Pro (-1)	3.09 ± 0.01	-36 ± 0.5	-18.4 ± 0.5	pH 6.0	UV	44
1α	*(S)*-*N*-(*p*-Nitrophenyl)-Pro	3.02 ± 0.01	-34.8 ± 0.5	-17.6 ± 0.5	pH 6.0	UV	44
1α	*(S)*-*N*-(*p*-Nitrophenyl)-Pro (-1)	3.07 ± 0.01	-35.8 ± 0.5	-18.2 ± 0.5	pH 6.0	UV	44
1α	*(S)*-Trp	1.60	-13.55	-4.41		UV	78
1α	*(RS)*-Trp	1.64	-0.053	9.25		UV	78
2α	Δ-Tris-(2,2'-dipyridyl)Ru (2+)	1.77 ± 0.07	-46.9 ± 0.4	-36.70 ± 0.3	D_2O, pD 7.0	NMR	52
2α	Λ-Tris-(2,2'-dipyridyl)Ru (2+)	1.89 ± 0.05	-36.8 ± 0.6	-26.00 ± 0.6	D_2O, pD 7.0	NMR	52
2α	Δ-Tris-(1,10-Phenantroline)Ru (2+)	1.73 ± 0.04	-40.5 ± 2.1	-30.40 ± 2.1	D_2O, pD 7.0	NMR	52
2α	Λ-Tris-(1,10-Phenantroline)Ru (2+)	2.03 ± 0.04	-34.3 ± 2.3	-22.40 ± 2.3	D_2O, pD 7.0	NMR	52
1β	*(R)*-3-Acetoxy-2,2-dimethyl-cyclohexan-1-one	2.89 ± 0.06			D_2O	NMR	116
1β	*(S)*-3-Acetoxy-2,2-dimethyl-cyclohexan-1-one	3.00 ± 0.13			D_2O	NMR	116
1β	*(R)*-Acetylmandelic acid (-1)	1.36 ± 0.17			pD 6.0	NMR	71
1β	*(S)*-Acetylmandelic acid (-1)	1.36 ± 0.17			pD 6.0	NMR	71
1β	*N*-Ac-*(R)*-Phe (-1)	1.78 ± 0.01	-8.14 ± 0.07	2.04 ± 0.08	pH 6.9	cal.	32
1β	*N*-Ac-*(S)*-Phe (-1)	1.83 ± 0.01	-8.17 ± 0.08	2.27 ± 0.09	pH 6.9	cal.	32
1β	*N*-Ac-*(R)*-Trp (-1)	1.10 ± 0.02	-25.5 ± 0.6	-19.2 ± 0.6	pH 6.9	cal.	32
1β	*N*-Ac-*(S)*-Trp (-1)	1.23 ± 0.01	-23.8 ± 0.4	-16.8 ± 0.4	pH 6.9	cal.	32
1β	*N*-Ac-*(R)*-Tyr (-1)	2.10 ± 0.01	-16.7 ± 0.3	-4.7 ± 0.3	pH 6.9	cal.	32
1β	*N*-Ac-*(S)*-Tyr (-1)	2.11 ± 0.01	-17.1 ± 0.3	-5.0 ± 0.3	pH 6.9	cal.	32
1β	*(S)*-Ala-*(S)*-Phe	0.60			urea 2 M	CE	80
1β	*(S)*-Ala-*(S)*-Phe (+1)	1.62			urea 2 M	CE	80
1β	*(R)*-Ala-*(R)*-Phe	0.30			urea 2 M	CE	80
1β	*(R)*-Ala-*(R)*-Phe (+1)	1.64			urea 2 M	CE	80

Host (charge)	**Guest (charge)**	**Log *K***	**Δ*H*°** (kJ mol^{-1})	**TΔ*S*°** (kJ mol^{-1})	**notes**	**method**	**ref.**
1β	*(S)*-Ala-*(R)*-Phe	1.36			urea 2 M	CE	80
1β	*(S)*-Ala-*(R)*-Phe (+1)	1.78			urea 2 M	CE	80
1β	*(R)*-Ala-*(S)*-Phe	1.61			urea 2 M	CE	80
1β	*(R)*-Ala-*(S)*-Phe (+1)	1.82			urea 2 M	CE	80
1β	*(R)*-Ala-*(R)*-Tyr	2.24 ± 0.08			pH 2.5	CE	97
1β	*(R)*-Ala-*(S)*-Tyr	2.04 ± 0.10			pH 3.5	CE	97
1β	*(S)*-Ala-*(S)*-Tyr	2.10 ± 0.13			pH 2.5	CE	97
1β	*(S)*-Ala-*(R)*-Tyr	1.91 ± 0.13			pH 3.5	CE	97
1β	*(1R,2S)*-2-Amino-1,2-diphenylethanol (+1)	1.74 ± 0.02	-10.0 ± 0.2	-0.1 ± 0.2	pH 4.8	cal.	32
1β	*(1S,2R)*-2-Amino-1,2-diphenylethanol (+1)	1.66 ± 0.02	-10.0 ± 0.2	-0.5 ± 0.2	pH 4.8	cal.	32
1β	*(R)*-1-Aminoindan.18-crown-6	3.32			pH 7	CE	112
1β	*(S)*-1-Aminoindan.18-crown-6	2.43			pH 7	CE	112
1β	*(R)*-Asp-*(R)*-Phe-OMe	1.66 ± 0.02			pH 2.5	CE	97
1β	*(R)*-Asp-*(R)*-Phe-OMe	1.53 ± 0.09			pH 3.5	CE	97
1β	*(S)*-Asp-*(S)*-Phe-OMe	1.58 ± 0.11			pH 2.5	CE	97
1β	*(S)*-Asp-*(S)*-Phe-OMe	1.46 ± 0.14			pH 3.5	CE	97
1β	*(R)*-Benzyl-glycidyl ether	2.37 ± 0.02	-9.2 ± 0.2	4.3 ± 0.3	pH 4.8	cal.	32
1β	*(S)*-Benzyl-glycidyl ether	2.36 ± 0.02	-9.3 ± 0.2	4.2 ± 0.2	pH 4.8	cal.	32
1β	2,3-*O*-Benzylidene-*(R)*-threitol	2.07 ± 0.01	-7.56 ± 0.08	4.25 ± 0.09	pH 4.8	cal.	32
1β	2,3-*O*-Benzylidene-*(S)*-threitol	2.06 ± 0.01	-7.49 ± 0.07	4.27 ± 0.08	pH 4.8	cal.	32
1β	*(2R,3R)*-3-Benzyloxy-1,2,4-butanetriol	1.92 ± 0.01	-8.07 ± 0.08	2.9 ± 0.1	pH 6.9	cal.	32
1β	*(2S,3S)*-3-Benzyloxy-1,2,4-butanetriol	1.93 ± 0.01	-7.79 ± 0.07	3.2 ± 0.1	pH 6.9	cal.	32
1β	*O*-Benzyl-*(R)*-Ser	1.85 ± 0.02	-8.9 ± 0.4	1.7 ± 0.4	pH 6.9	cal.	32
1β	*O*-Benzyl-*(S)*-Ser	1.84 ± 0.02	9.2 ± 0.3	1.3 ± 0.3	pH 6.9	cal.	32

1β	*N*-^{t}Boc-*(R)*-Ala(-1)	2.59 ± 0.01	-9.7 ± 0.1	5.1 ± 0.1	pH 6.9	cal.	32
1β	*N*-^{t}Boc-*(S)*-Ala(-1)	2.56 ± 0.01	-9.8 ± 0.1	4.8 ± 0.1	pH 6.9	cal.	32
1β	*N*-^{t}Boc-*(R)*-Ala methylester	2.82 ± 0.01	-13.82 ± 0.15	2.3 ± 0.2	pH 6.9	cal.	32
1β	*N*-^{t}Boc-*(S)*-Ala methylester	2.76 ± 0.01	-12.8 ± 0.1	3.0 ± 0.2	pH 6.9	cal.	32
1β	*N*-^{t}Boc-*(R)*-Ser(-1)	2.49 ± 0.01	-11 ± 0.1	3.2 ± 0.1	pH 6.9	cal.	32
1β	*N*-^{t}Boc-*(S)*-Ser(-1)	2.45 ± 0.01	-10.6 ± 0.1	3.4 ± 0.1	pH 6.9	cal.	32
1β	*N*-Cbz-*(R)*-Ala(-1)	2.17 ± 0.01	-8.9 ± 0.2	3.5 ± 0.2	pH 6.9	cal.	32
1β	*N*-Cbz-*(S)*-Ala(-1)	2.17 ± 0.01	-10 ± 0.2	2.4 ± 0.2	pH 6.9	cal.	32
1β	Cbz-*(S)*-Asp (-2)	1.87 ± 0.01	-9.59 ± 0.15	1.1 ± 0.2	pH 6.9	cal.	91
1β	Cbz-*(R)*-Asp (-2)	1.85 ± 0.01	-9.5 ± 0.1	1.1 ± 0.2	pH 6.9	cal.	91
1β	Cbz-*(S)*-Glu (-2)	1.93 ± 0.01	-10.49 ± 0.1	0.53 ± 0.15	pH 6.9	cal.	91
1β	Cbz-*(R)*-Glu (-2)	1.92 ± 0.01	-11.2 ± 0.1	-0.22 ± 0.1	pH 6.9	cal.	91
1β	*N*-Cbz-*(R)*-Glu-*(S)*-Tyr (-2)	2.06 ± 0.01	-14.8 ± 0.2	-3.0 ± 0.2	pH 6.9	cal.	43
1β	*N*-Cbz-*(S)*-Glu-*(S)*-Tyr (-2)	1.99 ± 0.01	-13.3 ± 0.2	-2.0 ± 0.2	pH 6.9	cal.	43
1β	*(1R,2R)*-1,2-Cyclohexanediol	1.93 ± 0.01	-3.98 ± 0.04	7.03 ± 0.07	pH 6.9	cal.	32
1β	*(1S,2S)*-1,2-Cyclohexanediol	1.93 ± 0.01	-4.21 ± 0.04	6.83 ± 0.07	pH 6.9	cal.	32
1β	*(R)*-1-Cyclohexyl ethylamine (+1)	2.52 ± 0.01	-7.85 ± 0.08	6.5 ± 0.1	pH 6.9	cal.	32
1β	*(S)*-1-Cyclohexyl ethylamine (+1)	2.52 ± 0.01	-7.87 ± 0.08	6.5 ± 0.1	pH 6.9	cal.	32
1β	*O,O'*-Dibenzoyl-*(R)*-tartaric acid (-2)	1.51 ± 0.03	-7.0 ± 0.8	1.6 ± 0.8	pH 6.9	cal.	32
1β	*O,O'*-Dibenzoyl-*(S)*-tartaric acid (-2)	1.30 ± 0.04	-4.9 ± 0.6	2.5 ± 0.6	pH 6.9	cal.	32
1β	*(M)*-1,12-Dimethyl-benzo[*c*]phenantrene-5,8-dicarboxylic acid (-2)	4.27 ± 0.21	-51.1 ± 0.8	-26.9 ± 1.1	D_2O, pD 7.0	NMR	124
1β	*(P)*-1,12-Dimethyl-benzo[*c*]phenantrene-5,8-dicarboxylic acid (-2)	3.34 ± 0.10	-35.1 ± 1.1	-15.9 ± 0.8	D2O, pD 7.0	NMR	124

Host (charge)	**Guest (charge)**	**Log *K***	**$\Delta H°$** (kJ mol^{-1})	**$T\Delta S°$** (kJ mol^{-1})	**notes**	**method**	**ref.**
1β	*(R)-N,N*-Dimethyl-1-ferrocenylethylamine(+1)	3.75 ± 0.02	-28.6 ± 0.5	-7.2 ± 0.5	pH 4.8	cal.	32
1β	*(S)-N,N*-Dimethyl-1-ferrocenylethylamine(+1)	3.83 ± 0.03	-28.7 ± 0.4	-6.9 ± 0.5	pH 4.8	cal.	32
1β	*O,O'*-Di-*p*-toluoyl-*(R)*-tartaric acid (-2)	2.02 ± 0.02	-5.78 ± 0.15	5.8 ± 0.2	pH 6.9	cal.	32
1β	*O,O'*-Di-*p*-toluoyl-*(S)*-tartaric acid (-2)	1.97 ± 0.04	-4.59 ± 0.15	6.7 ± 0.3	pH 6.9	cal.	32
1β	Gly-*(R)*-Phe	1.67 ± 0.01	-7.93 ± 0.15	1.6 ± 0.2	pH 6.1	cal.	32
1β	Gly-*(S)*-Phe	1.73 ± 0.01	-8.59 ± 0.15	1.3 ± 0.2	pH 6.1	cal.	32
1β	*(R)*-Hexahydromandelic acid (-1)	2.81 ± 0.01	-5.61 ± 0.07	10.44 ± 0.08	pH 6.9	cal.	32
1β	*(S)*-Hexahydromandelic acid (-1)	2.78 ± 0.01	-5.36 ± 0.05	10.51 ± 0.07	pH 6.9	cal.	32
1β	*(R,R)*-Hydrobenzoin	1.95			pH 7.0	CE	121
1β	*(S,S)*-Hydrobenzoin	2.28			pH 7.0	CE	121
1β	*(R,R)*-Hydrobenzoin-borate complex	2.02			pH 7.0	CE	121
1β	*(S,S)*-Hydrobenzoin-borate complex	2.45			pH 7.0	CE	121
1β	*(R)*-3-Hydroxy-2,2-dimethyl-cyclohexan-1-one	2.54 ± 0.03			D_2O	NMR	116
1β	*(S)*-3-Hydroxy-2,2-dimethyl-cyclohexan-1-one	2.51 ± 0.03			D_2O	NMR	116
1β	*(R,R)*-3-Hydroxy-2-methyl-2-(2-propinyl)-cyclohexan-1-one	3.05 ± 0.05			D_2O	NMR	116
1β	*(S,S)*-3-Hydroxy-2-methyl-2-(2-propinyl)-cyclohexan-1-one	2.99 ± 0.04			D_2O	NMR	116
1β	*(R)*-Leu-*(R)*-Phe	0.00			urea 2 M	CE	80
1β	*(R)*-Leu-*(R)*-Phe (+1)	1.67			urea 2 M	CE	80
1β	*(R)*-Leu-*(S)*-Phe	1.45			urea 2 M	CE	80
1β	*(R)*-Leu-*(S)*-Phe (+1)	1.97			urea 2 M	CE	80

1β	*(S)*-Leu-*(R)*-Phe	1.00											urea 2 M	CE	80
1β	*(S)*-Leu-*(R)*-Phe (+1)	1.95											urea 2 M	CE	80
1β	*(S)*-Leu-*(S)*-Phe	0.70											urea 2 M	CE	80
1β	*(S)*-Leu-*(S)*-Phe (+1)	1.63											urea 2 M	CE	80
1β	*(R)*-Mandelic acid (-1)	1.04	±	0.08	-4.9	±	0.3	1	±	0.6			pH 6.9	cal.	32
1β	*(S)*-Mandelic acid (-1)	0.95	±	0.10	-4.6	±	0.3	0.8	±	0.7			pH 6.9	cal.	32
1β	*(R)*-Mandelic acid methyl ester	1.83	±	0.01	-7.8	±	0.1	2.6	±	0.1			pH 6.9	cal.	32
1β	*(R)*-Mandelic acid methyl ester	1.78	±	0.02	-8.2	±	0.2	2	±	0.2			pH 4.8	cal.	32
1β	*(S)*-Mandelic acid methyl ester	1.86	±	0.01	-8.2	±	0.1	2.4	±	0.1			pH 6.9	cal.	32
1β	*(S)*-Mandelic acid methyl ester	1.82	±	0.01	-8.44	±	0.15	2	±	0.2			pH 4.8	cal.	32
1β	*(R)*-α-Methoxy-phenylacetic acid (-1)	1.04	±	0.08	-4.4	±	0.3	1.5	±	0.6			pH 6.9	cal.	32
1β	*(S)*- α-Methoxy-phenylacetic acid (-1)	1.00	±	0.04	-5.1	±	0.3	0.6	±	0.4			pH 6.9	cal.	32
1β	*(R)*- α-Methoxy-α-trifluoromethyl-phenylacetic acid (-1)	2.24	±	0.01	-17.48	±	0.15	-4.7	±	0.2			pH 6.9	cal.	32
1β	*(S)*- α-Methoxy-α-trifluoromethyl-phenylacetic acid (-1)	2.15	±	0.01	-16.35	±	0.15	-4.1	±	0.2			pH 6.9	cal.	32
1β	Methyl-*(R)*-3-bromo-2-methyl-propionate	2.42	±	0.04	-12.05	±	0.15	1.8	±	0.3			pH 6.9	cal.	32
1β	Methyl-*(S)*-3-bromo-2-methyl-propionate	2.43	±	0.03	-12.4	±	0.2	1.5	±	0.3			pH 6.9	cal.	32
1β	*(R)*-1-(1-Naphtyl)-ethylamine.18-crown-6	3.15											pH 7.0	CE	112
1β	*(S)*-1-(1-Naphtyl)-ethylamine.18-crown-6	3.32											pH 7.0	CE	112

Host (charge)	**Guest (charge)**	**Log *K***			**Δ*H*°** (kJ mol^{-1})			**TΔ*S*°** (kJ mol^{-1})			**notes**	**method**	**ref.**
1β	*(R)*-*N*-(*p*-Nitrophenyl)-Ala	2.58	±	0.04	-22.4	±	0.9	-7.7	±	0.9	pH 6.0	UV	44
1β	*(R)*-*N*-(*p*-Nitrophenyl)-Ala (-1)	2.60	±	0.03	-22.2	±	0.9	-7.4	±	0.9	pH 6.0	UV	44
1β	*(S)*-*N*-(*p*-Nitrophenyl)-Ala	2.74	±	0.04	-19.3	±	0.5	-3.7	±	0.5	pH 6.0	UV	44
1β	*(S)*-*N*-(*p*-Nitrophenyl)-Ala (-1)	2.73	±	0.04	-19.4	±	0.5	-3.9	±	0.5	pH 6.0	UV	44
1β	*(R)*-2-(*p*-Nitrophenyl)-amino-4-methyl-pentanol	3.07	±	0.02	-13.0	±	0.8	4.5	±	0.8	pH 6.0	UV	44
1β	*(S)*-2-(*p*-Nitrophenyl)-amino-4-methyl-pentanol	3.08	±	0.02	-12.8	±	0.8	4.8	±	0.8	pH 6.0	UV	44
1β	*(R)*-2-(*p*-Nitrophenyl)-amino-propanol	2.81	±	0.02	-18.3	±	0.4	-2.2	±	0.4	pH 6.0	UV	44
1β	*(S)*-2-(*p*-Nitrophenyl)-amino-propanol	2.75	±	0.02	-19.2	±	0.5	-3.5	±	0.5	pH 6.0	UV	44
1β	*(R)*-*N*-(*p*-Nitrophenyl)-pirrolidin-3-ol	2.98	±	0.01	-13.0	±	0.7	4.0	±	0.7	pH 6.0	UV	44
1β	*(S)*-*N*-(*p*-Nitrophenyl)-pirrolidin-3-ol	2.98	±	0.01	-13.0	±	0.7	4.0	±	0.7	pH 6.0	UV	44
1β	*(R)*-*N*-(*p*-Nitrophenyl)-Pro	2.93	±	0.02	-16.5	±	0.3	0.2	±	0.3	pH 6.0	UV	44
1β	*(R)*-*N*-(*p*-Nitrophenyl)-Pro (-1)	2.77	±	0.02	-14.3	±	0.4	1.5	±	0.4	pH 6.0	UV	44
1β	*(S)*-*N*-(*p*-Nitrophenyl)-Pro	3.01	±	0.02	-17.7	±	0.4	-0.5	±	0.4	pH 6.0	UV	44
1β	*(S)*-*N*-(*p*-Nitrophenyl)-Pro (-1)	2.82	±	0.04	-15.0	±	0.4	1.1	±	0.4	pH 6.0	UV	44
1β	*(R)*-*N*-(*p*-Nitrophenyl)-prolinol	3.11	±	0.01	-19.2	±	0.5	-1.4	±	0.5	pH 6.0	UV	44
1β	*(S)*-*N*-(*p*-Nitrophenyl)-prolinol	3.07	±	0.02	-18.6	±	0.4	-1.1	±	0.4	pH 6.0	UV	44
1β	*(R)*-Phe	2.21	±	0.06								pot.	79
1β	*(R)*-Phe (+1)	1.92	±	0.10								pot.	79
1β	*(S)*-Phe	2.19	±	0.02								pot.	79
1β	*(S)*-Phe (+1)	1.93	±	0.04								pot.	79
1β	*(R)*-Phe amide	2.00	±	0.01	-10.0	±	0.1	1.4	±	0.1	pH 10.0	cal.	32
1β	*(S)*-Phe amide	2.04	±	0.01	-10.6	±	0.1	1.0	±	0.1	pH 10.0	cal.	32
1β	*(R)*-Phe methylester (+1)	1.04	±	0.08	-5.6	±	0.8	0.3	±	0.9	pH 4.8	cal.	32
1β	*(S)*-Phe methylester (+1)	1.08	±	0.04	-5.0	±	0.5	1.2	±	0.6	pH 4.8	cal.	32
1β	*(R)*-Phe-*(R)*-Phe	1.64	±	0.16							pH 2.5	CE	97
1β	*(R)*-Phe-*(R)*-Phe	1.53	±	0.09							pH 3.5	CE	97

Host (charge)	Guest (charge)	Log *K*	$\Delta H°$ (kJ mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	notes	method	ref.
1β	*(S)*-Phe-*(S)*-Phe	1.54 ± 0.23			pH 2.5	CE	97
1β	*(S)*-Phe-*(S)*-Phe	1.49 ± 0.06			pH 3.5	CE	97
1β	*(R)*-2-Phenylbutyric acid (-1)	1.97 ± 0.01	-9.79 ± 0.15	1.5 ± 0.2	pH 6.9	cal.	32
1β	*(S)*-2-Phenylbutyric acid (-1)	1.98 ± 0.01	-9.91 ± 0.15	1.4 ± 0.2	pH 6.9	cal.	32
1β	*(R)*-3-Phenylbutyric acid (-1)	2.60 ± 0.01	-8.62 ± 0.09	6.24 ± 0.09	pH 6.9	cal.	32
1β	*(S)*-3-Phenylbutyric acid (-1)	2.63 ± 0.01	-8.86 ± 0.09	6.35 ± 0.09	pH 6.9	cal.	32
1β	*(R)*-1-Phenyl-1,2-ethanediol	1.79 ± 0.01	-7.54 ± 0.08	2.69 ± 0.09	pH 6.9	cal.	32
1β	*(S)*-1-Phenyl-1,2-ethanediol	1.80 ± 0.01	-7.30 ± 0.07	2.96 ± 0.08	pH 6.9	cal.	32
1β	*(R)*-Phelyllactic acid (-1)	1.94 ± 0.01	-9.34 ± 0.08	1.8 ± 0.1	pH 6.9	cal.	32
1β	*(S)*-Phelyllactic acid (-1)	1.92 ± 0.01	-8.65 ± 0.08	2.3 ± 0.1	pH 6.9	cal.	32
1β	*(R)*-2-phenylpropionic acid (-1)	1.53 ± 0.03	-8.81 ± 0.15	-0.1 ± 0.2	pH 6.9	cal.	32
1β	*(S)*-2-phenylpropionic acid (-1)	1.56 ± 0.02	-8.69 ± 0.15	0.2 ± 0.2	pH 6.9	cal.	32
1β	*(R)*-Phenylsuccinic acid (-1)	1.56 ± 0.06			pD 6.0	NMR	71
1β	*(S)*-Phenylsuccinic acid (-1)	1.53 ± 0.08			pD 6.0	NMR	71
1β	*(R)*-1,2,3,4-Tetrahydro-1-Naphtylamine.18-crown-6	2.71			pH 7.0	CE	112
1β	*(S)*-1,2,3,4-Tetrahydro-1-Naphtylamine.18-crown-6	2.90			pH 7.0	CE	112
1β	*(R)*-Trp	2.15 ± 0.06				pot.	79
1β	*(R)*-Trp (+1)	1.94 ± 0.08				pot.	79
1β	*(S)*-Trp	2.76 ± 0.08				pot.	79
1β	*(S)*-Trp (+1)	2.65 ± 0.08				pot.	79
1β	*(R)*-Tyr	2.37 ± 0.04				pot.	79
1β	*(R)*-Tyr (+1)	1.82 ± 0.11				pot.	79
1β	*(S)*-Tyr	2.26 ± 0.03				pot.	79
1β	*(S)*-Tyr (+1)	1.61 ± 0.10				pot.	79
1β	*(R)*-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-(1*H*-indol-3yl)-propionic acid	1.80 ± 0.14	-15.0 ± 3.7	-6.84 ± 3.4		NMR	84
1β	*(S)*-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-(1*H*-indol-3yl)-propionic acid.	1.67 ± 0.06	-38.4 ± 1.2	-28.89 ± 1.5		NMR	84
2β	*N*-Cbz-*(R)*-Ala (-1)	2.14 ± 0.02	-10.95 ± 0.06	1.37 ± 0.03	pH 7.2	cal.	35
2β	*N*-Cbz-*(S)*-Ala (-1)	2.10 ± 0.01	-4.7 ± 0.3	7.2 ± 0.4	pH 7.2	cal.	35
3β	*N*-Cbz-*(R)*-Ala (-1)	1.79 ± 0.01			pH 7.2	cal.	35
3β	*N*-Cbz-*(S)*-Ala (-1)	1.48 ± 0.03	-16.4 ± 0.4	-8.0 ± 0.6	pH 7.2	cal.	35
4β	*N*-Cbz-*(R)*-Ala (-1)	2.31 ± 0.01	-4.9 ± 0.1	8.3 ± 0.2	pH 7.2	cal.	35
4β	*N*-Cbz-*(S)*-Ala (-1)	2.20 ± 0.01	-13.12 ± 0.07	-0.59 ± 0.02	pH 7.2	cal.	35
5β (+1)	*(R)*-Acetylmandelic acid (-1)	1.72 ± 0.03			pD 6.0	NMR	71
5β (+1)	*(S)*-Acetylmandelic acid (-1)	1.75 ± 0.03			pD 6.0	NMR	71
5β (+1)	*N*-Acetyl-*(R)*-Phe (-1)	1.76 ± 0.01	-6.62 ± 0.15	3.5 ± 0.2	pH 6.9	cal.	33
5β (+1)	*N*-Acetyl-*(S)*-Phe (-1)	1.89 ± 0.01	-7.14 ± 0.07	3.66 ± 0.08	pH 6.9	cal.	33
5β (+1)	*N*-Acetyl-*(R)*-Trp (-1)	1.19 ± 0.02	-20.8 ± 0.7	-14 ± 0.7	pH 6.9	cal.	33
5β (+1)	*N*-Acetyl-*(S)*-Trp (-1)	1.42 ± 0.01	-17.8 ± 0.4	-9.7 ± 0.4	pH 6.9	cal.	33
5β (+1)	*N*-Acetyl-*(R)*-Tyr (-1)	2.06 ± 0.01	-12.4 ± 0.3	-0.7 ± 0.3	pH 6.9	cal.	33
5β (+1)	*N*-Acetyl-*(S)*-Tyr (-1)	2.13 ± 0.01	-15.1 ± 0.2	-3 ± 0.2	pH 6.9	cal.	33
5β (+1)	*N*-^{t}Boc-*(R)*-Ala (-1)	2.84 ± 0.02	-11.0 ± 0.3	5.2 ± 0.3	pH 6.9	cal.	33
5β (+1)	*N*-^{t}Boc-*(S)*-Ala (-1)	2.77 ± 0.01	-10.7 ± 0.2	5.1 ± 0.2	pH 6.9	cal.	33
5β (+1)	*N*-^{t}Boc-*(R)*-Ala methyl ester	2.60 ± 0.01	-13.73 ± 0.15	1.1 ± 0.2	pH 6.9	cal.	33

Host (charge)		Guest (charge)	Log *K*	$\Delta H°$ (kJ mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	notes	method	ref.
5β	(+1)	*N*-^{t}Boc-*(S)*-Ala methyl ester	2.55 ± 0.01	-12.94 ± 0.15	1.6 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(R)*-3-Bromo-2-methyl-1-propanol	2.06 ± 0.02	-8.5 ± 0.2	3.3 ± 0.3	pH 6.9	cal.	33
5β	(+1)	*(S)*-3-Bromo-2-methyl-1-propanol	2.05 ± 0.02	-9.41 ± 0.15	2.3 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*N*-Cbz-*(R)*-Ala(-1)	2.26 ± 0.01	-10.5 ± 0.2	2.4 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*N*-Cbz-*(S)*-Ala(-1)	2.24 ± 0.01	-10.6 ± 0.2	2.2 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*N*-Cbz-*(R)*-Asp (-2)	2.21 ± 0.01	-12.18 ± 0.15	0.45 ± 0.15	pH 6.9	cal.	91
5β	(+1)	*N*-Cbz-*(S)*-Asp (-2)	2.21 ± 0.01	-12.04 ± 0.15	0.54 ± 0.15	pH 6.9	cal.	91
5β	(+1)	*N*-Cbz-*(R)*-Glu (-2)	2.23 ± 0.01	-11.32 ± 0.15	1.38 ± 0.15	pH 6.9	cal.	91
5β	(+1)	*N*-Cbz-*(S)*-Glu (-2)	2.21 ± 0.01	-10.51 ± 0.15	2.1 ± 0.15	pH 6.9	cal.	91
5β	(+1)	*(R)*-1-Cyclohexyl ethylamine(+1)	2.27 ± 0.01	-6.86 ± 0.08	6.1 ± 0.1	pH 6.9	cal.	33
5β	(+1)	*(S)*-1-Cyclohexyl ethylamine(+1)	2.29 ± 0.01	-6.87 ± 0.08	6.2 ± 0.1	pH 6.9	cal.	33
5β	(+1)	*O,O'*-Dibenzoyl-*(R)*-tartaric acid (-2)	1.80 ± 0.01	-5.09 ± 0.15	5.2 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*O,O'*-Dibenzoyl-*(S)*-tartaric acid (-2)	1.64 ± 0.02	-3.66 ± 0.15	5.7 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*O,O'*-Di-*p*-toluoyl-*(R)*-tartaric acid (-2)	2.37 ± 0.01	-6.67 ± 0.1	6.9 ± 0.1	pH 6.9	cal.	33
5β	(+1)	*O,O'*-Di-*p*-toluoyl-*(S)*-tartaric acid (-2)	2.38 ± 0.02	-5.28 ± 0.15	8.3 ± 0.2	pH 6.9	cal.	33
5β	(+1)	Gly-*(R)*-Phe	1.59 ± 0.02	-7.4 ± 0.3	1.7 ± 0.3	pH 6.9	cal.	33
5β	(+1)	Gly-*(S)*-Phe	1.62 ± 0.02	-8.4 ± 0.2	0.9 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(R)*-Hexahydromandelic acid (-1)	3.36 ± 0.01	-10.3 ± 0.2	8.9 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(S)*-Hexahydromandelic acid (-1)	3.17 ± 0.01	-7.4 ± 0.2	10.7 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(R)*-Mandelic acid (-1)	1.95 ± 0.03			pD 6.0	NMR	71
5β	(+1)	*(R)*-Mandelic acid (-1)	1.74 ± 0.02	-6.75 ± 0.07	3.2 ± 0.1	pH 6.9	cal.	33
5β	(+1)	*(S)*-Mandelic acid (-1)	1.77 ± 0.03			pD 6.0	NMR	71
5β	(+1)	*(S)*-Mandelic acid (-1)	1.64 ± 0.02	-4.9 ± 0.1	4.5 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(R)*-Mandelic acid methyl ester	1.62 ± 0.05	-6.9 ± 0.5	2.8 ± 0.6	pH 6.9	cal.	33
5β	(+1)	*(S)*-Mandelic acid methyl ester	1.62 ± 0.03	-6.9 ± 0.2	2.4 ± 0.3	pH 6.9	cal.	33
5β	(+1)	*(R)*-α-Methoxy-phenylacetic acid (-1)	1.52 ± 0.04	-3.8 ± 0.3	4.9 ± 0.4	pH 6.9	cal.	33
5β	(+1)	*(S)*-α-Methoxy-phenylacetic acid (-1)	1.08 ± 0.11	-3.5 ± 0.6	2.7 ± 0.7	pH 6.9	cal.	33
5β	(+1)	*(R)*-α-Methoxy-α-trifluoromethyl-phenylacetic acid (-1)	2.75 ± 0.01	-19.1 ± 0.2	-3.4 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(S)*-α-Methoxy-α-trifluoromethyl-phenylacetic acid (-1)	2.57 ± 0.01	-16.2 ± 0.2	-1.5 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(R)*-α-methoxy-phenylacetic acid (-1)	1.92 ± 0.02			pD 6.0	NMR	71
5β	(+1)	*(S)*-α-methoxy-phenylacetic acid (-1)	1.73 ± 0.04			pD 6.0	NMR	71
5β	(+1)	*(R)*-2-Phenylbutyric acid (-1)	2.35 ± 0.01	-8.2 ± 0.15	5.2 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(S)*-2-Phenylbutyric acid (-1)	2.30 ± 0.01	-8.36 ± 0.15	4.8 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(R)*-3-Phenylbutyric acid (-1)	2.63 ± 0.02	-8.4 ± 0.2	6.6 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(S)*-3-Phenylbutyric acid (-1)	2.64 ± 0.01	-8.6 ± 0.2	6.5 ± 0.2	pH 6.9	cal.	33
5β	(+1)	*(R)*-Phenlyllactic acid (-1)	2.40 ± 0.01	-12.7 ± 0.3	1 ± 0.3	pH 6.9	cal.	33
5β	(+1)	*(S)*-Phenyllactic acid (-1)	2.28 ± 0.01	-10.5 ± 0.3	2.5 ± 0.3	pH 6.9	cal.	33
5β	(+1)	*(R)*-Phenylsuccinic acid (-1)	2.09 ± 0.02			pD 6.0	NMR	71
5β	(+1)	*(S)*-Phenylsuccinic acid (-1)	2.11 ± 0.02			pD 6.0	NMR	71
6β	(+1)	*(R)*-*N*-Acetyl-Phe	1.59			pH 6.9	CE	94
6β	(+1)	*(S)*-*N*-Acetyl-Phe	1.69			pH 6.9	CE	94
6β	(+1)	Cbz-*(R)*-Asp (-2)	2.05 ± 0.02	-10.6 ± 0.2	1.1 ± 0.2	pH 6.9	cal.	91

6β	(+1)	Cbz-*(S)*-Asp (-2)	2.05 ± 0.01	-11.0 ± 0.2	0.7 ± 0.2	pH 6.9	cal.	91
6β	(+1)	Cbz-*(R)*-Glu (-2)	2.06 ± 0.01	-10.11 ± 0.15	1.6 ± 0.2	pH 6.9	cal.	91
6β	(+1)	Cbz-*(S)*-Glu (-2)	2.08 ± 0.01	-10.9 ± 0.2	1.0 ± 0.2	pH 6.9	cal.	91
7β		*(R)*-Phe	4.78 ± 0.03			*I*=0.10 M	pot.	89
7β		*(R)*-Phe (-1)	3.82 ± 0.05			*I*=0.10 M	pot.	89
7β		*(S)*-Phe	4.83 ± 0.04			*I*=0.10 M	pot.	89
7β		*(S)*-Phe (-1)	4.12 ± 0.02			*I*=0.10 M	pot.	89
7β	(+2)	*(R)*-Phenylpropionic acid	2.93 ± 0.09			*I*=0.10 M	pot.	117
7β	(+2)	*(R)*-Phenylpropionic acid (-1)	2.90 ± 0.04			*I*=0.10 M	pot.	117
7β	(+2)	*(S)*-Phenylpropionic acid	2.54 ± 0.05			*I*=0.10 M	pot.	117
7β	(+2)	*(S)*-Phenylpropionic acid (-1)	2.80 ± 0.02			*I*=0.10 M	pot.	117
7β		*(R)*-Trp	5.11 ± 0.01			*I*=0.10 M	pot.	89
7β	(+1)	*(R)*-Trp (-1)	4.92 ± 0.01			*I*=0.10 M	pot.	89
7β		*(R)*-Trp (-1)	4.83 ± 0.02			*I*=0.10 M	pot.	89
7β	(+1)	*(R)*-Phe (-1)	4.34 ± 0.01			*I*=0.10 M	pot.	89
7β.Co^{++}		*(R)*-Trp (-1)	8.71 ± 0.06			*I*=0.10 M	pot.	102
7β.Ni^{++}		*(R)*-Trp (-1)	5.38 ± 0.06			*I*=0.10 M	pot.	102
7β.Cu^{++}		*(R)*-Trp (-1)	8.20 ± 0.04			*I*=0.10 M	pot.	102
7β.Zn^{++}		*(R)*-Trp (-1)	5.79 ± 0.01			*I*=0.10 M	pot.	102
7β		*(S)*-Trp	5.11 ± 0.02			*I*=0.10 M	pot.	89
7β		*(S)*-Trp (-1)	4.72 ± 0.03			*I*=0.10 M	pot.	89
7β	(+1)	*(S)*-Trp (-1)	4.92 ± 0.04			*I*=0.10 M	pot.	89
7β	(+1)	*(S)*-Phe (-1)	4.41 ± 0.01			*I*=0.10 M	pot.	89
Host (charge)		**Guest (charge)**	**Log *K***	**Δ*H*°** (kJ mol^{-1})	**TΔ*S*°** (kJ mol^{-1})	**notes**	**method**	**ref.**
7β.Co^{++}		*(S)*-Trp (-1)	8.54 ± 0.07			*I*=0.10 M	pot.	102
7β.Ni^{++}		*(S)*-Trp (-1)	5.41 ± 0.04			*I*=0.10 M	pot.	102
7β.Cu^{++}		*(S)*-Trp (-1)	7.86 ± 0.02			*I*=0.10 M	pot.	102
7β.Zn^{++}		*(S)*-Trp (-1)	5.79 ± 0.05			*I*=0.10 M	pot.	102
8β	(+2)	*(R)*-Phenylpropionic acid	2.60 ± 0.05			*I*=0.10 M	pot.	117
8β		*(R)*-Phenylpropionic acid (-1)	2.88 ± 0.04			*I*=0.10 M	pot.	117
8β	(+2)	*(S)*-Phenylpropionic acid	2.84 ± 0.04			*I*=0.10 M	pot.	117
8β		*(S)*-Phenylpropionic acid (-1)	2.67 ± 0.06			*I*=0.10 M	pot.	117
9β	(+2)	*(R)*-Phenylpropionic acid	2.62 ± 0.07			*I*=0.10 M	pot.	117
9β		*(R)*-Phenylpropionic acid (-1)	2.80 ± 0.02			*I*=0.10 M	pot.	117
9β	(+2)	*(S)*-Phenylpropionic acid	2.76 ± 0.06			*I*=0.10 M	pot.	117
9β		*(S)*-Phenylpropionic acid (-1)	2.80 ± 0.07			*I*=0.10 M	pot.	117
10β	(+1)	*(R)*-Phenylpropionic acid (-1)	2.40 ± 0.06			*I*=0.10 M	pot.	117
10β		*(R)*-Phenylpropionic acid (-1)	3.06 ± 0.11			*I*=0.10 M	pot.	117
10β	(+1)	*(S)*-Phenylpropionic acid (-1)	2.45 ± 0.12			*I*=0.10 M	pot.	117
10β		*(S)*-Phenylpropionic acid (-1)	3.25 ± 0.04			*I*=0.10 M	pot.	117
11β	(-2)	*(R)*-Phe	4.12 ± 0.03			*I*=0.10 M	pot.	89
11β	(-1)	*(R)*-Phe (-1)	4.85 ± 0.02			*I*=0.10 M	pot.	89
11β	(-2)	*(S)*-Phe	4.12 ± 0.05			*I*=0.10 M	pot.	89
11β	(-1)	*(S)*-Phe (-1)	4.85 ± 0.03			*I*=0.10 M	pot.	89
11β	(-2)	*(R)*-Phe (-1)	4.02 ± 0.06			*I*=0.10 M	pot.	89
11β	(-2)	*(S)*-Phe (-1)	4.00 ± 0.05			*I*=0.10 M	pot.	89
11β	(-2)	*(R)*-Trp	3.35 ± 0.09			*I*=0.10 M	pot.	89
11β	(-1)	*(R)*-Trp (-1)	4.25 ± 0.04			*I*=0.10 M	pot.	89
11β	(-2)	*(S)*-Trp	3.43 ± 0.07			*I*=0.10 M	pot.	89
11β	(-1)	*(S)*-Trp (-1)	4.33 ± 0.03			*I*=0.10 M	pot.	89
11β	(-2)	*(R)*-Trp (-1)	3.40 ± 0.10			*I*=0.10 M	pot.	89
11β	(-2)	*(S)*-Trp (-1)	3.30 ± 0.10			*I*=0.10 M	pot.	89
12β.Cu^{++}		*(R)*-Ala	7.44 ± 0.03			*I*=0.10 M	pot.	104
12β.$Cu^{++}.H^{+}$		*(R)*-Ala	9.26 ± 0.03			*I*=0.10 M	pot.	104
12β.Cu^{++}		*(S)*-Ala	7.43 ± 0.01			*I*=0.10 M	pot.	104

12β.$Cu^{++}.H^{+}$	*(S)*-Ala	9.26 ± 0.03			*I*=0.10 M	pot.	104
12β.Cu^{++}	*(R)*-Trp	7.88 ± 0.03			*I*=0.10 M	pot.	104
12β.Cu^{++}	*(S)*-Trp	8.25 ± 0.03			*I*=0.10 M	pot.	104
13β	*(S)*-Ala	1.96 ± 0.01			pH 7.2	UV	87
13β	*(R)*-Ala	2.55 ± 0.01			pH 7.2	UV	87
13β	*(S)*-Leu	2.46 ± 0.01			pH 7.2	UV	87
13β	*(R)*-Leu	2.47 ± 0.01			pH 7.2	UV	87
13β	*(S)*-Ser	2.00 ± 0.01			pH 7.2	UV	87
13β	*(R)*-Ser	1.71 ± 0.01			pH 7.2	UV	87
14β	(+)-Borneol	4.16 ± 0.01			pH 7.2	CD	51
14β	(-)-Borneol	4.39 ± 0.01			pH 7.2	CD	51
14β	(+)-Menthol	3.39 ± 0.01			pH 7.2	CD	51
14β	(-)-Menthol	2.97 ± 0.01			pH 7.2	CD	51
15β	*(R)*-Ala	2.39 ± 0.01			pH 7.2	UV	87
15β	*(S)*-Ala	2.07 ± 0.01			pH 7.2	UV	87
15β	*(R)*-Leu	1.38 ± 0.01			pH 7.2	UV	87
15β	*(S)*-Leu	2.30 ± 0.01			pH 7.2	UV	87

Host (charge)	**Guest (charge)**	**Log *K***	**$\Delta H°$** (kJ mol^{-1})	**$T\Delta S°$** (kJ mol^{-1})	**notes**	**method**	**ref.**
15β	*(R)*-2-Octanol	2.51 ± 0.01			pH 7.2	CD	51
15β	*(S)*-2-Octanol	2.46 ± 0.01			pH 7.2	CD	51
15β	*(R)*-Ser	1.89 ± 0.01			pH 7.2	UV	87
15β	*(S)*-Ser	2.44 ± 0.01			pH 7.2	UV	87
15β	*(R)*-Val	1.56 ± 0.01			pH 7.2	UV	87
15β	*(S)*-Val	1.77 ± 0.01			pH 7.2	UV	87
16β	*(R)*-Ala	2.10 ± 0.01			pH 7.2	UV	87
16β	*(S)*-Ala	2.37 ± 0.01			pH 7.2	UV	87
16β	*(R)*-Leu	1.82 ± 0.01			pH 7.2	UV	87
16β	*(S)*-Leu	2.52 ± 0.01			pH 7.2	UV	87
16β	*(R)*-Ser	1.66 ± 0.01			pH 7.2	UV	87
16β	*(S)*-Ser	2.07 ± 0.01			pH 7.2	UV	87
16β	*(R)*-Val	1.66 ± 0.01			pH 7.2	UV	87
16β	*(S)*-Val	1.79 ± 0.01			pH 7.2	UV	87
17β	*(R)*-Ala	1.72 ± 0.01			pH 7.2	UV	87
17β	*(S)*-Ala	2.06 ± 0.01			pH 7.2	UV	87
17β	*(R)*-Leu	1.83 ± 0.01			pH 7.2	UV	87
17β	*(S)*-Leu	1.77 ± 0.01			pH 7.2	UV	87
17β	*(R)*-Ser	1.76 ± 0.01			pH 7.2	UV	87
17β	*(S)*-Ser	2.43 ± 0.01			pH 7.2	UV	87
17β	*(R)*-Val	2.01 ± 0.01			pH 7.2	UV	87
17β	*(S)*-Val	1.85 ± 0.01			pH 7.2	UV	87
18β.Cu^{++}	*(R)*-Phe (-1)	11.29 ± 0.03			*I*=0.10 M	pot.	105
18β.Cu^{++}	*(S)*-Phe (-1)	11.72 ± 0.04			*I*=0.10 M	pot.	105
18β.$Cu^{++}.H^{+}$	*(R)*-Phe (-1)	4.39 ± 0.03			*I*=0.10 M	pot.	105
18β.$Cu^{++}.H^{+}$	*(S)*-Phe (-1)	5.34 ± 0.05			*I*=0.10 M	pot.	105
18β.$Cu^{++}.H^{+}$	*(R)*-Ala (-1)	4.85 ± 0.05			*I*=0.10 M	pot.	105
18β.$Cu^{++}.H^{+}$	*(S)*-Ala (-1)	4.88 ± 0.05			*I*=0.10 M	pot.	105
19β (+2)	*(R)*-Phenylsuccinic acid (-1)	2.43 ± 0.02			pD 6.0	NMR	71
19β (+2)	*(S)*-Phenylsuccinic acid (-1)	2.52 ± 0.03			pD 6.0	NMR	71
20β (+2)	*N*-Ac-*(R)*-Tyr (-1)	2.16 ± 0.01	-19.2 ± 0.2	-6.9 ± 0.2	pH 6.9	cal.	43
20β (+2)	*N*-Ac-*(S)*-Tyr (-1)	2.11 ± 0.01	-19.1 ± 0.2	-7.0 ± 0.2	pH 6.9	cal.	43
20β (+2)	Cbz-*(R)*-Asp (-2)	2.25 ± 0.01	-12.9 ± 0.2	-0.1 ± 0.2	pH 6.9	cal.	91
20β (+2)	Cbz-*(S)*-Asp (-2)	2.26 ± 0.01	-12.9 ± 0.2	0.0 ± 0.2	pH 6.9	cal.	91
20β (+2)	Cbz-*(R)*-Glu (-2)	2.13 ± 0.01	-10.0 ± 0.1	2.16 ± 0.1	pH 6.9	cal.	91

											5			
20β	(+2)	Cbz-*(S)*-Glu (-2)	2.28	±	0.01	-12.79	±	0.1	0.2	±	0.15	pH 6.9	cal.	91
20β	(+2)	*N*-Cbz-*(R)*-Glu-*(S)*-Tyr (-2)	2.14	±	0.01	-13.6	±	0.2	-1.4	±	0.2	pH 6.9	cal.	43
20β	(+2)	*N*-Cbz-*(S)*-Glu-*(S)*-Tyr (-2)	2.04	±	0.01	-14.5	±	0.2	-2.9	±	0.2	pH 6.9	cal.	43
21β	(+2)	*N*-Ac-*(R)*-Tyr (-1)	2.31	±	0.01	-19.7	±	0.2	-6.5	±	0.2	pH 6.9	cal.	43
21β	(+2)	*N*-Ac-*(S)*-Tyr (-1)	2.32	±	0.01	-19.5	±	0.2	-6.3	±	0.2	pH 6.9	cal.	43
21β	(+2)	Cbz-*(R)*-Asp (-2)	2.13	±	0.01	-8.92	±	0.15	3.2	±	0.2	pH 6.9	cal.	91
21β	(+2)	Cbz-*(S)*-Asp (-2)	2.15	±	0.02	-9.45	±	0.15	2.8	±	0.2	pH 6.9	cal.	91
21β	(+2)	Cbz-*(R)*-Glu (-2)	2.05	±	0.01	-6.85	±	0.15	4.9	±	0.2	pH 6.9	cal.	91
21β	(+2)	Cbz-*(S)*-Glu (-2)	2.12	±	0.01	-8.9	±	0.15	3.2	±	0.2	pH 6.9	cal.	91
21β	(+2)	*N*-Cbz-*(R)*-Glu-*(S)*-Tyr (-2)	2.20	±	0.01	-13.1	±	0.3	-0.6	±	0.3	pH 6.9	cal.	43
21β	(+2)	*N*-Cbz-*(S)*-Glu-*(S)*-Tyr (-2)	2.09	±	0.01	-13.5	±	0.3	-1.6	±	0.3	pH 6.9	cal.	43
22β	(+2)	*N*-Ac-*(R)*-Tyr (-1)	2.13	±	0.01	-17.1	±	0.2	-4.9	±	0.2	pH 6.9	cal.	43
22β	(+2)	*N*-Ac-*(S)*-Tyr (-1)	2.23	±	0.01	-19.1	±	0.2	-6.4	±	0.2	pH 6.9	cal.	43
22β	(+2)	Cbz-*(R)*-Asp (-2)	2.06	±	0.01	-8.23	±	0.15	3.6	±	0.2	pH 6.9	cal.	91
22β	(+2)	Cbz-*(S)*-Asp (-2)	2.07	±	0.01	-7.83	±	0.15	4.0	±	0.2	pH 6.9	cal.	91
Host (charge)		**Guest (charge)**	**Log *K***			**Δ*H*°** (kJ mol^{-1})			**TΔ*S*°** (kJ mol^{-1})			**notes**	**method**	**ref.**
22β	(+2)	Cbz-*(R)*-Glu (-2)	1.97	±	0.01	-7.52	±	0.15	3.7	±	0.2	pH 6.9	cal.	91
22β	(+2)	Cbz-*(S)*-Glu (-2)	2.03	±	0.01	-7.8	±	0.15	3.8	±	0.2	pH 6.9	cal.	91
22β	(+2)	*N*-Cbz-*(R)*-Glu-*(S)*-Tyr (-2)	2.08	±	0.01	-12.3	±	0.2	-0.4	±	0.2	pH 6.9	cal.	43
22β	(+2)	*N*-Cbz-*(S)*-Glu-*(S)*-Tyr (-2)	2.04	±	0.01	-13.5	±	0.2	-1.9	±	0.2	pH 6.9	cal.	43
23β	(-7)	*(R)*-Benzoin	2.60									borate buf. pH 9.0	CE	122
23β	(-7)	*(S)*-Benzoin	2.72									borate buf. pH 9.0	CE	122
23β	(-7)	*(R)*-Benzoin methyl ether	2.84									borate buf. pH 9.0	CE	122
23β	(-7)	*(R)*-Benzoin methyl ether	3.02									borate buf. pH 9.0	CE	122
23β	(-7)	*(R,R)*-Hydrobenzoin	1.98									borate buf. pH 9.0	CE	122
23β	(-7)	*(S,S)*-Hydrobenzoin	2.13									borate buf. pH 9.0	CE	122
24β	(+7)	*(R)*-Ac-Leu	3.38	±	0.02							D_2O. pD 6.0	NMR	37
24β	(+7)	*(S)*-Ac-Leu	3.39	±	0.02							D_2O. pD 6.0	NMR	37
24β	(+7)	*(R)*-Ac-Phe	3.30	±	0.03							D_2O. pD 6.0	NMR	37
24β	(+7)	*(S)*-Ac-Phe	3.34	±	0.03							D_2O. pD 6.0	NMR	37
24β	(+7)	*(R)*-Ac-Trp	3.15	±	0.02							D_2O. pD 6.0	NMR	37
24β	(+7)	*(S)*-Ac-Trp	3.36	±	0.02							D_2O. pD 6.0	NMR	37
24β	(+7)	*(R)*-Ac-Leu	1.70	±	0.03							D_2O. pD 6.0	NMR	37
24β	(+7)	*(S)*-Ac-Leu	1.76	±	0.03							D_2O. pD 6.0	NMR	37
24β	(+7)	*(R)*-Ac-Phe	1.74	±	0.06							D_2O. pD 6.0	NMR	37
24β	(+7)	*(S)*-Ac-Phe	1.83	±	0.05							D_2O. pD 6.0	NMR	37
24β	(+7)	*(R)*-Ac-Trp	1.81	±	0.04							D_2O. pD 6.0	NMR	37
24β	(+7)	*(S)*-Ac-Trp	2.00	±	0.02							D_2O. pD 6.0	NMR	37
24β	(+7)	*(R)*-Ac-Val	3.12	±	0.03							D_2O. pD 6.0	NMR	37
24β	(+7)	*(S)*-Ac-Val	3.32	±	0.03							D_2O. pD 6.0	NMR	37
25β	(-7)	*(R,R)*-Ala-Ala methyl ester (+1)	1.62	±	0.02							D_2O. pD 7.0	NMR	90
25β	(-7)	*(S,S)*-Ala-Ala methyl ester (+1)	1.38	±	0.05							D_2O. pD 7.0	NMR	90
25β	(-7)	*(R,R)*-Ala-Leu methyl ester (+1)	2.52	±	0.01							D_2O. pD 7.0	NMR	90
25β	(-7)	*(S,S)*-Ala-Leu methyl ester (+1)	2.45	±	0.01							D_2O. pD 7.0	NMR	90
25β	(-7)	*(R,R)*-Ala-Trp methyl ester (+1)	2.66	±	0.05							D_2O. pD 7.0	NMR	90
25β	(-7)	*(R,S)*-Ala-Trp methyl ester (+1)	2.46	±	0.04							D_2O. pD 7.0	NMR	90
25β	(-7)	*(S,R)*-Ala-Trp methyl ester (+1)	2.56	±	0.04							D_2O. pD 7.0	NMR	90

Host (charge)	Guest (charge)	Log K	$\Delta H°$ (kJ mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	notes	method	ref.
25β (-7)	*(S,S)*-Ala-Trp methyl ester (+1)	2.40 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	Gly-*(R)*-Trp methyl ester (+1)	2.41 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	Gly-*(S)*-Trp methyl ester (+1)	2.18 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	*(R)*-Leu methyl ester (+1)	1.53 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	*(R)*-Leu-Trp methyl ester (+1)	2.67 ± 0.05			D_2O. pD 7.0	NMR	90
25β (-7)	*(S)*-Leu methyl ester (+1)	1.40 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	*(S)*-Leu-Trp methyl ester (+1)	2.48 ± 0.04			D_2O. pD 7.0	NMR	90
25β (-7)	*(R,R)*-Leu-Trp methyl ester (+1)	1.98 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	*(S,S)*-Leu-Trp methyl ester (+1)	1.94 ± 0.02			D_2O. pD 7.0	NMR	90
25β (-7)	*(S)*-Phe methyl ester	3.18 ± 0.04			D_2O. pD 7.0	NMR	37
25β (-7)	*(R)*-Phe methyl ester	3.20 ± 0.04			D_2O. pD 7.0	NMR	37
25β (-7)	*(S)*-Phenylglycine methyl ester	2.41 ± 0.02			D_2O. pD 7.0	NMR	37
25β (-7)	*(R)*-Phenylglycine methyl ester	2.45 ± 0.02			D_2O. pD 7.0	NMR	37
25β (-7)	*(R,R)*-Trp-Ala methyl ester (+1)	2.20 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	*(S,S)*-Trp-Ala methyl ester (+1)	2.18 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	*(R)*-Trp methyl ester	2.74 ± 0.02			D_2O. pD 7.0	NMR	37
25β (-7)	*(R)*-Trp Methyl ester (+1)	2.20 ± 0.02			D_2O. pD 7.0	NMR	90
25β (-7)	*(S)*-Trp methyl ester	2.58 ± 0.02			D_2O. pD 7.0	NMR	37
25β (-7)	*(S)*-Trp methyl ester (+1)	2.08 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	Δ-Tris-(1,10-Phenantroline)Ru (2+)	3.10 ± 0.02	-11.4 ± 1.0	6.6 ± 0.6	D_2O. pD 7.0	NMR	52
25β (-7)	Δ-Tris-(1,10-Phenantroline)Ru (2+)		-6.7 ± 1.0	18.4 ± 1.0	D_2O. no salt	NMR	52
25β (-7)	Λ-Tris-(1,10-Phenantroline)Ru (2+)	2.77 ± 0.03	-4.4 ± 1.2	11.7 ± 1.3	D_2O. pD 7.0	NMR	52
25β (-7)	Λ-Tris-(1,10-Phenantroline)Ru (2+)		-10 ± 1.2	14.1 ± 0.7	D_2O. no salt	NMR	52
25β (-7)	Δ-Tris-(1,10-Phenantroline)Rh (3+)	3.18 ± 0.02	-6.1 ± 0.1	12 ± 0.1	D_2O. pD 7.0	NMR	52
25β (-7)	Λ-Tris-(1,10-Phenantroline)Rh (3+)	3.02 ± 0.02	-4.4 ± 0.1	12.8 ± 0.1	D_2O. pD 7.0	NMR	52
25β (-7)	*(R,R)*-Val-Trp methyl ester (+1)	2.43 ± 0.03			D_2O. pD 7.0	NMR	90
25β (-7)	*(S,S)*-Val-Trp methyl ester (+1)	2.34 ± 0.04			D_2O. pD 7.0	NMR	90
26β	*(R)*-Ala-*(R)*-Tyr	2.00 ± 0.06			pH 2.5	CE	97
26β	*(R)*-Ala-*(R)*-Tyr	1.95 ± 0.06			pH 2.5	CE	97
26β	*(R)*-Ala-*(R)*-Tyr	1.52 ± 0.06			pH 3.5	CE	97
26β	*(R)*-Ala-*(R)*-Tyr	1.49 ± 0.06			pH 3.5	CE	97
26β	*(R)*-Asp-*(R)*-Phe-OMe	1.92 ± 0.08			pH 2.5	CE	97
26β	*(S)*-Asp-*(S)*-Phe-OMe	1.86 ± 0.1			pH 2.5	CE	97
26β	*(R)*-Asp-*(R)*-Phe-OMe	1.7 ± 0.07			pH 3.5	CE	97
26β	*(S)*-Asp-*(S)*-Phe-OMe	1.63 ± 0.07			pH 3.5	CE	97
26β	Benzyl-2-(*R*)-(1-hydroxy)-propyl-nitroxide radical	2.40 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*S*)-(1-hydroxy)-propyl-nitroxide radical	2.39 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*R*)-(1-hydroxy)-butyl-nitroxide radical	2.44 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*S*)-(1-hydroxy)-butyl-nitroxide radical	2.42 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*R*)-(1-hydroxy-4-methyl)-pentyl-nitroxide radical	2.55 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*S*)-(1-hydroxy-4-methyl)-pentyl-nitroxide radical	2.53 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*R*)-(1-hydroxy-2-phenyl)-ethyl-nitroxide radical	2.39 ± 0.02			D_2O:CD_3OD 10% v	NMR	73

26β	Benzyl-2-(*S*)-(1-hydroxy-2-phenyl)-ethyl-nitroxide radical	2.44 ± 0.02				D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*R*)-(1-hydroxy-3-phenyl)-propyl-nitroxide radical	2.88 ± 0.02				D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*S*)-(1-hydroxy-3-phenyl)-propyl-nitroxide radical	2.83 ± 0.02				D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*R*)-(1-hydroxy-3-indolylmethyl)-propyl-nitroxide radical	2.75 ± 0.05				D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*S*)-(1-hydroxy-3-indolylmethyl)-propyl-nitroxide radical	2.77 ± 0.04				D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-(*R*)-(1-phenyl)-ethylamine	2.91 ± 0.08				D_2O:CD_3OD 10% v	NMR	73

Host (charge)	**Guest (charge)**	**Log *K***	**$\Delta H°$** (kJ mol^{-1})	**$T\Delta S°$** (kJ mol^{-1})	**notes**	**method**	**ref.**
26β	Benzyl-(*S*)-(1-phenyl)-ethylamine	2.82 ± 0.07			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-(*R*)-(1-phenyl)-ethyl-nitroxyde radical	3.18 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-(*S*)-(1-phenyl)-ethyl-nitroxyde radical	3.06 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*R*)-(1-methoxy)-butyl-nitroxide radical	2.64 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*S*)-(1-methoxy)-butyl-nitroxide radical	2.61 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*R*)-(1-methoxy-2-phenyl)-butyl-nitroxide radical	2.66 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
26β	Benzyl-2-(*S*)-(1-methoxy-2-phenyl)-butyl-nitroxide radical	2.58 ± 0.02			D_2O:CD_3OD 10% v	NMR	73
27β	*(R)*-Ala-*(R)*-Tyr	1.49 ± 0.10			pH 2.5	CE	97
27β	*(R)*-Ala-*(R)*-Tyr	0.75 ± 0.08			pH 3.5	CE	97
27β	*(S)*-Ala-*(S)*-Tyr	1.43 ± 0.11			pH 2.5	CE	97
27β	*(S)*-Ala-*(S)*-Tyr	0.85 ± 0.06			pH 3.5	CE	97
27β	*(R)*-Phe-*(R)*-Phe	1.75 ± 0.05			pH 2.5	CE	97
27β	*(R)*-Phe-*(R)*-Phe	1.26 ± 0.17			pH 3.5	CE	97
27β	*(S)*-Phe-*(S)*-Phe	1.73 ± 0.07			pH 2.5	CE	97
27β	*(S)*-Phe-*(S)*-Phe	1.28 ± 0.16			pH 3.5	CE	97
28β	*N*-3,5-dinitrobenzyl-*(R)*-Ala	1.15			$CDCl_3$	NMR	114
28β	*N*-3,5-dinitrobenzyl-*(S)*-Ala	1.55			$CDCl_3$	NMR	114
29β	*N*-3,5-dinitrobenzyl-*(R)*-Ala	0.95			$CDCl_3$	NMR	114
29β	*N*-3,5-dinitrobenzyl-*(S)*-Ala	1.17			$CDCl_3$	NMR	114
30β	*N*-Cbz-*(R)*-Ala (-1)	2.19 ± 0.01	-7.9 ± 0.4	4.6 ± 0.4	pH 7.2	cal.	35
30β	*N*-Cbz-*(S)*-Ala (-1)	2.06 ± 0.01	-24.2 ± 1.2	-12.4 ± 1.2	pH 7.2	cal.	35
31β	*N*-Cbz-*(S)*-Ala (-1)	1.97 ± 0.01	-11.41 ± 0.01	-0.15 ± 0.01	pH 7.2	cal.	35
31β	*N*-Cbz-*(R)*-Ala (-1)	2.31 ± 0.01	-5.62 ± 0.03	7.58 ± 0.02	pH 7.2	cal.	35
32β	*(R,R)*-Hydrobenzoin	1.78			pH 7.0	CE	121
32β	*(S,S)*-Hydrobenzoin	2.18			pH 7.0	CE	121
32β	*(R,R)*-Hydrobenzoin-borate complex	1.81			pH 7.0	CE	121
32β	*(S,S)*-Hydrobenzoi*N*-borate complex	2.15			pH 7.0	CE	121
33β	Gly-β-*(R)*-Asp-*(R)*-Phe	1.75			pH 3.6	CE	99
33β	Gly-β-*(R)*- Asp-*(R)*-Phe	1.35			pH 5.25	CE	99
33β	Gly-β-*(S)*-Asp-*(S)*-Phe	1.84			pH 3.6	CE	99
33β	Gly-β-*(S)*-Asp-*(S)*-Phe	1.43			pH 5.25	CE	99
33β	Gly-β-*(R)*-Asp-*(S)*-Phe	1.66			pH 3.6	CE	99
33β	Gly-β-*(R)*-Asp-*(S)*-Phe	1.59			pH 5.25	CE	99

Host (charge)	Guest (charge)	Log *K*	Δ*H*° (kJ mol^{-1})	TΔ*S*° (kJ mol^{-1})	notes	method	ref.
33β	Gly-β-*(S)*-Asp-*(R)*-Phe	1.70			pH 3.6	CE	99
33β	Gly-β-*(S)*-Asp-*(R)*-Phe	1.58			pH 5.25	CE	99
33β	*(R)*-Ala-*(R)*-Phe	2.02 ± 0.04			pH 2.5	CE	98
33β	*(R)*-Ala-*(R)*-Phe	2.01 ± 0.01			pH 3.8	CE	98
33β	*(R)*-Ala-*(R)*-Phe	1.22 ± 0.04			pH 5.3	CE	98
33β	*(S)*-Ala-*(S)*-Phe	1.98 ± 0.05			pH 2.5	CE	98
33β	*(S)*-Ala-*(S)*-Phe	2.00 ± 0.01			pH 3.8	CE	98
33β	*(S)*-Ala-*(S)*-Phe	1.25 ± 0.04			pH 5.3	CE	98
33β	*(R)*-Phe-*(R)*-Phe	2.19 ± 0.04			pH 2.5	CE	98
33β	*(R)*-Phe-*(R)*-Phe	2.32 ± 0.04			pH 3.5	CE	98
33β	*(R)*-Phe-*(R)*-Phe	1.44 ± 0.04			pH 5.3	CE	98
Host (charge)	**Guest (charge)**	**Log *K***	**Δ*H*°** (kJ mol^{-1})	**TΔ*S*°** (kJ mol^{-1})	**notes**	**method**	**ref.**
33β	*(S)*-Phe-*(S)*-Phe	2.14 ± 0.04			pH 2.5	CE	98
33β	*(S)*-Phe-*(S)*-Phe	2.29 ± 0.04			pH 3.5	CE	98
33β	*(S)*-Phe-*(S)*-Phe	1.46 ± 0.04			pH 5.3	CE	98
1γ	*N*-Cbz-*(R)*-Glu-*(S)*-Tyr (-2)	1.99 ± 0.01	-25.6 ± 0.2	-14.3 ± 0.2	pH 6.9	cal.	43
1γ	*N*-Cbz-*(S)*-Glu-*(S)*-Tyr (-2)	1.60 ± 0.02	-22.3 ± 0.4	-13.2 ± 0.4	pH 6.9	cal.	43
1γ	Cbz-*(R)*-His(-1)	1.11 ± 0.07	-30 ± 3	-24 ± 3	pH 6.9	cal.	82
1γ	Cbz-*(S)*-His(-1)	1.20 ± 0.05	-28 ± 2	-21 ± 2	pH 6.9	cal.	82
1γ	Cbz-*(R)*-Phe(-1)	2.24 ± 0.01	-11.9 ± 0.2	0.9 ± 0.2	pH 6.9	cal.	82
1γ	Cbz-*(S)*-Phe(-1)	2.27 ± 0.01	-12.8 ± 0.2	-0.1 ± 0.2	pH 6.9	cal.	82
1γ	Cbz-*(R)*-Trp(-1)	1.72 ± 0.04	-31 ± 2	-21 ± 2	pH 6.9	cal.	82
1γ	Cbz-*(S)*-Trp(-1)	1.76 ± 0.04	-31 ± 2	-21 ± 2	pH 6.9	cal.	82
1γ	Cbz-*(R)*-Tyr(-1)	2.24 ± 0.01	-19.2 ± 0.3	-6.4 ± 0.3	pH 6.9	cal.	82
1γ	Cbz-*(S)*-Tyr(-1)	2.28 ± 0.01	-20.4 ± 0.2	-7.4 ± 0.2	pH 6.9	cal.	82
1γ	*(M)*-1,12-dimethyl-benzo[*c*]phenantrene-5,8-dicarboxylic acid (-2)	3.49 ± 0.01	-30.2 ± 1.4	-10.3 ± 1.4	D_2O, pD 7.0	NMR	124
1γ	*(P)*-1,12-dimethyl-benzo[*c*]phenantrene-5,8-dicarboxylic acid (-2)	2.84 ± 0.01	-16 ± 0.3	0.1 ± 0.2	D_2O, pD 7.0	NMR	124
1γ	*(R)*-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-phenylpropionic acid	2.51 ± 0.03	-33.0 ± 3.4	-18.71 ± 3.5		NMR	84
1γ	*(S)*-2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)-3-phenylpropionic acid	2.62 ± 0.02	-24.63 ± 0.01	-9.7 ± 0.12		NMR	84
2γ (-8)	Δ-Tris-(1,10-phenantroline)Ru (2+)	3.06 ± 0.02	-12.9 ± 0.5	5 ± 0.5	D_2O pD 7.0	NMR	52
2γ (-8)	Λ-Tris-(1,10-phenantroline)Ru (2+)	2.95 ± 0.02	-15.1 ± 0.9	2 ± 1	D_2O pD 7.0	NMR	52
3γ	*(R)*-Methyl lactate		-45.47	-11.81	5.37% in SE54	GC	23
3γ	*(R)*-Methyl lactate		-39.67	-10.66	10.08% in SE54	GC	23
3γ	*(S)*-Methyl lactate		-43.87	-7.54	5.37% in SE54	GC	23
3γ	*(S)*-Methyl lactate		-38.00	-6.33	10.08% in SE54	GC	23

MULTICOMPONENT REACTIONS WITH 1,3-DICARBONYL DERIVATIVES: APPLICATIONS TO THE SYNTHESIS OF POLYFUNCTIONALIZED HETEROCYCLES

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Abstract. *The aim of this contribution is to present an overview of the high synthetic potential of multicomponent reactions (MCRs) involving the specific reactivity of easily accessible 1,3-dicarbonyl derivatives. Recent developments of these new useful methodologies valuable for the selective construction of highly functionalized heterocycles of high synthetic and biological values are surveyed.*

Contents

1. Introduction

Although not a very new problem, both the economic and ecologic pressures, coupled with the concomitant emergence of high-throughput screening, are playing increasingly significant roles in the

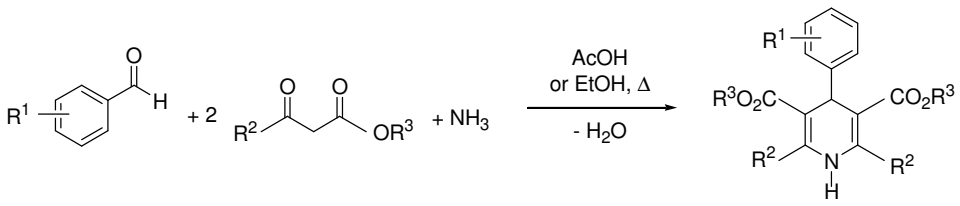
development of modern synthetic organic chemistry.[1] Selectivity, atom economy,[2] time saving, environmental friendliness, cost effectiveness and the reconciliation of molecular complexity with experimental simplicity are some of the pieces of the puzzle needing to be assembled by modern academic and industrial synthetic chemists to reach the maximum of efficiency.[3] All these constraints have resulted in tremendous development of new concepts and new methodologies able to produce valuable elaborated compounds.[4] In this context, utilisation of multicomponent reactions (MCRs) involving domino processes,[5] with at least three different simple substrates[6] reacting in a well-defined manner to form a single compound, has emerged as a powerful strategy.[7] This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis[8] and are particularly well-adapted for combinatorial chemistry.[9] Since the first MCR reported in 1850 by Strecker,[10] this well-known concept,[11] also widely represented in nature, has been extensively used in both liquid-phase[7] and solid-phase[12] chemistry for the rapid assembly of complex heterocyclic structures of importance for pharmaceutical development.[13]

Although isocyanide-based MCRs,[14] introduced in 1921 by Passerini,[15] generally predominate nowadays for the construction of widely diverse heterocycles,[16] one of the first substrate classes involved in a MCR was that of 1,3-dicarbonyl derivatives, with Hantzsch's dihydropyridine synthesis[17] appearing as early as 1882. The aim of this review is to present an overview of the high synthetic potential of MCRs involving the specific reactivity of easily accessible 1,3-dicarbonyl derivatives[18] and to stress their more recent utilization for the development of new useful methodologies valuable for the selective construction of highly functionalised small organic molecules of high synthetic and biological values. This presentation focuses only on MCRs involving at least three different substrates, with no discussion being made of transformations dealing with the utilisation of a two-fold excess of 1,3-dicarbonyls with another substrate.[19]

2. Hantzsch's heterocyclic syntheses

2.1. 1,4-Dihydropyridine and pyridine syntheses

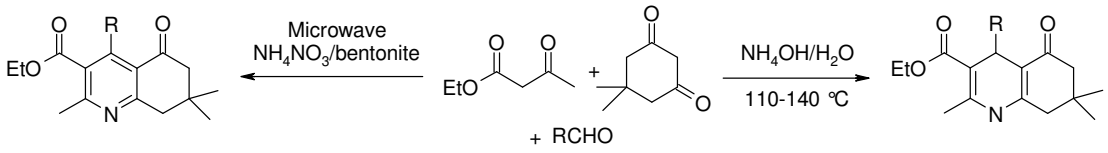
1,3-Dicarbonyl derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a large variety of synthetic transformations.[18] Their versatility and effectiveness as potential multicomponent substrates were first discovered and utilised by Arthur Hantzsch in 1882,[17] with the one-pot, four-component synthesis of symmetrically substituted 1,4-dihydropyridines (Scheme 1). Thanks to the simplicity of the method and the availability of starting materials, this procedure was widely applied in the search for new heterocyclic derivatives presenting new pharmacological properties.[20]



Scheme 1

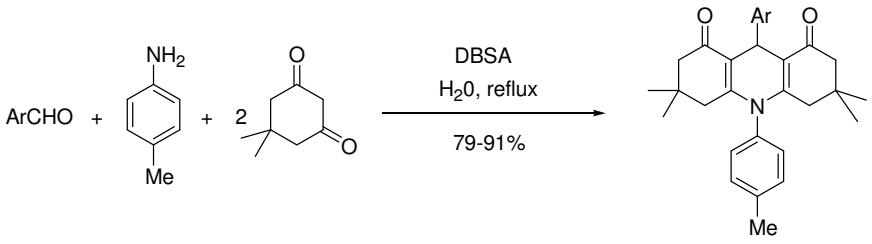
The great biologic importance of the 1,4-dihydropyridine nucleus has over the years prompted the development of new improved methodologies, including solid-phase synthesis,[21] and activation with a

catalyst such as molecular sieves and pyridine,[21a] or more recently Lewis acids[22] and iodo(trimethyl)silane.[23] Replacement of ammonia by ammonium acetate allowed the efficient synthesis of Hantzsch's compounds under mild and solvent-free conditions.[24] Alternatively, microwave irradiation[25] represents an important improvement in the transformation and has also been applied for the direct synthesis of pyridines[26] by concomitant *in situ* aromatisation of the 1,4-dihydropyridine intermediates[27] in the presence of ammonium nitrate supported on bentonite clay.[28] Not only traditional β-ketoesters, but also, for example, malonaldehyde[29] and, more interestingly, cyclic 1,3-diketones can participate in this MCR, allowing four-components Hantzsch's syntheses of unsymmetrically substituted 1,4-dihydropyridines or pyridines with good selectivity depending on the reaction conditions (Scheme 2).[25a,27,30]



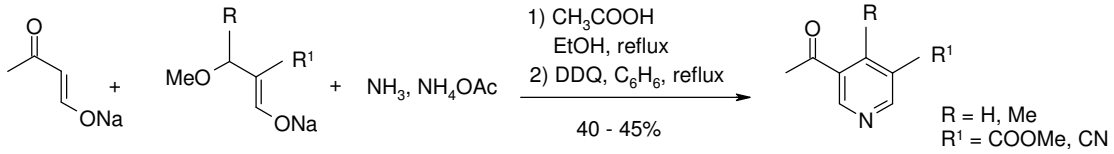
Scheme 2

Recently, reactions of aromatic aldehydes, *p*-toluidine and two equivalents of dimedone in water were also carried out in the presence of *p*-dodecylbenzenesulfonic acid (DBSA) as a Brönsted acid-surfactant-combined catalyst (Scheme 3).[31] This method provides 1,8-dioxo-decahydroacridines with high yields, while combining several advantages such as environment friendliness, simple work-up procedure and use of a green solvent.



Scheme 3

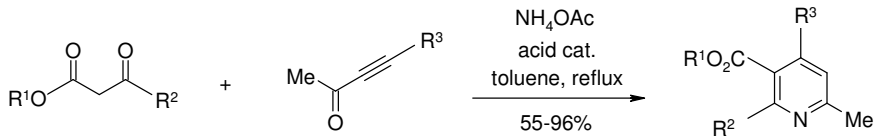
Also of interest is the one-pot formation of simple 3,5-disubstituted 1,4-dihydropyridines, which upon oxidation gave the pyridines involved in the total synthesis of the alkaloid iosalamarine.[32] The key transformation consisted of a cyclocondensation of sodium salts of functionalized malonoacetaldehydes[29a] in the presence of ammonium acetate, followed by DDQ oxidation (Scheme 4).



Scheme 4

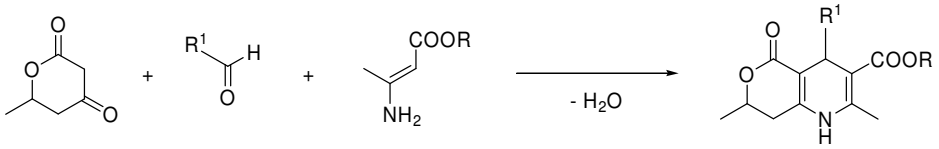
More recently, it was reported that alkynones could also be used as substrates, allowing direct access to polysubstituted pyridines (Scheme 5).[33] This sequential addition-elimination-Michael addition-

cyclodehydration process would be related to the indirect Hantzsch pyridine synthesis, but with the advantage of total control over regiochemistry and access to the target heterocycle in the correct oxidation state without addition of any oxidant.



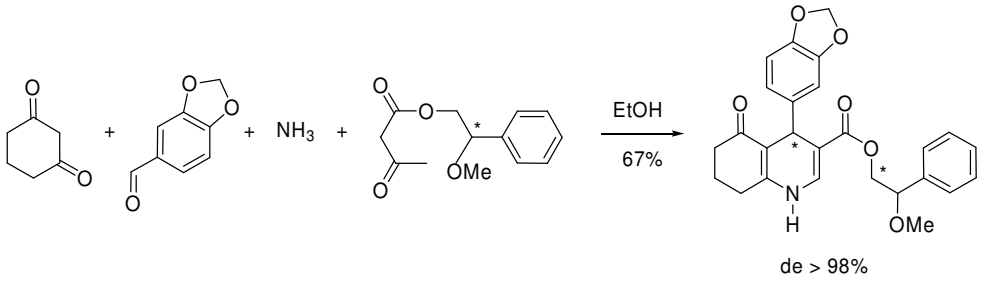
Scheme 5

Another possibility for efficient formation of unsymmetrical dihydropyridines is to perform the condensation with aldehydes with use of a 1,3-dicarbonyl derivatives in the presence of a preformed enamino ester intermediates.[34] For example, utilisation of a β-ketolactone and simple acyclic primary amino esters in condensations with aldehydes gave the corresponding fused heterocycles in high yields (Scheme 6). This approach has recently been exploited for the synthesis of (pyrazolo)quinolinones,[35] deazadihydropterins, [22a] ferrocene-containing heterocycles,[36] and glycosyl 1,4-dihydropyridines.[37]



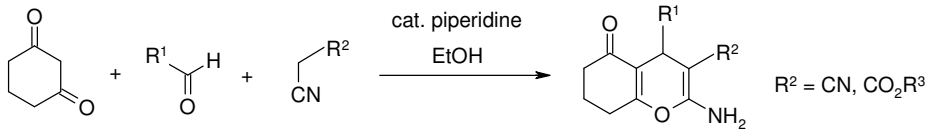
Scheme 6

Since a stereogenic center is formed during a Hantzsch-style MCR, diastereoselective transformations, starting either with chiral enamino derivatives[34,38] or with chiral β-ketoesters, have been studied.[39] An interesting example involves the four-component condensation between a mandelic keto ester derivative, 3,4-(methylenedioxy)benzaldehyde and 1,3-cyclohexanedione in the presence of ammonia, resulting in high asymmetric induction to give the expected dihydropyridine in up to 98% diastereomeric excess[39a] (Scheme 7).



Scheme 7

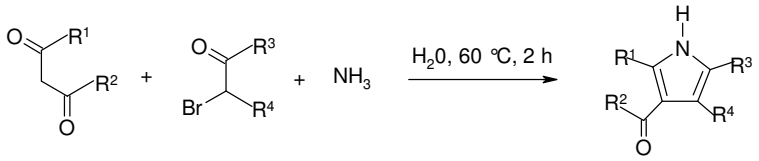
A variation of the Hantzsch reaction for the synthesis of 4*H*-pyran analogues of 1,4-dihydropyridines has been proposed by Bayer AG.[34] 1,3-Cyclohexanedione was condensed with an aldehyde and a nitrile bearing an activated methylene group in the presence of a catalytic amount of piperidine (Scheme 8). More recently, it was reported that the same sequence could be conducted under microwave irradiation and solvent free conditions, using sodium bromide as catalyst.[40]



Scheme 8

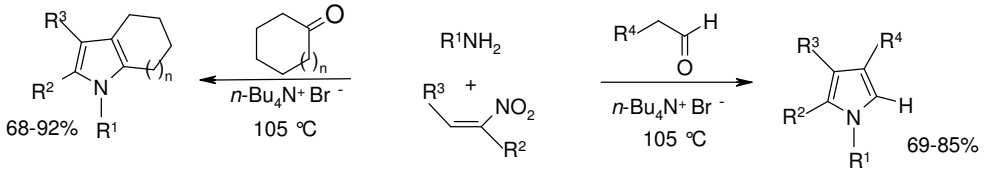
2.2. Pyrrole syntheses

Another contribution by Hantzsch in the field of MCRs concerns the synthesis of pyrroles from a β-ketoester or a β-ketoamide, an α-halogenated carbonyl compound and aqueous ammonia[41] (Scheme 9) and it is also amenable to solid-support conditions.[42]



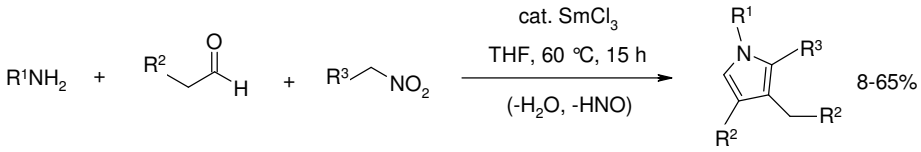
Scheme 9

An important variation, with the utilisation of nitroolefins in the condensation with ketones and primary amines, was reported by Meyer in 1981.[43] This has recently been optimised and generalised to monocyclic and fused-bicyclic pyrroles through the use of molten ammonium salt as a medium for the reaction (Scheme 10).[44]



Scheme 10

Also of interest is the unprecedented samarium(III)-catalysed four-component coupling reaction of aldehydes, amines, and nitroalkanes (Scheme 11),[45] which can be performed either on the surface of silica gel or under microwave irradiation conditions.[46]



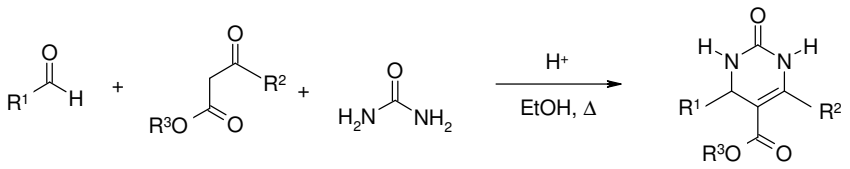
Scheme 11

3. Biginelli dihydropyrimidine syntheses

3.1. The Biginelli condensation

In 1893, shortly after Hantzsch's discovery, Biginelli published a related transformation with urea as the amine component, allowing the facile preparation of multiply functionalised dihydropyrimidines (Scheme 12).[47] Although the synthetic potential of this particular condensation remained unexplored until the beginning of the 1980s, it is now recognised as a powerful heterocyclic synthesis with many important

applications.[48] The increasing interest in the dihydropyrimidine scaffold (DHPMs), known as "Biginelli compounds", is mainly due to their therapeutic and pharmacological properties.[49] The dihydropyrimidone-5-carboxylate core is also present in several marine alkaloids possessing interesting biological activities.[50]

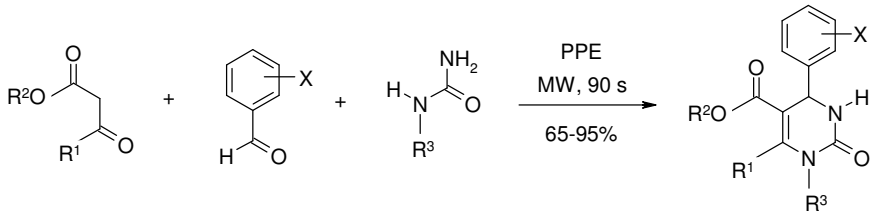


Scheme 12

3.2. Variations of the traditional Biginelli condensation

The traditional Biginelli one-pot procedure, in its simplest form, is catalysed by mineral acids, typically hydrochloric acid. In spite of its high simplicity, this method suffers from long reaction times and low to moderate yields (20-60%) especially with aliphatic and some substituted aromatic aldehydes. Some other protic acid promoters, such as *p*-toluenesulfonic acid,[51] potassium hydrogen sulphate[52] or reusable silica sulfuric acid,[53] have been used in order to overcome these drawbacks. Moreover, the elucidation of the mechanism[54] has prompted renewed interest in improving the efficiency of this process, and so a large variety of reaction conditions have been investigated, with the aim of increasing the yield by favouring the formation and interception of iminium ion intermediates. In this context, several improved procedures have recently been reported, including the use of various Lewis acids,[55] lithium salts,[56] transition metal complexes,[57] zinc chloride[58] or cadmium chloride,[59] bismuth[60] and indium[61] derivatives, samarium diiodide[62] or other lanthanide compounds.[63] Iodine,[64] iodotrimethylsilane[65] and trimethylsilyltriflate,[66] and also polyphosphate ester (PPE)[67] or reusable polyaniline-bismoclite complex[68] have also been reported to catalyse the Biginelli condensation.

Significant rate and yields enhancement were also reported for Biginelli reactions carried out under microwave irradiation conditions, either in combination with PPE[69] or not.[70] Under these solvent-free conditions, large amount of products can be obtained in short reaction times, and with at least >95% purity by a simple aqueous workup procedure (Scheme 13).

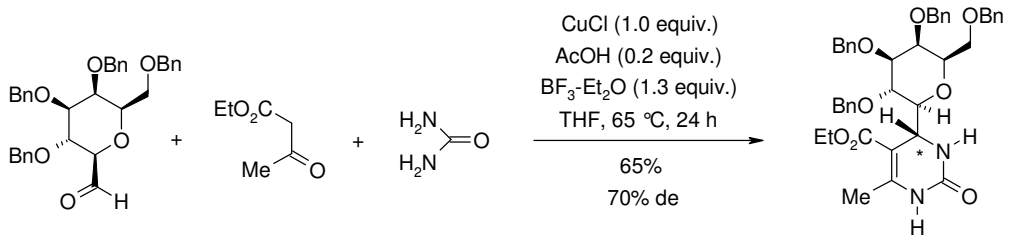


Scheme 13

In addition, various solvent-free procedures have been reported to be efficient alternatives to the classical Biginelli condensation.[71] Thus, montmorillonite KSF clay has been used as a solid acid catalyst for this transformation.[72] Furthermore, a combination of KSF clay and microwave irradiation gave a faster and higher-yielding one-pot synthesis of dihydropyrimidinones.[73] These compounds can also be synthesised in high yields in the presence of catalytic amounts of room temperature ionic liquids.[74] Finally, it has recently been reported that not only trialkylammonium halides,[75] but also the very inexpensive and easily available

ammonium chloride,[76] efficiently catalyze the three-component Biginelli condensation under neutral and solvent-free conditions.

In order to exploit its synthetic potential, the original cyclocondensation has been extended widely to include variations in all three components. Meldrum's acid and barbituric acid derivatives,[77] or benzocyclic ketones and substituted α-keto acids[78] have been used as alternative substrates, while substituted ureas proved able to replace the urea component,[79] affording some novel drug-like dihydropyrimidinone scaffolds in good to excellent yields. The aldehyde component has been widely varied, including not only many aromatic, but also aliphatic and heterocyclic aldehydes. Of these, cyclic hemiaminals furnished high yields of DHPMs when acetonitrile/trifluoroacetic acid was used as a reaction medium.[80] Also of particular interest are reactions in which the aldehyde is derived from a carbohydrate, affording access to *C*-glycosylated dihydropyrimidinones (Scheme 14). Although the Biginelli reaction has mostly been carried out in its achiral version, it's noteworthy that in this case a satisfactory asymmetric induction was observed, affording chiral products with given configuration at the C-4 stereocenter of the DMPH ring.[81]



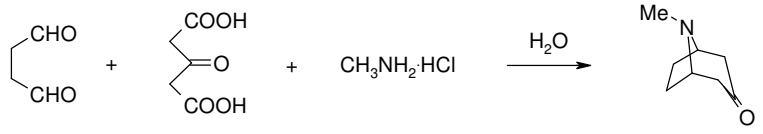
Scheme 14

The Biginelli condensation is particularly useful for the creation of DHPM libraries, and so some combinatorial approaches of this sequence have been described in the literature.[82] In this context, the reaction has been successfully adapted to solid-phase techniques[83] and fluorous-phase conditions.[84]

4. MCRs based on the Mannich reaction

4.1. The Robinson-Schöpf reaction an its variants

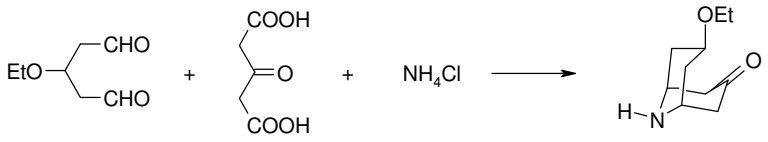
In 1917, Robinson described the synthesis of tropinone through a double Mannich condensation involving succinaldehyde, methylamine and acetone.[85] In 1937, Schöpf improved this reaction by replacing acetone by 1,3-acetonedicarboxylic acid or its diester derivatives.[86] It was thus shown that the reaction can be run under biogenetic-like conditions (*i.e.* the *α,ϖ*-dialdehyde undergoes a decarboxylative double Mannich condensation with methylamine hydrochloride and acetonedicarboxylic acid to furnish the expected azabicyclo[3.2.1]octanone) (Scheme 15).



Scheme 15

Later, Paquette and Heimaster studied a variant of this reaction and published an efficient synthesis of tricyclic amino ketones through the introduction of a cyclic 1,3-dialdehyde into the classical sequence.[87]

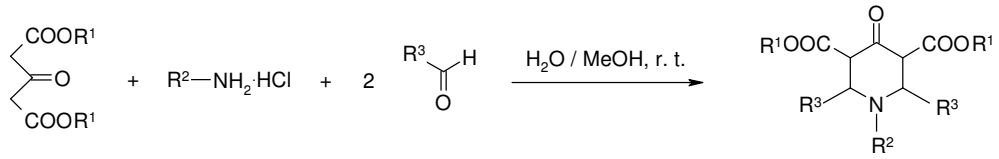
More recently, some studies of the reactivity of tropinone derivatives, prepared by the Robinson-Schöpf methodology, were also reported.[88] Similarly, cyclocondensation with functionalised 1,3-dialdehydes such as β-ethoxyglutaraldehyde in the presence of ammonium chloride afforded the corresponding 9-azabicyclo[3.3.1]nonanones in good yields (Scheme 16).



Scheme 16

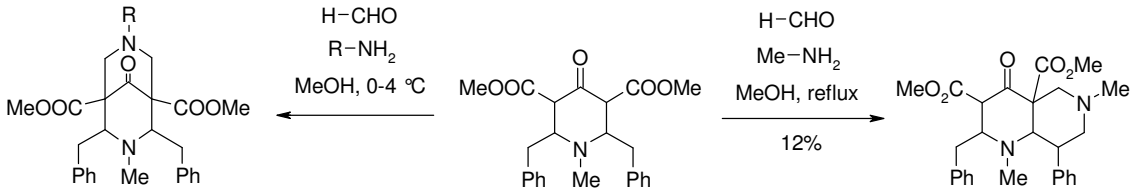
4.2. Other MCRs based on the double Mannich condensation

Numerous other azacycles are accessible through double Mannich condensation. As early as 1934, Mannich described the synthesis of piperidones by condensation of a salt of an aliphatic primary amine, 1,3-dimethyl acetonedicarboxylate and two equivalents of an aliphatic aldehyde in protic solvent and at room temperature.[89] Two years later, he developed the same reaction with formaldehyde (Scheme 17).[90]

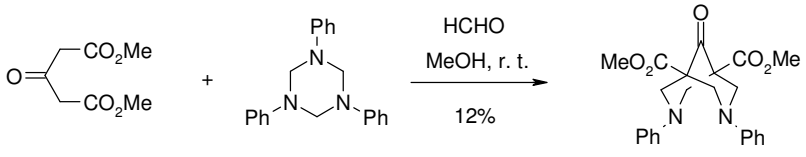


Scheme 17

Piperidones can in turn be involved in a double Mannich condensation with formaldehyde and methylamine, allowing efficient access, depending on the reaction conditions, either to diazabicyclo-[3.3.1]nonanones,[91] sometimes called bispidines, or to unexpected 1,6-naphthyridine derivatives (Scheme 18).[92]



Scheme 18



Scheme 19

However, *N,N'*-diarylbispidinone derivatives cannot be obtained directly from aromatic amine in this way. To overcome this drawback, Gogoll and co-workers developed a condensation of dimethylacetone

dicarboxylate with formaldehyde and trimeric methyleneaniline, in methanol at room temperature, representing a direct synthesis of a bispidine derivative from an aromatic amine (Scheme 19).[93]

Finally, applications of this sequence to cyclic substrates such as 1,3,5-tricarbonyl[94] derivatives, β-ketoesters[95] or β-ketoamides[96] allowed access to azabicyclo[3.2.1]octanones or azabicyclo[3.3.1]-nonanones (Figure 1).[97]

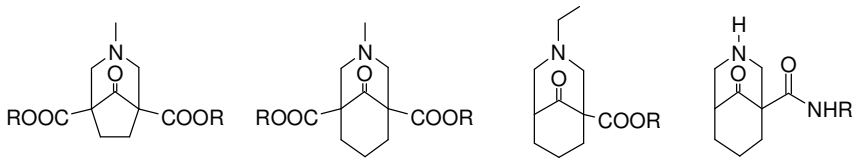
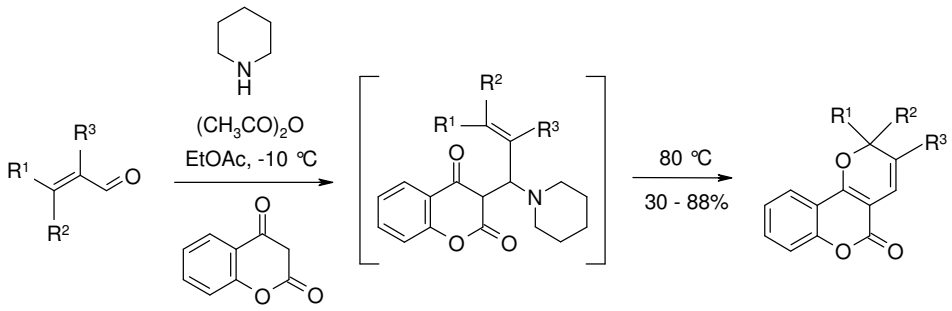


Figure 1

In 1962, Hohenlohe-Oehringen reported a novel three-component synthesis of piperidones by a combination of the Mannich condensation and the Michael addition with use of a γ-unsaturated β-ketoester as starting material.[98] Alternatively, α,β-unsaturated carbonyl compounds can also be used in the Mannich sequence in combination with 1,3-dicarbonyls. Thus, Cravotto and co-workers recently reported that 4-hydrocoumarin reacts with α,β-unsaturated iminium salts derived from enals other than acrolein to give 1,2-addition products.[99] The resulting adducts further evolves through electrocyclization to afford *2H*-pyrano[3,2-*c*]coumarins with moderate to good yields (Scheme 20).

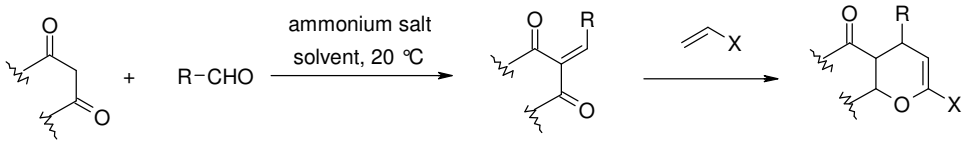


Scheme 20

5. MCRs based on the Knoevenagel reaction

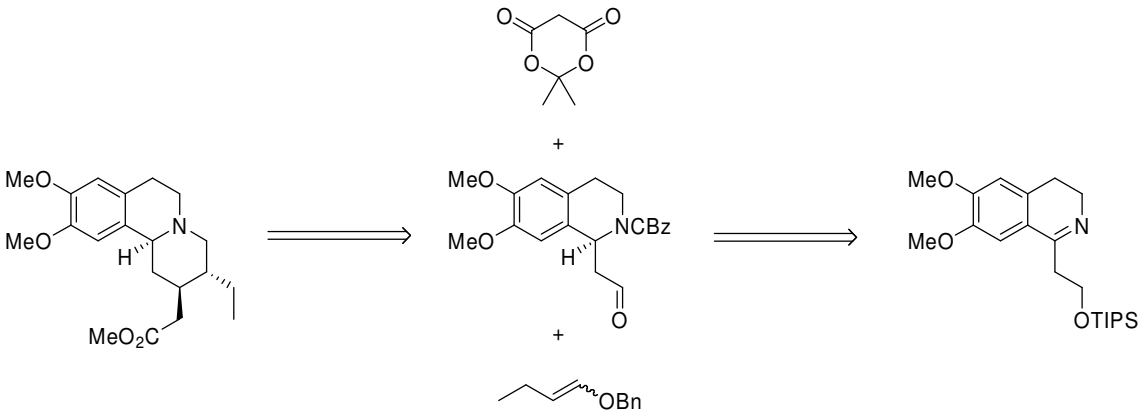
5.1. The domino-Knoevenagel hetero-Diels-Alder reaction

In the domino-Knoevenagel hetero-Diels-Alder reaction,[5a,100] a highly reactive alkene moiety is first formed *in situ* through a Knoevenagel condensation beween an aldehyde and a cyclic or acyclic 1,3-dicarbonyl compound. In the subsequent step, the resulting 1-oxa-1,3-butadiene can undergo a cycloaddition with a dienophile such as an enol ether or an enamine to afford functionalised dihydropyranes (Scheme 21). In this sequence, ammonium salts are used as mild catalysts at room temperature in a wide range of solvents.



Scheme 21

For the domino-Knoevenagel hetero-Diels-Alder reaction in its intermolecular three-component version, there are almost no limitations concerning the natures of the aldehyde, the 1,3-dicarbonyl compound and the enol ether. As a catalyst, the neutral ammonium salt ethylenediammonium diacetate (EDDA) or piperidinium acetate are commonly used. The yields are as high as in the "two-component reaction", although the selectivity decreases and mixtures of *cis* and *trans* adducts are obtained. The Knoevenagel condensation and the subsequent cycloaddition usually take place at ambient temperature, but they can also be promoted by Lewis acids, allowing the domino sequence to proceed at lower temperatures. In addition, this sequence has been adapted to solid phase synthesis, allowing generation of combinatorial libraries.[101] Enantiomerically pure products can also be obtained through the use of enantiomerically pure aldehydes[102] or 1,3-dicarbonyl compounds,[103] or in the presence of chiral Lewis acids.[104] For all these reasons, the range of applications of this sequence is very large, especially in the field of natural product synthesis.[105] For example, Tietze's group described recently the enantioselective total syntheses of *Ipecacuanha* alkaloid emetine and *Alangium* alkaloid tubulosine.[106] The strategy is based on an elegant stereochemical combinatoric approach involving a domino-Knoevenagel hetero-Diels-Alder sequence with optically pure aldehydes obtained by a catalyst-controlled hydrogenation of cyclic imines (Scheme 22).[107]

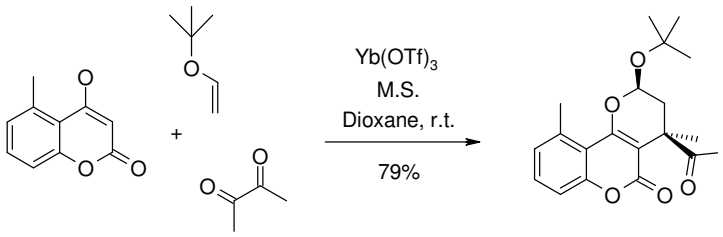


Scheme 22

5.2. Variants of the domino-Knoevenagel hetero-Diels-Alder reaction

Some variants of the domino Knoevenagel hetero-Diels-Alder reaction have been developed, further illustrating the high synthetic potential of this sequence. Here we give two recent examples.

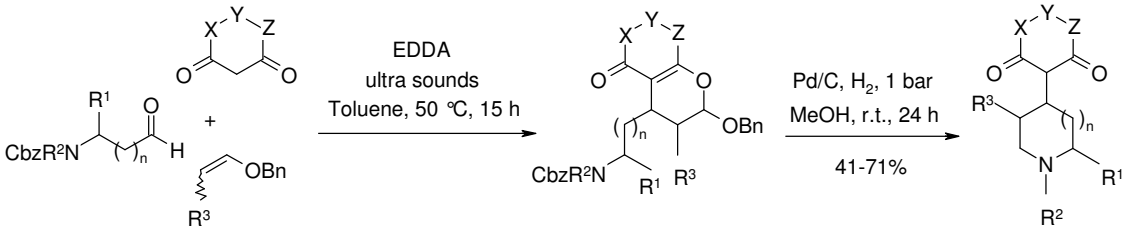
To begin with, the total synthesis of (±)-Preethulia Coumarin was achieved by starting from 4-hydroxy-5-methylcoumarin, with a new type of Lewis acid catalysed three-component domino-Knoevenagel hetero-Diels-Alder reaction as a key step.[108] The sequence employed α-dicarbonyl compounds as electrophilic carbonyl component to generate chromandiones, and vinyl ethers to trap them (Scheme 23).



Scheme 23

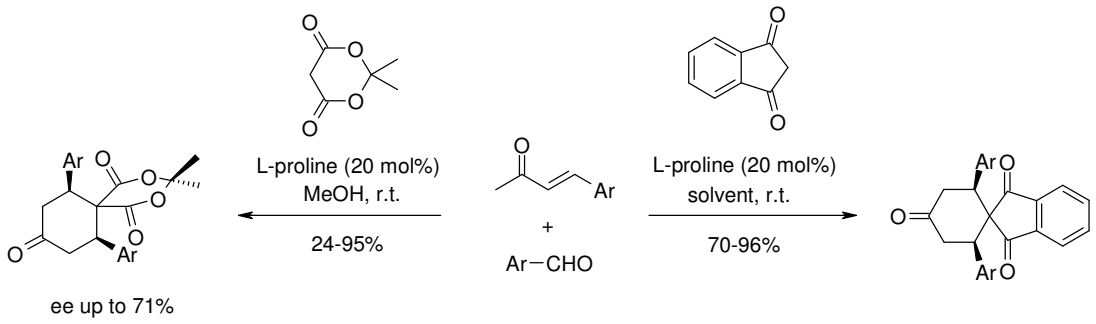
Optimisation of the sequence resulted in the use of activated molecular sieves, and ytterbium triflate as a catalyst. Under these conditions, a total diastereoselectivity was observed during the cycloaddition step.

Another modified domino-Knoevenagel hetero-Diels-Alder reaction, involving the use of amino aldehydes as electrophilic carbonyl components, was published at the same time by Tietze and co-workers (Scheme 24).[109] Condensation of a 1,3-dicarbonyl compound with an amino aldehyde and an enol ether, followed by an intramolecular reductive amination, resulted in the formation of betaines, which could be precipitated from the solution in high purity. This sequence illustrated a novel concept in combinatorial chemistry, combining the advantages of reactions in solution with those of solid-phase synthesis.



Scheme 24

As a complement to the dienophile character of Knoevenagel adducts, Barbas III and co-workers showed that enamines derived from L-proline and enones act as dienes in a concerted [4+2] cycloaddition with arylidene intermediates derived from 1,3-dicarbonyls. Indeed, they found that L-proline catalysed three-component asymmetric domino- Knoevenagel Diels-Alder reactions of readily available enones, arylaldehydes and either 1,3-indanediones[110] or Meldrum's acid,[111] affording highly substituted spiro[cyclohexane-1,2'-indan]-1',3',4-triones or spiro[5,5]undecane-1,5,9-triones, respectively. The reaction proceeded in a highly diastereoselective fashion and usually with excellent yields and up to 71% ee (Scheme 25).



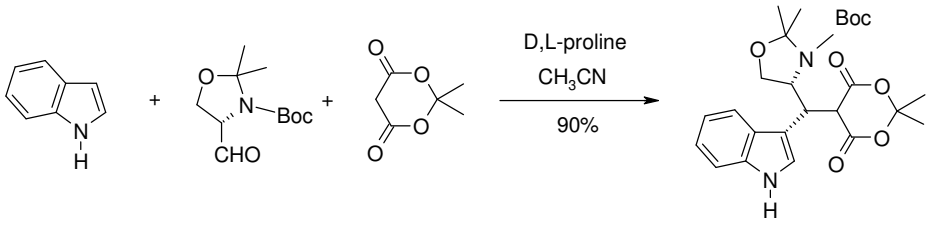
Scheme 25

5.3. Combinations of the Knoevenagel reaction with Michael addition

So far, we have described synthetic applications in which Knoevenagel products react as heterodienes or dienophiles. Because of their structures, however, they can also be viewed as Michael acceptors, and can react with a variety of nucleophiles. Multicomponent reactions combining Knoevenagel condensation and Michael addition have therefore been developed, and have found interesting applications in organic synthesis.

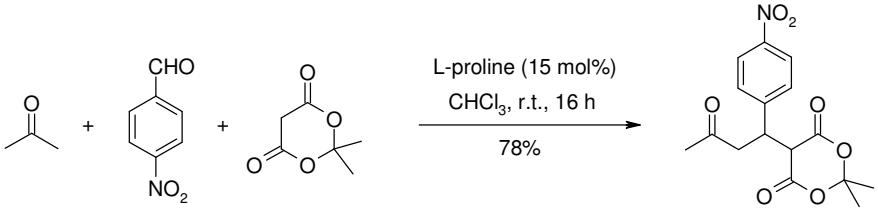
Apart from the 1,3-dicarbonyl itself,[112] a variety of nucleophiles have been used in the tandem Knoevenagel condensation/Michael addition. Among them, enamines have been extensively studied. As

examples, condensation of indole,[113] or more recently indolin-2-one[114] with Meldrum's acid and various aldehydes resulted in the one-pot synthesis of ethyl indolylpropionates and of spiro[pyrrolidine-3,3'-indolinones], respectively, in a so-called Yonemitsu condensation. Extending this three-component reaction to 2-substituted indoles, Sapi and co-workers recently reported an easy access to functionalised tetrahydrocarbazoles.[115] Finally, a variant of this reaction consisting on the diastereoselective trimolecular condensation of indole, Meldrum's acid and Garner's aldehyde (Scheme 26) was reported as a key step in the synthesis of chiral 2',3'-pyranone(pyrrolidinone)-fused tryptamines[116] and 3,4-heterocycle-annulated tetrahydro-β-carbolines.[117]



Scheme 26

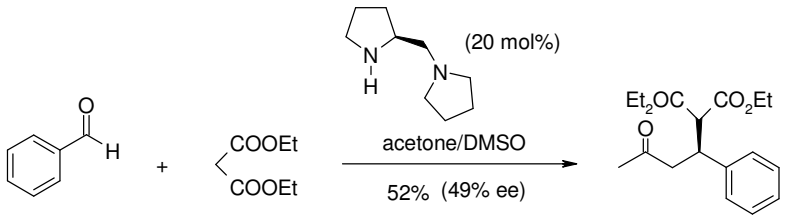
In 2001, List and Castello reasoned that alkylidene derivatives and enamines should be generable *in situ* from ketones, aldehydes and Meldrum's acid by use of a catalytic amount of proline. In this way they developed a novel three-component reaction consisting of a direct catalytic Michael addition of unmodified ketones to α,β-unsaturated carbonyl compounds, avoiding the use of preformed enolate equivalents, but unfortunately without any enantioselectivity (Scheme 27).[118]



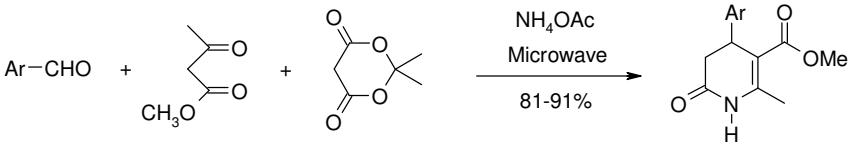
Scheme 27

At the same time, Barbas and co-workers reported an enantioselective version of this reaction using (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine as the catalyst.[119] Thus, Michael adducts with up to 91% *ee*s were obtained by treatment of alkylidene malonates with simple unactivated ketones under mild conditions. In the multicomponent variant of this sequence, one-pot treatment of benzaldehyde with diethyl malonate in an acetone/DMSO mixture, in the presence of 20 mol % of the chiral amine, resulted in the formation of the desired keto ester in 52% yield and with 49% *ee* (Scheme 28).

Another example of the use of enamines as nucleophile in the tandem Knoevenagel condensation/Michael addition involving a four-component reaction was recently reported. 4-Aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones were prepared in one-pot condensations from Meldrum's acid, methyl acetoacetate and the appropriate benzaldehyde in the presence of ammonium acetate as the source of ammonia under microwave irradiation conditions in the absence of solvent (Scheme 29).[120]



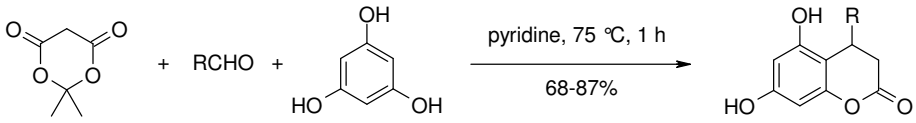
Scheme 28



Scheme 29

In this example, ressembling the Hantzsch dihydropyrimidine synthesis, the reaction consists of several successive steps with prior formation of two intermediates: the compound resulting from Knoevenagel condensation between Meldrum's acid and benzaldehyde and the enamino ester produced from acetoacetate and ammonia. The key step of the overall reaction is the Michael-type addition of the enamino ester to the Knoevenagel product, followed by decarboxylative cleavage of the Meldrum's acid nucleus. A similar reaction with dimedone and utilisation of ionic liquids as catalysts under solvent-free conditions, affording polyhydroquinoline derivatives in high yields, was developed very recently.[121]

Finally, it has also been reported that phenol derivatives can be used as nucleophiles in the tandem Knoevenagel condensation/Michael addition. In this way, the methylene derivatives resulting from the reaction between aldehydes and Meldrum's acid have been intercepted with phloroglucinol, offering a convenient route to certain dihydrocoumarins (Scheme 30).[122]

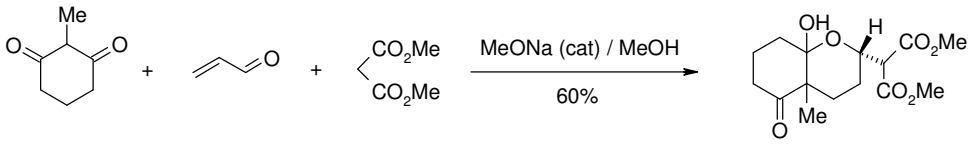


Scheme 30

6. MCRs based on Michael addition

As illustratred in the preceding paragraphs, MCRs involving 1,3-dicarbonyl compounds and based on Mannich or Knoevenagel condensations are numerous and well-documented in the literature. In contrast, only a few examples of MCRs involving such substrates and based on the Michael addition as starting point have been reported so far.

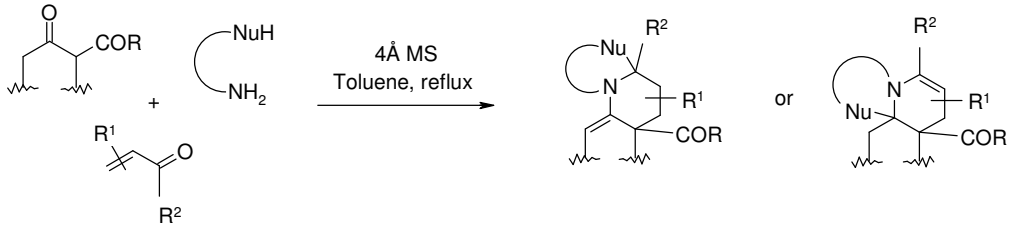
To begin with, in 1979 Eschenmoser and co-workers described a fragmentational approach to macrolides, starting from substrates accessible through a spectacular three-component condensation of acrolein, 2-methyl-1,3-cyclohexanedione and dimethyl malonate (Scheme 31).[123] The Michael addition of 2-methyl-1,3-cyclohexanedione to acrolein in methanol was catalysed by sodium methoxide, and the resulting adduct was condensed with dimethyl malonate in a one-pot reaction. A crystalline bicyclic keto hemiacetal diester was produced in 60% yield as a single diastereomer containing three stereogenic centers, in which the stereochemistry of the ring junction has not been clearly elucidated.



Scheme 31

After these pioneering results, MCRs initiated by Michael additions remained unexplored for over 20 years. As part of our continuing efforts directed towards the development of new domino transformations initiated by Michael addition,[5c,124] five years ago[125] we developed the first multicomponent domino reaction between 1,3-dicarbonyl derivatives, α,β-unsaturated aldehydes or ketones, and primary amines, providing a one-pot route to polyheterocyclic compounds of biological and pharmaceutical interests. Products are generally obtained with good purity simply by heating a mixture of the three components at reflux in toluene in the presence of 4-Å molecular sieves, followed by simple filtration through a short pad of celite.

The structures of the products obtained through this sequence strongly depend on the nature of the amine. Therefore, by using ω-functionalized primary amines, we were able to prepare fused polyheterocyclic or spiro-type polyheterocyclic compounds bearing aminal functions (Scheme 32).



Scheme 32

As illustrated in Figure 2, a large variety of polyheterocycles have been synthetised, starting from functionalised primary amines including aliphatic α,ω-diamines, amino-alcohols, amino-thiols or aromatic diamines. Various substrates such as (ethoxycarbonyl)piperidone, cyclic β-ketoesters or 1,3-diketones can be used in this sequence.

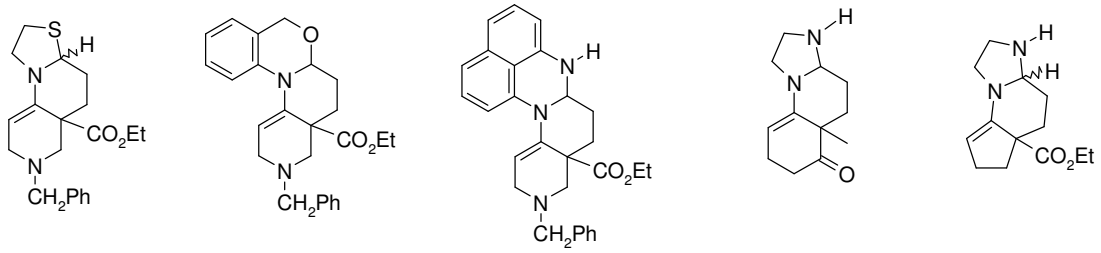


Figure 2

When *o*-hydroxyaniline was used as primary amine, a spiro-type tetracyclic compound was obtained (Figure 3). In the particular case of the use of an aminodiol, the one-pot sequence resulted in the formation of up to three new cycles, five novel bonds, and up to five stereogenic centres.

Alternatively, the introduction of various unfunctionalized primary amines into this three-component domino reaction resulted in the formation of other families of polyheterocycles. The reaction between

commercially available (ethoxycarbonyl)piperidone, acrolein and a primary amine in toluene at reflux and in the presence of 4-Å molecular sieves therefore resulted in the formation either of 1,6-hydronaphthyridines or of amino azabicyclo[3.3.1]nonanones, depending on the substitution of the amines (Scheme 33).[126]

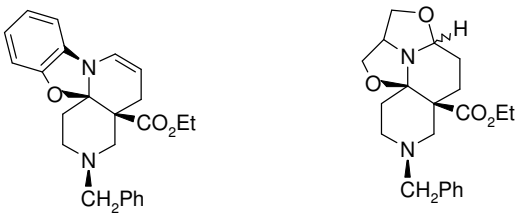
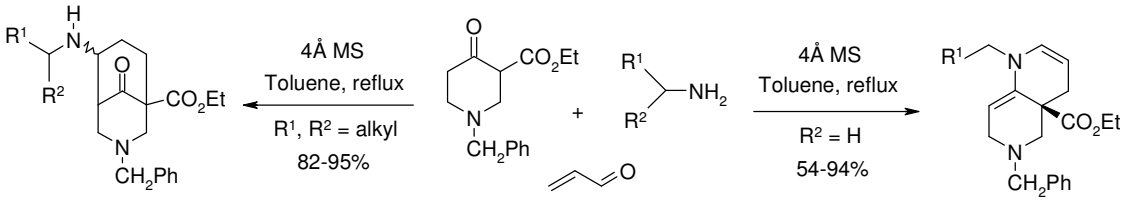
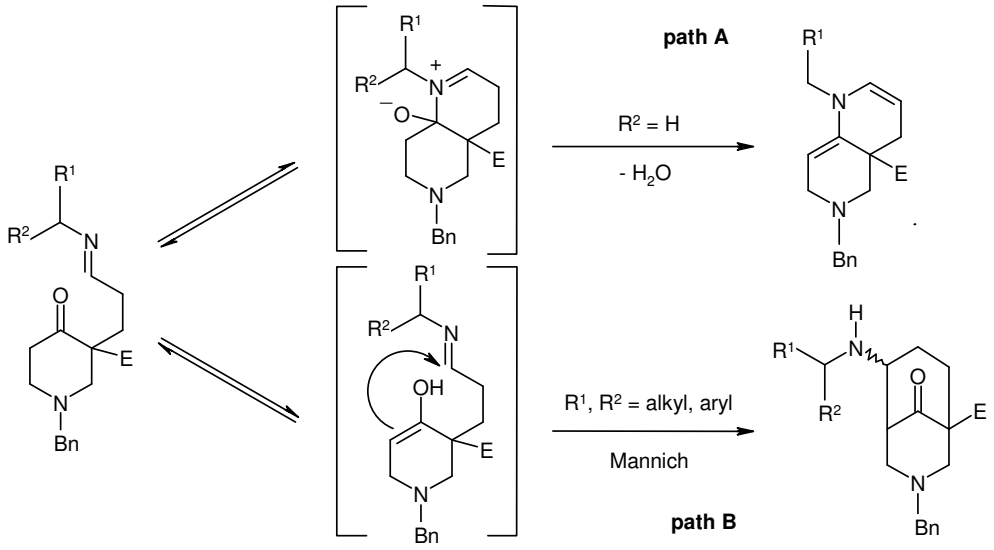


Figure 3



Scheme 33

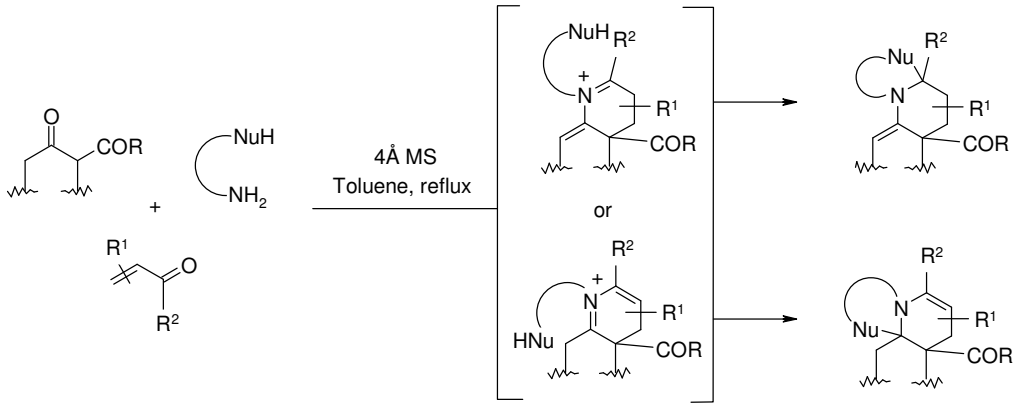
From a mechanistic point of view, we have shown[125,127] that the first step of the reaction consists of a molecular sieves-initiated Michael addition of the β-ketoester to acrolein to give the corresponding adduct, which reacts chemoselectively with the primary amine to form an aldimine (Scheme 34).



Scheme 34

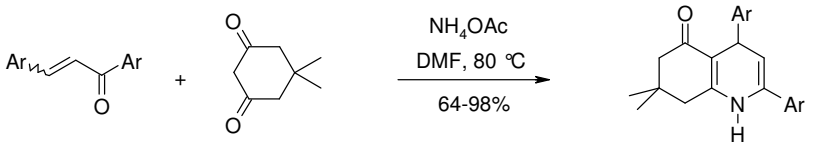
Then, depending on the substitution of the amine,[128] subsequent reversible nucleophilic addition of the aldimine to the ketone, providing an iminium intermediate, may be observed. In the case of unfunctionalised primary amines, when R^2 is H, dehydration occurs on the iminium, giving access to the 1,6-hydronaphthyridines (Scheme 33, path A). Alternatively, when R^1 and R^2 are alkyl or aryl groups, steric interactions disfavour the formation of the iminium, and the intramolecular Mannich reaction then takes place to afford the amino azabicyclo[3.3.1]nonanones (Scheme 33, path B).

In the case of nucleophilic functionalized amines, the two possible iminium intermediates can be trapped by the nucleophilic function, leading to the formation of fused or spiro-type polyheterocycles bearing aminal functions (Scheme 35).



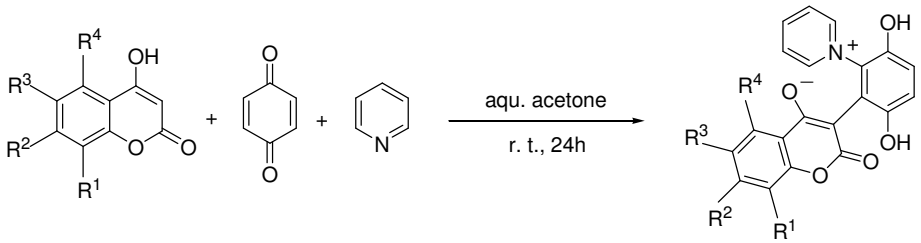
Scheme 35

At the same time, some other developments of Michael addition-initiated MCRs were reported in the literature. In 2002, for example, a series of substituted 5-oxo-octahydroquinoline derivatives were prepared in high yields from dimedone and 1,3-diaryl-2-propen-1-one in DMF at 80 °C in the presence of ammonium acetate (Scheme 36).[129] After the Michael addition, the resulting 1,5-dicarbonyl adduct is cyclodehydrated with ammonium acetate as ammonia source.



Scheme 36

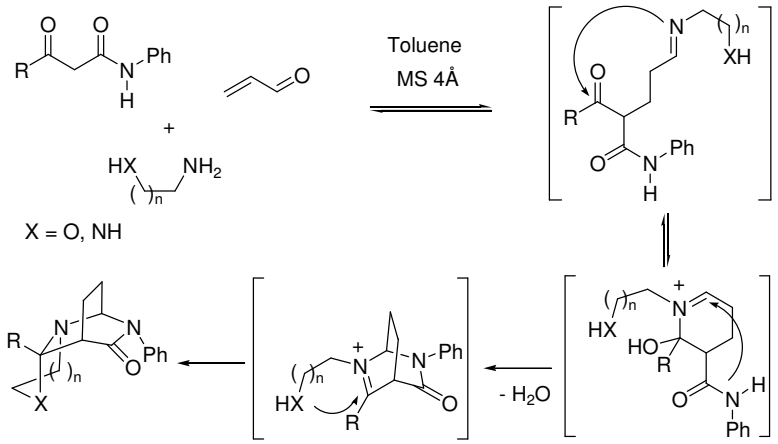
In 2004, an interesting three-component reaction between pyridine, *p*-benzoquinone and various 4-hydroxycoumarins was reported, leading to stable zwitterionic compounds (Scheme 37).[130] The authors proposed a possible mechanism consisting on the Michael addition of 4-hydroxycoumarin into *p*-benzoquinone, followed by the attack of pyridine at the 3-position.



Scheme 37

Finally, in 2005, we published a conceptually novel multicomponent domino reaction from simple β-ketoamides, which are involved not only as substrates but also as nucleophilic partners, leading to original

scaffolds having a highly functionalised 2,6-diazabicyclo[2.2.2]octane skeleton (2,6-DABCO) (Scheme 38).[131] The key steps of this one-pot process are the successive formation of two iminium intermediates, trapped *in situ* by two different nucleophiles, one being substrate itself and the other one resulting from the heterofunctionalisation of amine partners.



Scheme 38

A range of valuable new elaborated polycyclic structures were synthesised in good to excellent yields by simply heating a toluene solution of β-ketoamides, acrolein and functionalised amines, in the presence of 4Å molecular sieves. These neutral heterogeneous conditions proved to be of general applicability and a series of expected bridged bicyclic products were obtained, by simple filtration through a short pad of Celite, with generally very high chemical purity (Figure 4).

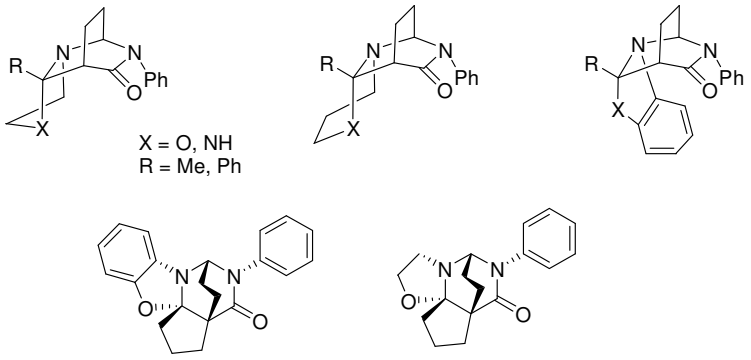


Figure 4

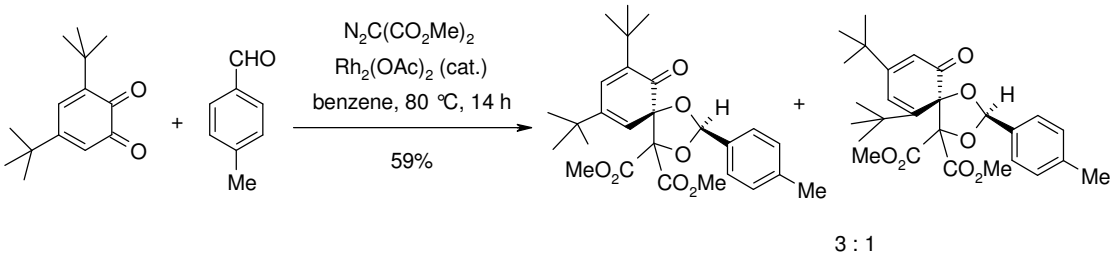
In all cases, the totally diastereoselective obtention of a single product is observed with concomitant formation of up to three new cycles, five different bonds including two C-C ones, and up to five stereogenic centers, two of them being chemically differentiable nitrogen atoms. Moreover, the one-pot sequence is step- and atom-economic and also ecologically benign since water is the only by-product, easily trapped by molecular sieves.

7. Miscellaneous

Other MCRs involving 1,3-dicarbonyls or their synthetic equivalents have received more and more attention in the last few years. Some of the more recent examples in this field are reported in the following sections.

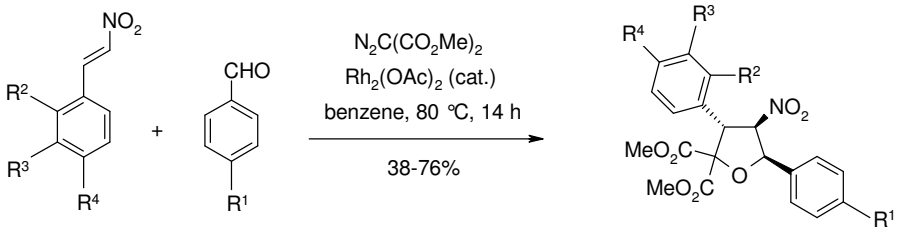
7.1. Metal-catalyzed MCRs involving 1,3-dicarbonyl derivatives

In 2003, Nair and co-workers published the synthesis of novel spiro-dioxolanes through a facile three-component, rhodium-catalysed reaction of bis(methoxycarbonyl)carbene, aldehydes and *o*-quinones.[132] Rh(II)-catalysed decomposition of dimethyl diazomalonate in the presence of *p*-tolualdehyde and 3,5-di-*tert*-butyl-1,2-benzoquinone, for example, afforded a 3:1 regioisomeric mixture of dioxolanes (Scheme 39).



Scheme 39

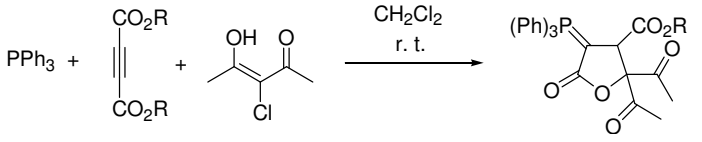
This multicomponent reaction probably involves the formation of a carbonyl ylide through the reaction between a carbene and the aldehyde and its trapping by the quinone carbonyl. The reaction was found to be general with respect to a variety of aromatic aldehydes and 1,2-benzoquinone. This sequence has more recently been developed with β-nitrostyrenes, providing highly substituted tetrahydrofuran derivatives (Scheme 40).[133]



Scheme 40

7.2. MCRs involving 1,3-dicarbonyls in combination with acetylenic derivatives

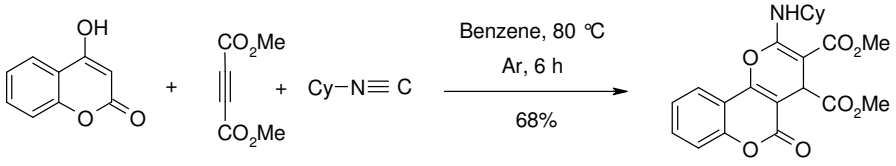
In 1997, three-component reactions between triphenylphosphine, 3-chloropentane-2,4-dione and dialkyl acetylenedicarboxylates were reported. This procedure revealed to be an acceptable preparation of butyrolactones with variable functionalities (Scheme 41).[134]



Scheme 41

More recently, Nair and co-workers reported a novel approach to pyran-annulated heterocyclic systems, through an efficient multicomponent reaction involving the interception of the zwitterionic intermediate between dimethyl acetylenedicarboxylate and isocyanides with some active methylene compounds.[135] As an illustration, treatment of 4-hydroxycoumarin with dimethyl acetylenedicarboxylate and

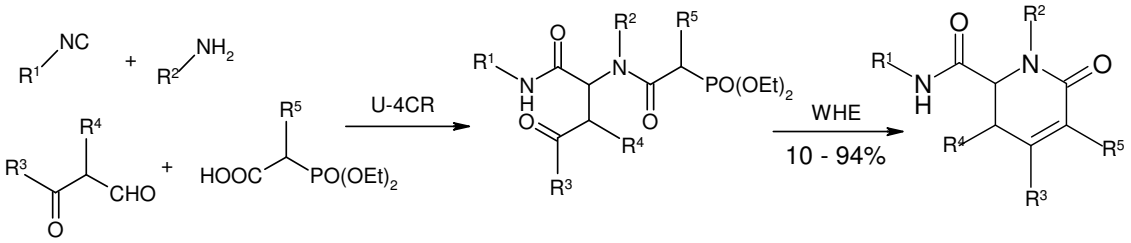
stoechiometric amount of cyclohexyl cyanide at reflux in benzene afforded the corresponding product in 68% yield (Scheme 42).



Scheme 42

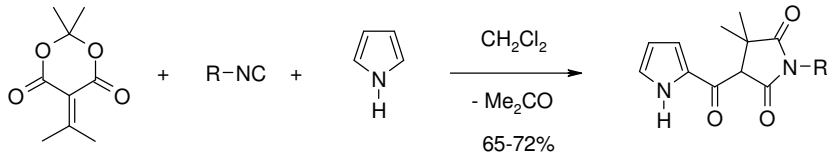
7.3. MCRs involving 1,3-dicarbonyls in combination with isocyanide derivatives

In a recent publication, Dömling and co-workers demonstrated that isocyanides, primary amines, β-ketoaldehydes, and phosphonoacetic acids react smoothly at ambient temperature in methanol to afford the corresponding Ugi products (Scheme 43).[136] A subsequent Wittig ring-closing reaction, in its Horner/Wadsworth/Emmons variant, afforded highly substituted pyridones in low to excellent yields.



Scheme 43

Contemporaneously, Yavari and Habibi reported a three-component synthesis of pyrrolidine-2,5-diones involving a 1,3-diester derivative as substrate.[137] 5-isopropylidene Meldrum's acid smoothly underwent reaction with alkyl isocyanides in the presence of pyrrole or indole to give the corresponding products in good yields (Scheme 44).



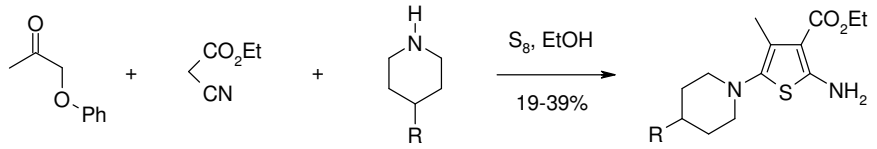
Scheme 44

7.4. MCRs involving cyanomalonate derivatives

In the last few years, cyanomalonate derivatives -which can be regarded as 1,3-dicarbonyl equivalents- have gained considerable attention as useful substrates in multicomponent reactions. Most of these sequences are initiated by a Knoevenagel condensation between cyanoacetates, cyanoketones or malononitrile and carbonyl compounds.

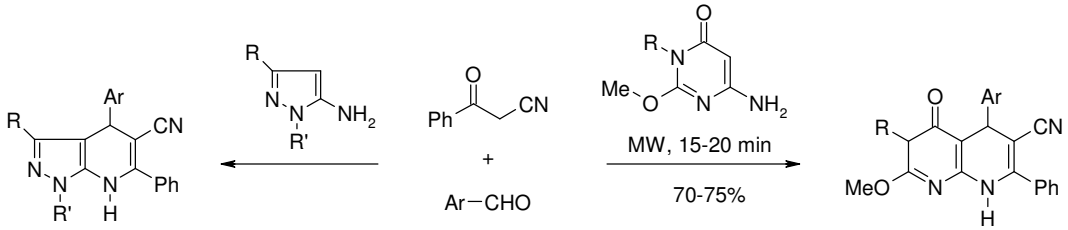
In 1965, Gewald reported a three-component condensation of a β-keto ester, a cyanoacetate and elemental sulfur in the presence of an organic base to yield a thiophene nucleus.[138] This reaction remained unexploited until 1999, when McKibben and Castelhano published an improvement of the reaction

conditions for semi-automated synthesis to provide tetrasusbstituted thiophenes.[139] Following this work, Pinto *et al.* described the four-component preparation of 5-aminothiophenes through an extension of the Gewald's reaction (Scheme 45).[140] Condensation of ethyl cyanoacetate, phenoxyacetone, elemental sulphur and various cyclic secondary amines, for example, provided the corresponding 5-aminothiophenes in moderate yields.



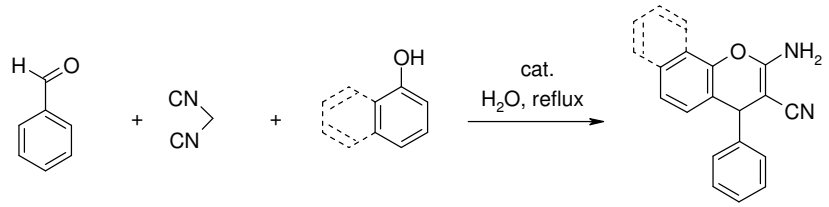
Scheme 45

In the case of α-cyanoketones, Quiroga and co-workers described a simple and efficient synthesis of pyrazolopyridines which are interesting biological targets, through three-component reactions involving aminopyrazoles, benzoylacetonitrile and various aromatic aldehydes (Scheme 46).[141] More recently, by replacing aminopyrazoles by aminopyrimidines, they succeeded in the development of a regioselective, facile and practical method for the preparation of novel pyrimidinones.[142] The synthesis was conducted with the aid of microwave irradiation under solvent-free conditions, providing the corresponding products in good yields.



Scheme 46

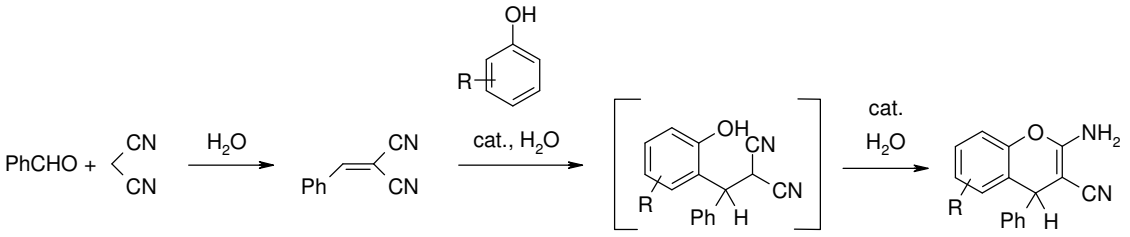
Malononitrile has also been widely exploited; to begin with, Ballini and co-workers in 2001 reported a three-component process for the synthesis of 2-amino-2-chromenes simply by heating a mixture of an aldehyde, malononitrile and a phenol at reflux in water in the presence of a catalytic amount of cetyltrimethylammonium chloride (Scheme 47).[143] More recently it was shown that tetrabutylammonium bromide[144] and basic alumina[145] could also act as catalysts for this transformation.



Scheme 47

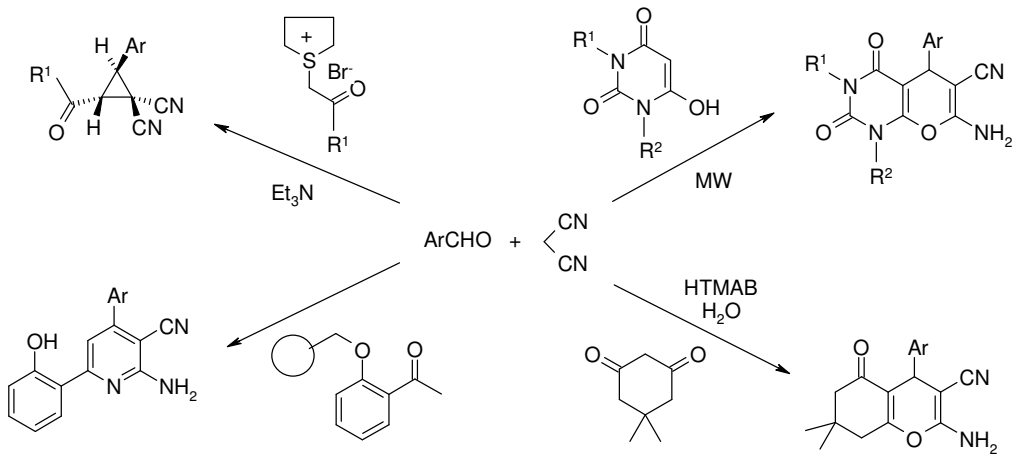
The key step in this one-pot sequence involves the *ortho*-C-alkylation of the phenol with the electrophilic C=C double bond of the Knoevenagel adduct resulting from the condensation of malononitrile

with the aldehyde. A subsequent nucleophilic addition of the phenolic OH group to the CN moiety produces the final 2-amino-2-chromene (Scheme 48).

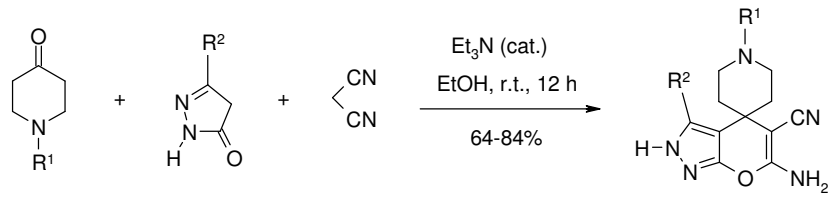


Scheme 48

Some other nucleophiles have been introduced in this one-pot sequence, providing simple access to various polyheterocycles (Scheme 49). As one example, microwave-assisted use of barbituric acids under solvent-free conditions gave pyrano[2,3-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines in excellent yields.[146] A clean synthesis of tetrahydrobenzo[*b*]pyran derivatives, with dimedone as nucleophile and hexadecyltrimethyl ammonium bromide as catalyst in aqueous media, has also been reported.[147] This transformation was adaptable to solid-phase conditions, as illustrated by the efficient synthesis of 3-cyano-6-(2-hydroxyphenyl)pyridines through condensation of hydroxyacetophenone immobilised on Wang resin with malonitrile and various aldehydes.[148] Finally, the three-component reaction of sulfonium salts, malonitrile and aldehydes in ionic liquid, in the presence of Et_3N, provided a convenient synthesis of substituted 1,1-dicyanocyclopropanes.[149]



Scheme 49



Scheme 50

Finally, in 2002, Evans and co-workers reported a three-component condensation of substituted piperidin-4-one, pyrazol-5-ones and malononitrile in the presence of a catalytic amount of Et_3N, giving

highly substituted spiro-pyrazolopyrans in good yields (Scheme 50).[150] On replacement of the chemical base by an electrogenerated base, the authors showed that the sequence became more regioselective and the yields ca. 12-15% greater than those of the reaction catalysed by chemical bases.

8. Conclusion

This critical selection of diverse MCRs developed over more than a century clearly shows that simple 1,3-dicarbonyl derivatives still constitute versatile substrates in organic chemistry and can be accommodated in many diverse synthetic pathways. The high synthetic potential of these very easily accessible reagents has found numerous applications, especially for the synthesis of complex heterocyclic structures found in important natural and unnatural compounds. Future development of new synthetic transformations making use of the high reactivity of 1,3-dicarbonyls towards many other substrates should enlarge the scope of this field, allowing the facile and selective construction of highly functionalised small organic molecules of high synthetic and biological values.

We are currently engaged in efforts to develop new MCRs with 1,3-dicarbonyl systems, especially transformations involving Michael additions and Knoevenagel reactions.[151]

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FRONTIERS IN BIOPHOTONICS: HETEROCYCLE-BASED PHOTOSENSITIZERS FOR PHOTODYNAMIC THERAPY (PDT)

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Abstract. *An overview of photosensitizers for photodynamic therapy is presented. It is not intended as an exhaustive description of the state of the art but just to account for the relevance of the use of number of heterocycles in this fascinating topic. According to this strategy no photosensitizers syntheses are described herein and the interested reader is expected to check with the original literature.*

Contents

1. Introduction

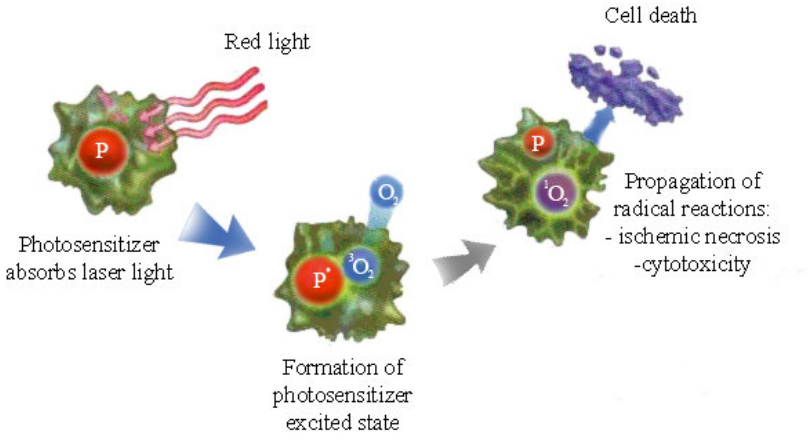
Photodynamic therapy[1] (PDT) is a new promising technique for the treatment of cancer disease, which involves the use of two non-toxic components (light and a photosensitizer) that once combined can induce cellular and tissue damage *via* singlet oxygen generation (Scheme 1). Ancient egyptians were the first to employ light to treat a wide variety of diseases, including psoriasis, rickets, vitiligo and skin cancer. But the real therapeutic use of light began only in the last century. Raab was the first scientist to report on the toxic

effect due to the combination of light and acridine orange on living paramecium.[2] The modern era of PDT started in the 1960s, when Lipson and colleagues introduced a preparation called *Haematoporphyrin Derivative*. This preparation was found to be localized in tumours and emit fluorescence when irradiated in the UV (366 nm). After that the *Haematoporphyrin Derivative* was investigated for a decade as a diagnostic agent for cancer, it was understood that, upon changing the irradiation conditions, the PDT effect could be turned from detection to photodegradation of tumours.

This kind of observation was first reported by Diamond in 1972; in the same years Weishaup identified singlet oxygen as the cytotoxic agent in the photodynamic process.[3] In 1974 Dougherty showed that fluoresceine could be used to reduce the growth rate of mammary tumours in animals. Because of its poor singlet oxygen generation and penetration into organic tissues, new photosensitizers, most of them possessing a porphyrinic skeleton, were studied.

The first photodynamic experiment on humans was carried out by Kelly and Snell in 1976; they found that the *Haematoporphyrin Derivative* could be used as an aid for the diagnosis and treatment of some bladder carcinoma.[4]

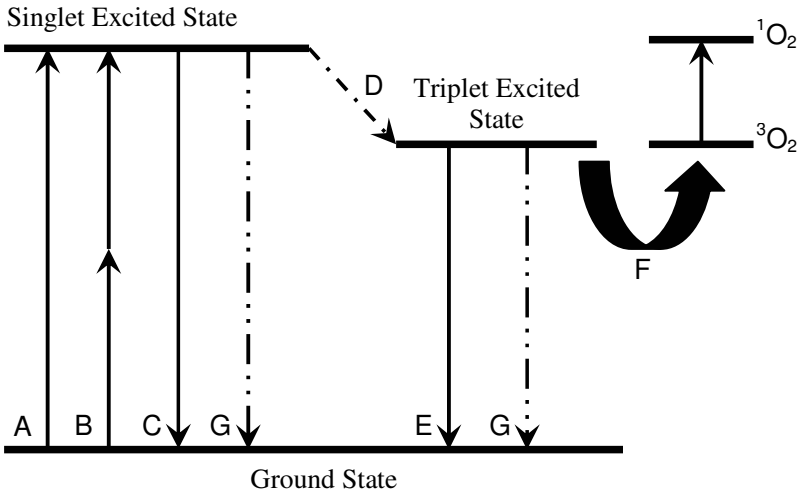
After several years spent in the isolation and identification of the active fractions of the *Haematoporphyrin Derivative*, a more purified version named Photofrin® was produced and approved for clinical use in United States, Canada, Netherlands, Japan and France against early- and late-stage lung cancers and oesophageal cancers and dysphasia, with other indications pending.[5] In addition to the approved indications, clinical trials are under way to evaluate the use of PDT for brain cancers, skin, prostate, cervix, and peritoneal cavity.[6] The most recent research is focused on the development of more powerful photosensitizers able to target selectively cancer cells[7] and specifically designed to work only upon longer wavelength irradiation with consequent better penetration in the living tissues.[8] Researchers are also investigating ways to improve the light delivery equipment in terms of focusing and wavelength selection. From the time when Photofrin® was FDA approved, many of the mechanisms of PDT action have been elucidated, several new photosensitizers prepared[6] and a wider scope for PDT demonstrated.



Scheme 1
Mechanism of action of PDT.

1.1. PDT Mechanism of action

The singlet oxygen generation process in PDT[3] can be accounted by a simplified Jablonski diagram (Scheme 2).[9]



Scheme 2

A simplified Jablonski diagram showing the various modes of excitation and relaxation in a molecule: (A) excitation *via* one-photon absorption; (B) excitation *via* two-photon absorption; (C) fluorescence; (D) intersystem crossing; (E) phosphorescence; (F) non-radiative transfer of energy to produce singlet oxygen; (G) internal conversion.

The photosensitizer is first excited to its singlet excited state *via* one (A) or two-photon absorption (B) of light of the appropriate wavelength. The photosensitizer can then relax back to its ground state by fluorescence (C) or can pass on its triplet excited state *via* intersystem crossing (D).

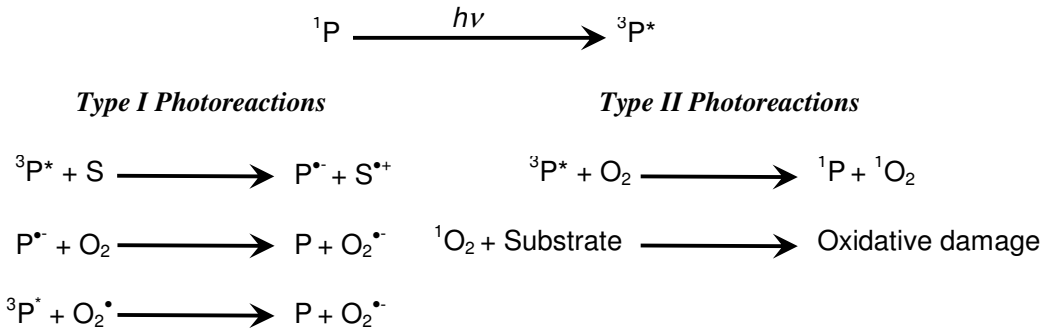
From the triplet excited state the photosensitizer can relax back to the ground state by phosphorescence (E) or transfer energy to another molecule *via* a radiationless transitions (F). Moreover, the photosensitizer can loose energy through internal conversion or radiationless transitions during collisions with other molecules (G).[9] If oxygen is present in the environment,[10] the photosensitizer can transfer its energy to oxygen to form singlet oxygen ($^1O_2$), a highly reactive oxygen species that can interact with a large number of biological substrates, inducing oxidative damage and eventually cell death (H). This kind of reaction is defined as a Type II mechanism. It is generally accepted that this is the dominant process in PDT[11] and that singlet oxygen is the primary citotoxic agent. However, there is also a Type I mechanism that becomes important at low oxygen concentration or in a more polar environment.

In this process the photosensitizer can react directly *via* electron transfer with organic substrates or the solvent or else another photosensitizer to yield free radicals and radical ions. These free radical species are highly reactive and can easily interact with molecular oxygen to generate superoxide anion or hydroxyl radicals with consequent biological damage.

1.2. Oxygen in PDT

Ground state oxygen exists uniquely as triplet state with two unpaired electrons distributed in the highest occupied orbitals. The spin-selection rule reduces its reactivity towards singlet ground state species, the vast majority of the known compounds. The first oxygen excited state is described by a fully occupied orbital and a completely unoccupied one; this state has an energy only 23 kcal above that of the ground state. This singlet state can easily react with other singlet state molecules because its radiative decay to the triplet ground state is a spin-forbidden transition resulting in a long-lived and highly reactive excited state (Scheme

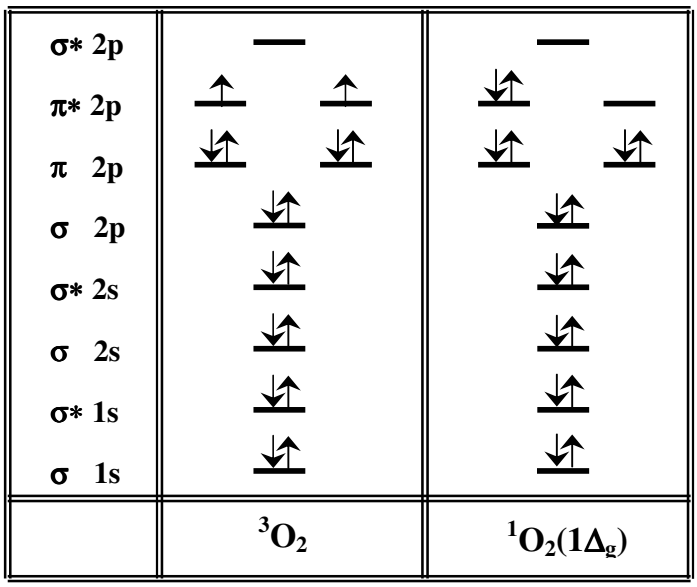
4). It should be noted that actually there are two singlet oxygen allowed states. The first one ($1\Delta_g$) has two electron in one p* orbital as reported in Scheme 4. The second singlet oxygen state is termed $1\sigma_g$ and displays one electron with pair spin on each of the two p* orbital (this state behaves as a diradical species). However, due to the relatively short life time of $1\sigma_g$ (comparable with that of the $1\Delta_g$ state only in the gas phase), the $1\Delta_g$ form is the prevalent one both in solution and in the solid state and is commonly referred as the singlet oxygen species in photodynamic therapy.[12]



Scheme 3

Type-I and Type-II photoreactions, where ^1P and $^3P^*$ are the photosensitizer in the ground state and the triplet excited state respectively, S is the substrate molecule, P^- is the reduced photosensitizer molecule, S^+ is the oxidized substrate molecule, O_2 is the molecular oxygen at the ground state, O_2^- is the superoxide anion, $O_2^{\bullet}$ is the superoxide radical, P^+ is the oxidized photosensitizer and $^1O_2$ is the oxygen in the singlet excited state.

The lifetime of $^1O_2$ depends on the nature of the solvent (Table 1), but commonly it ranges from 10-100 μs in organic solvents. Since singlet oxygen reacts so readily, PDT-induced oxidative damaged is highly localized to a region no larger in diameter than the thickness of a cell membrane.



Scheme 4

Molecular orbital diagrams showing the electron distribution in the ground state and in the first excited state.

Table 1. Lifetimes of singlet oxygen in various solvents.

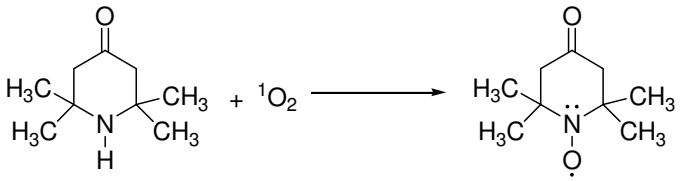
Solvent	τ (μs)	Solvent	τ (μs)
H_2O	2	$CHCl_3$	60±15
MeOH	7	CS_2	200
EtOH	12	$CDCl_3$	300±100
C_6H_{12}	17	CCl_4	700±200
D_2O	20	Freon 11	1000±200
C_6H_6	24	C_6F_6	3900
CH_3COCH_3	26	Air 1 atm	~76000

1.3. Detection and evaluation of singlet oxygen

The detection of singlet oxygen is difficult due to its excited state nature, although a long living one. Several analytical techniques have been developed and in the following subsection we will describe the most commonly employed ones.

Singlet oxygen luminescence: as $^1O_2$ decays back to the ground state, some of the energy is emitted as phosphorescence. The light from singlet oxygen appears in the infrared region at 1269 nm[13-15] and can be detected in biological system using a solid-state near-infrared detector.[16]

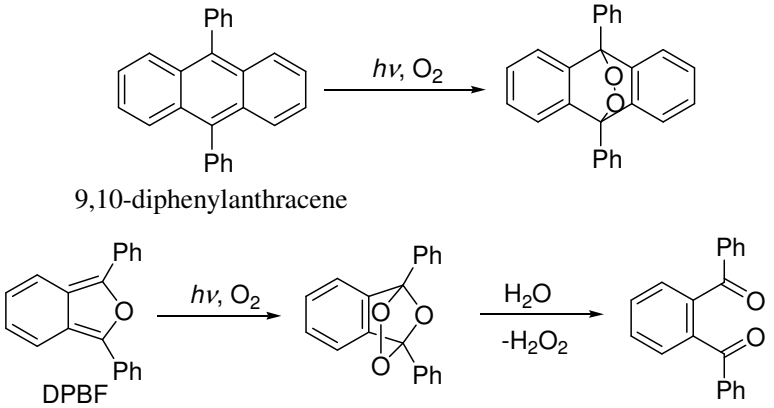
Electron paramagnetic resonance: one of the most common detection methods is based on electron paramagnetic resonance (EPR), a highly sensitive technique in the detection of free radicals. The reaction of $^1O_2$ with a stable molecule can generate a moderate long-lived free radical acting as a spin label and enabling an unambiguous identification. As an example the spin label 2,2,6,6-tetramethly-4-piperidone (TEMP) can react with singlet oxygen to form a stable nitroxide radical adduct, 2,2,6,6-tetramethyl-4-piperidone-*N*-oxyl (TEMPO), easily detectable by EPR.[17] The oxidation of 2,2,6,6-tetramethyl-4-piperidone with singlet oxygen to 2,2,6,6-4-piperidone-*N*-oxyl formation is shown in Scheme 5.



Scheme 5

Chemical quenchers: chemical trapping by spectroscopic probes is also specific and much more sensitive than the detection of the 1270 nm emission.[18] The photochemical methods do not require large instrumental efforts and can be easily carried out with a simple UV-Vis spectrophotometer. A mixture of the photosensitizer, oxygen and the quencher, a molecule able to selectively react with $^1O_2$, is irradiated at the photosensitizer absorption wavelength. The quencher reaction usually involves an interruption in its conjugation path with a consequent UV-Vis bleaching, easily monitored by absorption spectroscopy. The singlet oxygen rate of formation is proportional to the slope of the absorption loss plotted against light-irradiation time. The most common chemical quencher in organic solvents are: a) 9,10-diphenylanthracene,

which reacts specifically with $^1O_2$ to form an endoperoxide. Evidence for $^1O_2$ production[19] is provided by the decrease in absorbance of antracene at 355 nm, b) 1,3-diphenylisobenzofuran (DPBF) behaves similarly (decrease of its λ_{max} at 410 nm) (Scheme 6).[20] In aqueous environments the *p*-nitrosodimethylaniline is commonly employed (λ_{max} = 440 nm).



Scheme 6

2. Photosensitizers

Photosensitizers[21] are chromophores able to efficiently generate singlet oxygen upon irradiation at their HOMO-LUMO transition wavelengths. There are hundreds of natural and synthetic dyes that can act as photosensitizers for PDT, ranging from active principles extracted from plants to complex synthetic macrocycles. An optimized photosensitizer must posses quite a unique collection of different properties:

1. a sharp and intense absorption band mainly localized in the biological tissues transparency window (700-900 nm);
2. good solubility in a biological environment;
3. an almost complete dark non toxicity;
4. high singlet oxygen sensitization quantum yield;
5. preferential localization within the tumour;
6. easy after-treatment removal from the body.

Table 2 provides an overview of the spectroscopic features of various photosensitizers currently in clinical or preclinical trials.

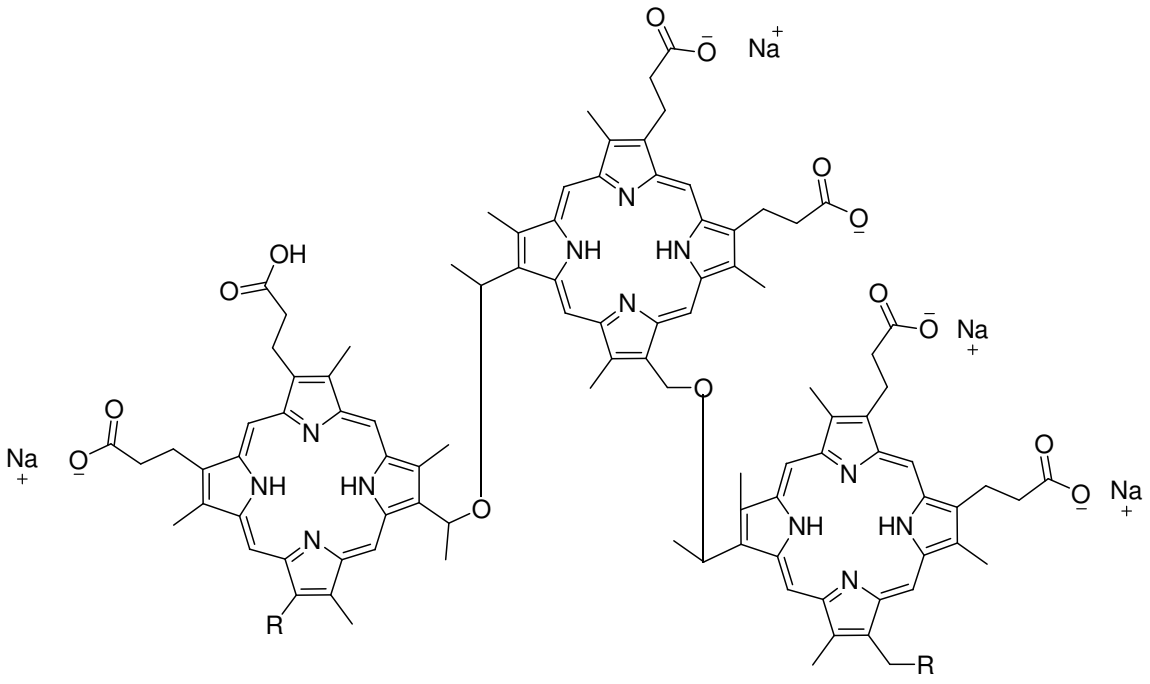
2.1. Photofrin®

The first generation photosensitizers - up to now still the only one approved by FDA for human treatment - are haematoporphyrin derivatives[31] such as Photofrin® (Scheme 7).

Haematoporphyrin derivatives were originally described by Lipson *et al* in 1961 and are prepared[32] by acetylation of haematoporphyrin (Hp), followed by neutralisation prior to alkaline hydrolysis. The resulting mixture contains haematoporphyrin, hydroxyethylvinyldeuteroporphyrin (HVD) and protoporphyrin (Pp), as well as a complex dimeric and oligomeric fraction containing ester, ether and carbon-carbon linkages[33] of haematoporphyrin. HpD is typically 45% monomeric/dimeric porphyrins and 55% oligomeric material, the latter being accountable for the tumor localising activity of HpD *in vivo*. Partial purification of the most active of these oligomers by high performance liquid chromatography (HPLC) or size-exclusion gel chromatography lead to Photofrin®, 90-95% of which is the active component.[34]

Table 2. Spectroscopic features of the photosensitizers presently investigated in clinical or preclinical trials.

Photosensitizer	λ (nm)	ε ($M^{-1} cm^{-1}$)	Φ_Δ
Haematoporphyrin derivative	630	3.0×10^3	0.6[22]
5-Aminolaevulinic acid (protoporphyrin IX)	635	$<5.0\times10^3$	0.6[23]
Verteporfin	690	3.5×10^4	0.7[24]
Tin etiopurpurin	660	2.8×10^4	0.6[25]
Temoporfin	652	3.0×10^4	0.43[48]
Cd(II)Texaphyrins	732	4.2×10^4	0.69[26]
Phthalocyanines	670-680	2.5×10^5	0.34[27]
Naphthalocyanines	750-780	$>10^5$	0.3-0.5[27]
N-aspartyl chlorin e6	664	4.0×10^4	0.8[28]
Rhodamines	511	2.0×10^4	0.02[29]
Hypericin	590	4.4×10^4	0.4[30]



Scheme 7

Photofrin® (porfimer sodium) is marketed by Axacan Pharma Ltd and is used in the PDT of tumors (lung, oesophageal, bladder, gastric and cervical) and high-grade dysplasia (HGD) in Barrett's oesophagus (BE) (http://www.qlt-pdt.com[35]). Moreover, Photofrin® promoted PDT is under investigation as a possible therapy against Karposi's sarcoma, cancers of the head, neck, brain, intestine, lung, breast, and skin. Other possible target afflictions include psoriasis and arterial restenosis.[36,37]

Photofrin®-mediated PDT has proved successful for a wide range of cancers; nonetheless a number of drawbacks and side effects are well-documented. Being this drug a complex mixture, there are questions concerning the identity of the active components and also the reproducibility of the synthetic process. The treatment commonly involves the use of laser light at 630 nm. At this wavelength the laser beam can only penetrate in the tissue to a maximum depth of 3-10 mm, clearly limiting the therapy applicability to superficial diseases. After treatment, cutaneous light sensitization can last for several weeks and patients are advised to avoid bright light during this period. Due to all of these drawbacks and according to the requirements discussed in paragraph 2, new photosensitisers have been synthesised. The so called "second generation" photosensitisers include modified porphyrins, chlorines, bacteriochlorins, phthalocyanines, naphthalocyanines, pheophorbides, purpurins and squaraines.

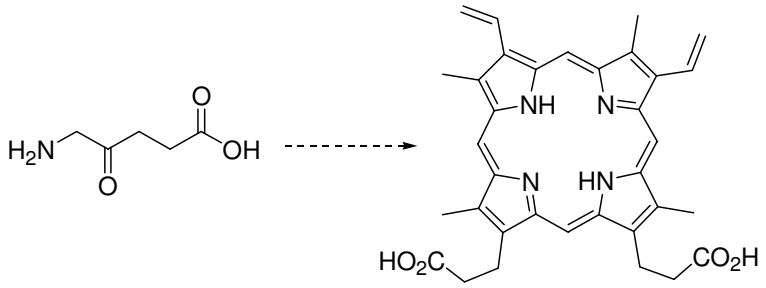
2.2. 5-Aminolevulinic acid

Aminolevulinic acid[38] (ALA) is the metabolic precursor of the real photosensitizer, protoporphyrin IX (PpIX). The synthesis of ALA is normally tightly controlled by feedback inhibition of the ALA synthetase presumably by intracellular heme levels. ALA, when provided to the cell, bypasses this control point and results in the accumulation of PpIX, which is converted into heme by ferrochelatase through the addition of iron to the PpIX nucleus.

Marketed by DUSA Pharmaceuticals (Toronto, Canada) under the name Levulan®, Aminolevulinic acid is applied topically (directly to the skin) on the face or scalp to treat actinic keratosis lesions. Unlike porfimer sodium, it does not reach other parts of the body. Therefore the lesions are sensitive to light but the rest of the body is not.

Photosensitization following application of Levulan® occurs through the metabolic conversion of ALA to PpIX (see Scheme 8) that when exposed to light of the appropriate wavelength and energy produces the photodynamic reaction. The tumor selectivity of ALA is a consequence of the increased permeability of abnormal keratin, increased levels of porphobilinogen deaminase, decreased levels of iron and decreased activity of ferrochelatase in the tumour cells. These conditions result in an accumulation of protoporphyrin IX in diseased cells, resulting in selectivity for the target tissue.[39] About 14 to 18 hours after the agent is applied (usually the next day), the area is treated with a blue light source for about 15 minutes (see http://www.dusapharm.com). The company has also announced Phase I/II clinical trials involving Levulan® as a treatment for acne, for the removal of unwanted hair, and for the photodetection of bladder cancer. Other clinical trials are under way using ALA as a therapy for non-melanoma skin cancer,[40] endometrial ablation,[41] late-stage oesophageal cancer,[42] gastrointestinal cancer,[37] Barrett's oesophagus[43] and psoriasis.[41] Because of the low molecular weight and polar properties of ALA, it can also be used as a topical PDT agent against a number of dermatological conditions and has been shown to be effective against superficial basal cell carcinomas, Bowen's disease, erythroplasia of Queyrat, cutaneous T-cell lymphoma and hirsutism.[41]

Because photosensitisation is still porphyrin-mediated, excitation of PpIX also occurs at 630 nm, offering no advantage over HpD in the tissue penetration depth. The hydrophilic nature of ALA also limits drug penetration through the skin, however this problem may be solved by the use of lipophilic ALA esters which can penetrate cells more easily. PhotoCure AS (Oslo, Norway) is going to market the methyl ALA ester, P1202, and is studying its potential against basal cell carcinomas and other skin lesions together with several conditions that have been shown to be treated effectively by ALA.[36]

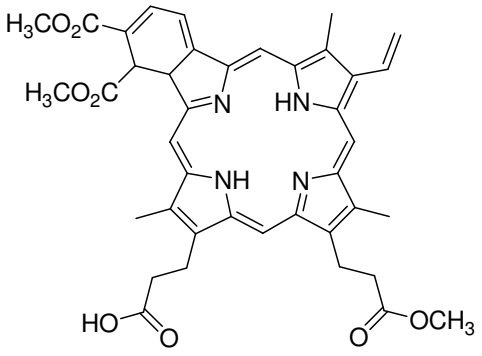


5-Aminolevulinic acid Protoporphyrin IX

Scheme 8

2.3. Verteporfin

Visudyne™ was the first approved photodynamic therapy agent for wet age-related macular degeneration (AMD) the leading cause of blindness in people over the age of 55. Visudyne™ is a verteporfin (Scheme 9) and was launched in 2000 by QLT PhotoTherapeutics and distributed by Novartis Ophthalmics (see http://www.qlt-pdt.com).[44] Moreover, in 2001 it was also approved for the treatment of pathological myopia (a form of nearsightedness) and presumed ocular histoplasmosis (a fungal infection of the eye). Verteporfin is also in Phase III clinical trials for cutaneous non-melanoma skin cancer and Phase I/II trials against other non-melanoma skin cancers (such as multiple non-melanoma skin cancer),[45] psoriasis,[46] and psoriatic and rheumatoid arthritis. Extensive preclinical work has been carried out using verteporfin as a therapy for multiple sclerosis and Barrett's oesophagus and as an agent to achieve endometrial ablation and bone marrow purging.[45] Showing a much stronger absorbance at a longer wavelength (690 nm), verteporfin enables an in depth tissue light penetration 50% greater than that achievable with Photofrin® at 630 nm. It is also readily absorbed by the tumour - reaching an optimal tumour-normal tissue ratio 30-150 minutes after intravenous injection - and cleared from the body so that skin photosensitivity lasts only a few days.



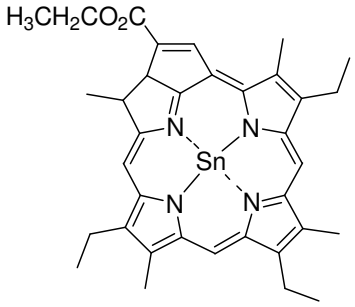
Verteporfin

Scheme 9

2.4. Tin etiopurpurin

Miravant Medical Technologies (Santa Barbara, CA, USA) has developed a tin etiopurpurin (SnET2)[47] marked as Photorex™ (Scheme 10) as part of their PhotoPoint™ procedure. The PhotoPoint procedure is an emerging treatment method based on drugs that respond to light. When administered to the body, PhotoPoint drugs are designed to preferentially accumulate in rapidly reproducing (hyperproliferating) cells and blood vessels based on the metabolic characteristics of these tissues. Since a number of disease conditions involve

tissue proliferation, PDT has a range of potential applications. Photorex™ is among the most developed of Miravant's light-activated compounds, and has completed two Phase III clinical trials for the treatment of wet AMD. Miravant has developed additional photosensitizers for dermatology, cardiovascular diseases and oncology that are now under phase II and preclinical investigation respectively.

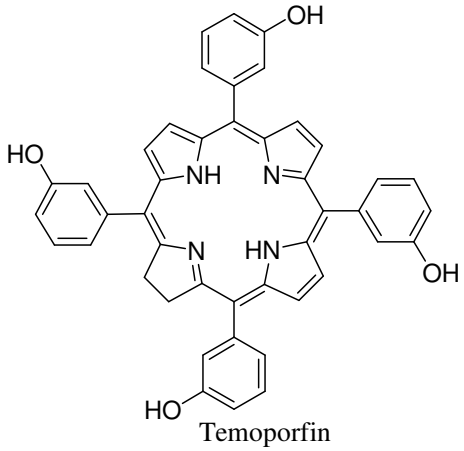


Tin etiopurpurin

Scheme 10

2.5. Temoporfin

Foscan® is a photosensititizing agent containing temoporfin (Scheme 11) or tetra(*m*-hydroxyphenyl) chlorin (*m*THPC)[32,48] and is marketed by Scotia Pharmaceuticals (Guildford, Surrey, UK) as a new second-generation photosensitizer for PDT (see www.bibliotecpharma.com). In 2001, Foscan® was approved in the European Union, Norway & Iceland for the palliative treatment of patients with advanced head and neck cancer who have failed prior therapies and are unsuitable for radiotherapy, surgery or systemic chemotherapy. Foscan® is also in clinical trials for late stage oesophageal cancer and dysplasia in Barrett's oesophagus.[42] Future trials using this photosensitizer in Europe, the US and the Far East against malignant and non-malignant diseases are anticipated and will include trials against gastric and prostatic cancers, hyperplasia, field sterilization after cancer surgery and for the control of antibiotic-resistant bacteria. In addition, topical formulations of temoporfin are being developed to compete with ALA against skin cancers and other dermatological conditions.



Temoporfin

Scheme 11

Foscan® requires an activation wavelength of 652 nm, with a delay of 4 days between injection into the bloodstream and activation with laser light. This allows for accumulation of the photosensitiser in the cancer cells. Temoporfin could be one of the most phototoxic of all the second-generation photosensitizers currently

being investigated. It requires very low doses (as little as 0.1 mg kg^{-1}) as well as an unusually low light dose (as low as 10 J cm^{-2}), making it 100-fold more photoactive than Photofrin®, which requires drug doses of 2-5 mg kg^{-1} and strong light doses (100-200 J cm^{-2}).[36] The reasons behind this exceptionally high activity are not fully known. While improved optical properties and singlet oxygen quantum yields can partially explain this increased phototoxicity, the explanation appears to reside in the subtumoral and subcellular localization of the compound, still under investigation.[49,50]

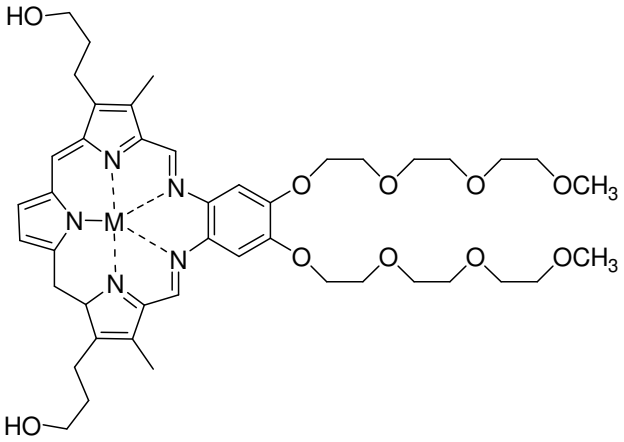
Table 3. Photosensitizers currently in clinical trials or late preclinical development (in italic indications that are registered in one or more countries).

Photosensitizer	Tradename	Clinical Application
Haematoporphyrin derivative	Photofrin®	*Oesophageal, lung, bladder, gastric and cervical cancer, HDG in Barrett's oesophagus,* Head and neck, intestinal, lung, skin, bladder and metastatic breast cancer, Kaposi's sarcoma, psoriasis, arterial restenosis.
5-Aminolevulinic acid (ALA)	Levulan®	*Actinic keratoses* Hair removal, acne, non-melanoma skin, oesophageal and gastrointestinal cancer, endometrial ablation, psoriasis, Barrett's oesophagus
Verteporfin	Visudyne™	*Macular degeneration*
	Verteporfin	Non-melanoma skin cancer, psoriasis Psoriatic and rheumatoid arthritis, multiple sclerosis, Barrett's oesophagus, endometrial ablation, bone marrow purging
Tin etiopurpurin	Photorex™	Macular degeneration
Temoporfin	Foscan®	*Head and neck cancer* Oesophageal cancer, Barrett's oesophagus Gastric and prostate cancer, hyperplasia, sterilization, antibiotic, skin cancer
Texaphyrins	Lutrin™	Breast cancer
	Antrin™	Angioplasty
	Optrin™	Macular degeneration
	Xcytrin™	Brain methastases
Phthalocyanine	CGP55847	Squamous cell carcinoma of upper aerodigestive tract, psoriasis
Phthalocyanine	Photosens	Endobronchial lesions, head and neck tumours
N-aspartyl chlorin e6	NPe6	Endobronchial lung cancer and cutaneous malignancies
Rhodamines	TH9402	Bone marrow purging

2.6. Texaphyrins

Texaphyrins (Scheme 12) are small ring-shaped molecules containing a heavy metal cation in the center and are marketed by Pharmacyclics (Sunnyvale, CA, USA) as photosensitizers (see http://www.pcyc.com). Under the trade name Lutrin™, lutetium texaphyrin is undergoing Phase II clinical trials as a possible therapy for breast cancer. The main advantage of using texaphyrins as PDT agents is that such a molecule can be activated at the remarkably long wavelength of 732 nm, thus enabling a deep tissues and blood penetration. In fact the treatment can be carried out effectively on larger tumours or at a greater

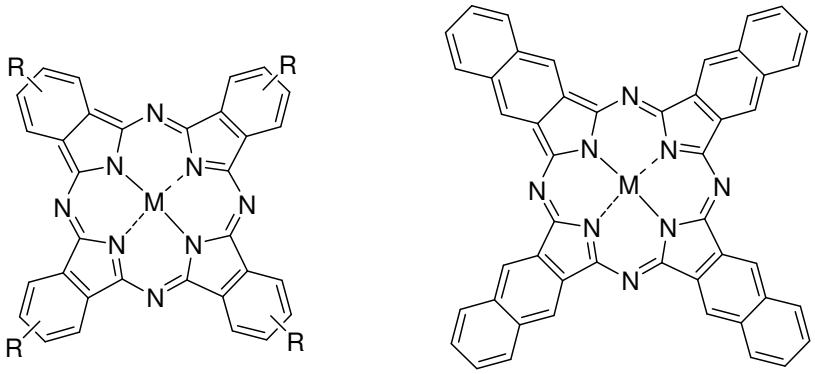
depth with reduced damage to adjacent normal tissues. The lutetium texaphyrin derivative, Antrin™ photoangioplasty for the treatment of peripheral artery disease (PAD, *i.e.*, blockages of the arteries in the lower extremities), is also in Phase II clinical trials, while another derivative, Optrin™, is in Phase II trials for age-related macular degeneration. In addition, the company is also developing radiosensitizers and chemosensitizers based on the gadolinium texaphyrin, Xcytrin™, currently in Phase III clinical trials for the treatment of brain metastases.



Scheme 12

2.7. Phthalocyanines

Phthalocyanines are a class of azaporphyrins in which the 3,4-positions of pyrrole ring are fused to benzene rings and bridged by aza nitrogens rather than methine carbons (Scheme 13). Their major absorption band is typically around 680 nm; this enable for the use of light of longer wavelength with increased tissue penetration. A long-life triplet state is required for efficient photosensitisation and this criteria may be fulfilled by the incorporation of a diamagnetic metal such as Zn or Al into the phthalocyanine macrocycle. Their solubility can be improved by substituents at the periphery of the macrocycle.[51]



Phthalocyanines Naphthalocyanines

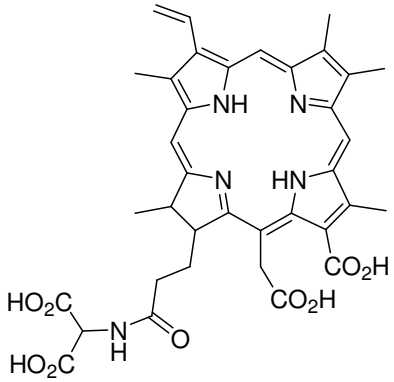
Scheme 13

Ciba-Geigy Ltd (Basel, Switzerland), now part of the Novartis Group, in partnership with QLT PhotoTherapeutics, has developed a zinc phthalocyanine (CGP55847) that has been in Phase I/II clinical trials in Switzerland for patients with squamous cell carcinomas of the upper aerodigestive tract.[52] The oncological centre of the Russian Academy of Medical Sciences (Moscow, Russia) and the surgical clinic of

the Moscow Medical Academy (Moscow, Russia) are developing a mixture of sulphonated aluminium phthalocyanine derivatives against a wide variety of cutaneous and endobronchial lesions; it has been used to treat malignancy and infection and it has been proved successful with head and neck tumours including the lip, pharynx, larynx and tongue.[53-56] Naphtocyanines are phtalocyanines with a further benzene ring in the periphery. The absorption peak of these compounds is red-shifted by 100 nm with respect to the parent phthalocyanines (770 nm versus 680 nm); this shift increases the therapeutic depth of application enabling the therapy exploitation also in the case of melanomas.[57-59]

2.8. *N*-Aspartyl chlorin e6[60]

Talaporfin (*N*-aspartyl chlorin e6, Npe6; Scheme 14)[61] is under study as photosensitizer for PDT.[62,63] It was developed by Nippon Petrochemical (Osaka, Japan), and is licensed to Miji Seika only for Japan and South East Asia. It consists of chlorin e6 in chlorophyll and L-aspartic acid. Talaporfin has completed phase I clinical trials in the US for cutaneous malignancies,[37] while phase II clinical trials are under test in Japan for endobronchial lung cancer.[36] The photodynamic activity of Npe6 also involves a combination of vascular (indirect effect) and direct anti-tumour photodamage, which is a further potential advantage of this photosensitizer.[64]



N-Aspartyl chlorin e6

Scheme 14

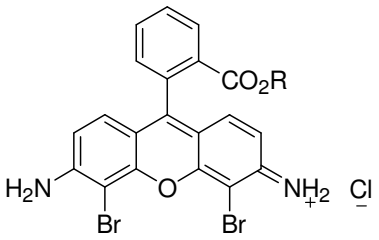
2.9. Rhodamines

The commercial dye rhodamine 123 is a poor phototoxin because of its high fluorescence quantum yield.[65]

This problem was remedied by Celmed's researchers by adding heavy atoms such as bromine to the heterocycle (Scheme 15). In fact, the addition of heavy atoms to the chromophore increases the intersystem crossing efficiency from the singlet to the triplet state by a spin-orbit coupling effect. Moreover, the addition of halogens to the chromophore also red-shifts the absorption maximum.

The new halogenated rhodamine, Theralux™ (TH9402), is marked by Celmed BioSciences Inc. (see www.celmedbio.com) and is currently evaluated in Phase I/II clinical trials for the prevention of acute graft-versus-host disease (aGvHD), the purge of cancerous cells from bone marrow transplants in non-Hodgkin's lymphoma (NHL) and the treatment of chronic GvHD and other autoimmune diseases by extracorporeal photochemotherapy (ECP).

The most outstanding results of this photosensitizer are: the high selectivity for undesired cells, the broad range of potential applications, the high purging efficiency and the safety results in clinical trials.

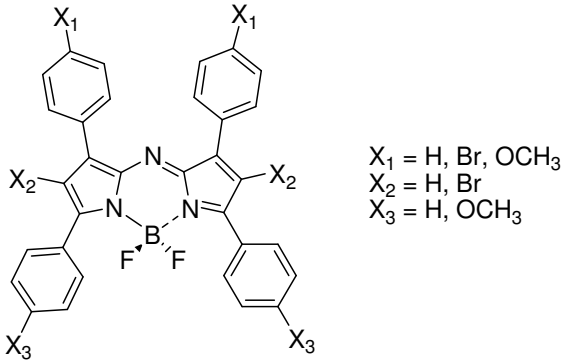


Brominated rhodamines

Scheme 15

2.10. Azadipyrromethenes

Azadipyrromethenes were firstly developed in 1940s[66] but only in recent years their therapeutic properties were studied. O'Shea and co-workers[67] developed a new class of photosensitizers based on substituted azadipyrromethenes (Scheme 16) with excitation wavelength in the near IR, high singlet oxygen generation efficiency and able to induce toxicity *in vitro* upon illumination. Moreover O'Shea group demonstrate that it is possible to modulate the key properties of the new photosensitizers with minor structural modifications. Although very promising, these dyes are not yet on clinical trial.

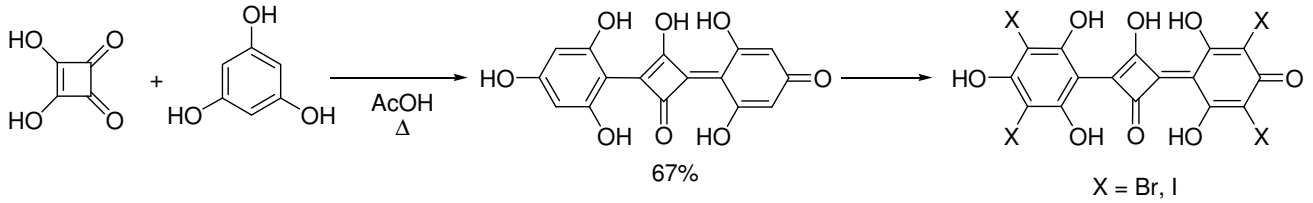


Scheme 16

2.11. Squaraines

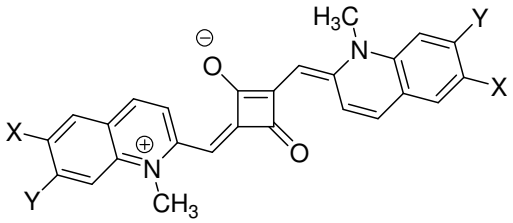
Squaraines are a class of dyes characterized by a sharp and intense low energy absorption band, associated with a remarkably high extinction coefficient in the order of 100-500 x 10^3 M^{-1} cm^{-1}. Their intrinsic inter system crossing efficiency goes from poor to modest but can be effectively enhanced, as described for rhodamine derivatives, by means of the heavy atom effect, typically bromine or iodine. Scheme 17 shows, as an example, a class of squaraine dyes derived from the condensation of squaric acid with phloroglucinol (1,3,5-trihydroxybenzene) and its halogenation derivatives. Biological essays[68] demonstrated that the halogenated chromophores display *in vitro* phototoxicity comparable to that of other porphyrins-derived PDT molecules.

In the last decade several studies have focused on the design and synthesis of innovative squaraine dyes but only a few of them deals with photodynamic therapy. Ramaiah and co-workers[69] described a series of new quinaldine-based squaraine dyes (Scheme 18) focusing on the substituent effect on the electronic properties of the final dye.



Scheme 17

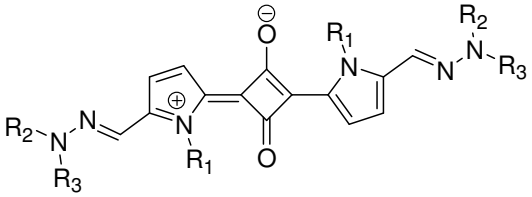
The Authors showed that the quinaldinium salts functionalized with electron-donating substituents hinder the formation of the squaraine while electron-withdrawing substituents facilitate the formation of the corresponding dye. These effects provide valuable information on the choice of substituent for the design and synthesis of novel and efficient photosensitizers for PDT.



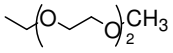
a) X = OH, Y = H
b) X= OEt, Y =H
c) X= OH, Y= Br
d) X= H, Y = H
e) X = I, Y = H
f) X = Br, Y = H
g) X = NO_2, Y = H
h) X = CN, Y = H

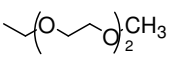
Scheme 18

Pagani and co-workers[70] designed and characterized three new classes of pyrrole-related squaraine dyes with extended conjugation (Scheme 19). All of these chromophores show a sharp and intense absorption band in the biological window (700-1100 nm), inherent singlet oxygen generation capabilities and moreover a good water solubility. Although their singlet oxygen generation efficiencies still require optimisation, squaraines are believed to play a major role in modern PDT.

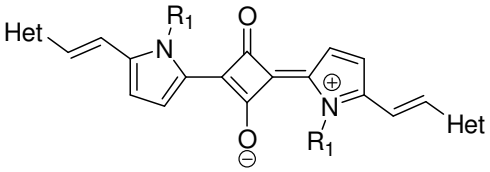


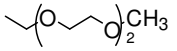
a) R_1= CH_3, R_2 = R_3 = Ph

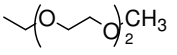
b) R_1=  R_2 = R_3 = Ph

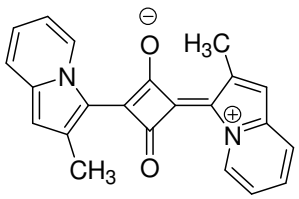
c) R_1=  R_2 = R_3 = CH_3

d) R_1= CH_3, R_2 = H, R_3 = p-Br-Ph



a) R_1=  Het = pyrid-4-yl

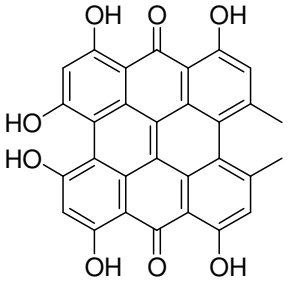
b) R_1=  Het = quinol-4-yl



Scheme 19

2.12. Hypericin

Hypericin[71] is multicyclic quinone (Scheme 20) endowed with absorption wavelength at around 590 nm.[65] Recent studies have shown that PDT with hypericin successfully inhibits tumour growth in mouse tumour models *via* apoptosis and necrosis.[72-74] Promising results have been obtained also on tumour diagnostic applications; in fact the sensitivity of hypericin for detecting carcinoma *in situ* seems to be of 93% and the specificity of 98.5%. These results confirmed that hypericin accumulates specifically in superficial urothelial lesions thereby fulfilling one of the most important prerequisite for PDT.



Hypericin

Scheme 20

2.13. Two-photon photosensitizers

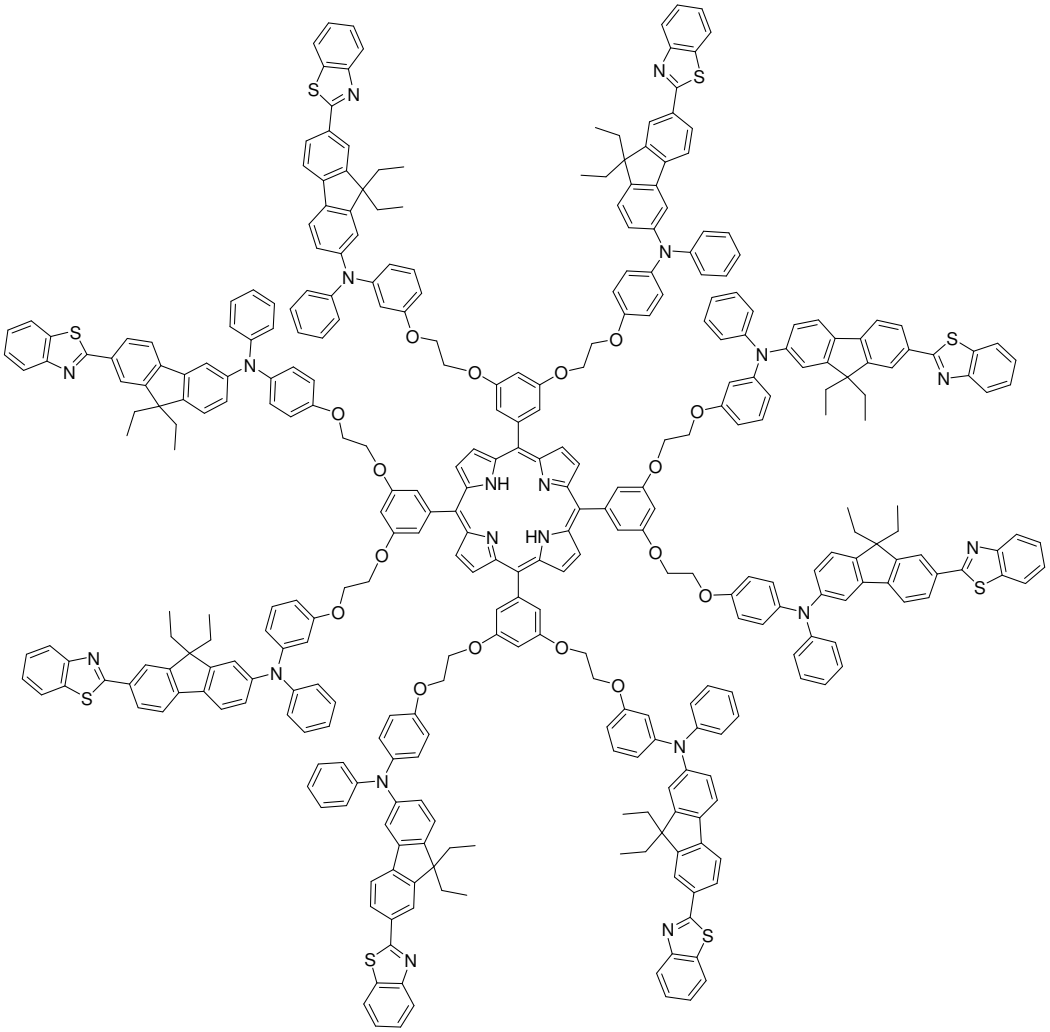
All currently approved and employed PDT photosensitisers work with excitation wavelengths in the 630-690 nm range. In this spectral region light cannot penetrate the skin by more than 2-4 mm. The photodynamic effect is generally seen up to 2-3 times deeper than that. As a result, the largest attainable depth of PDT-induced cellular changes could reach up to 15 mm, but in most cases it is much less than half of that. For this reason, the increase of light penetration is considered to be an important factor in widening the clinical efficacy of PDT. As we have discussed in the previous section, possible approaches rely on the design of new photosensitizers absorbing at longer wavelength in the NIR region. Another approach is the use of two-photon absorption as a mechanism for photosensitizer activation. Properly designed organic molecules, in the presence of intense laser pulses, can simultaneously absorb two photons (TPA), of the same or different energy, to be promoted to one of its two-photon symmetry-allowed excited states, the energy of which is higher than that of the ground state by the sum of the energies of the two absorbed photons.[75]

In two-photon excitation (TPE) the simultaneous absorption of two photons in the near-infrared region (NIR, λ = 700-1500 nm) can promote a molecule into its singlet excited state. Then, as in One Photon Excited-PDT, the excited molecule can undergo intersystem crossing into its triplet state from which the PDT effect occurs. The use of TPE is advantageous for several reasons:

1. Ability to work with a smaller more confined treatment area
2. Deeper penetration into diseased tissues (low scattering, almost no tissue absorption)
3. Avoid photodamage to healthy tissue. The small TPE-PDT volume provides the possibility of performing PDT on intricate tissues, such as the retina, as well as targeting individual cells. Comparably, in OPE the photosensitizer is necessarily excited along the entire path of the laser leading to a large amount of out focus damage to healthy tissue.

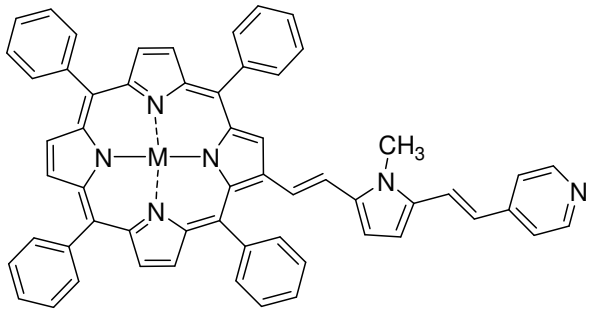
The idea of using two-photon excitation for PDT has been proposed by many investigators.[76] However, the two-photon absorption cross-section of existing photosensitizers has been too small to be of practical significance until very recently.[76c]

Using efficient two-photon pumped up-converting dyes in conjunction with a PDT photosensitizer, Bhawalkar proposed a novel approach to PDT at NIR frequencies involving a resonant energy transfer. In this approach, an efficient two-photon absorbing dye is excited by short laser pulse. The dye molecule transfers the energy to the covalently bonded photosensitizer. The photosensitizer is thus excited to its singlet state and from there the now familiar path (intersystem crossing and energy transfer to oxygen) efficiently leads to singlet oxygen. The same approach was used by Fréchet and Prasad[77] who also exploited the light harvesting concept. In this case a single porphyrin is covalently linked to eight two-photon absorbing units, thus significantly enhancing the probability to sensitize singlet oxygen (Scheme 21). The singlet oxygen generation in this configuration is 17 times than that measured for the porphyrin alone.



Scheme 21

Another interesting approach was developed by Pagani *et al.*[78] who synthesized a new class of functionalized porphyrins, in which the macrocycle is conjugated to a short push-pull fragment (Scheme 22). The effect of the "arm" is to enhance the singlet oxygen generation and the TPA cross-section up to 3.5 times with respect to the unfunctionalized porphyrins.



Scheme 22

In the last years most of the effort on the development of two-photon PDT was made from the MPA Technologies Inc..[79] Its researchers designed and synthesized bi- and trifunctional agents for PDT. Bifunctional agents include a targeting moiety linked to a two-photon photodynamic chromophore where the targeting moiety is able to accumulate rapidly in the tissue of choice (*e.g.* tumour) and not in healthy ones. Trifunctional agents include a targeting moiety and a photodynamic agent (one- or two-photon excitable) as described for the bifunctional agents, together with a fluorescent probe enabling for the rapid three-dimensional imaging of diseased tissues.

Two-photon photodynamic therapy is currently an active area of both *in vitro* and *in vivo* studies. However, at the current time there have been no FDA-approved two-photon PDT protocols for cancer treatment.

3. Conclusion and perspectives

Photodynamic therapy is a simple and economic therapy for the treatment of cancer and other nonneoplastic diseases often otherwise involving an invasive surgery. After the success exhibited by Photofrin®, a wide number of photosensitizers has been synthesized and tested in PDT. Several second generation photosensitizers are now used in clinic or are under clinical trials. Unfortunately each photosensitizer actually employed shows one or more drawbacks that limit its range of action, causing a continuous development of new photosensitizers with optimal properties for treating a wide range of cancer and diseases.

Acknowledgments

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SYNTHESIS OF 1,4-DIAZABICYCLO[X.Y.0]ALKANES; SCAFFOLDS OF DIPEPTIDE MIMETICS AND PROLINE DERIVED NATURAL PRODUCTS

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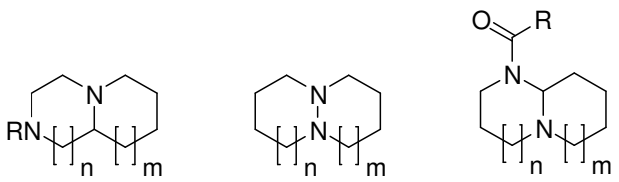
Abstract. *This review summarizes synthetic strategies to 1,4-diazabicyclo[X.Y.O]alkanes, including our own work and the contributions of other groups to the field. Since diazabicycloalkane scaffolds form the core structure of diverse natural products and peptide mimetics, applications of these structures in natural product syntheses and as peptide mimetics in bioorganic and medicinal chemistry will be highlighted.*

Contents

1. Introduction

Diazabicycloalkane scaffolds like **1**-**3** in Figure 1 form the core structure of various peptide mimetics and natural products with interesting biological profiles and might therefore be considered privileged structures in medicinal chemistry.[1]



1 **2** **3**

Common diazabicycloalkane scaffolds.

Figure 1

This review focuses on the 1,4-diazabicyclo[X.Y.0]alkane motif **1**. Synthetic strategies to these heterocycles as well as closely related analogs are discussed and their applications in natural product synthesis or medicinal chemistry are outlined.

2. Diazabicycloalkane natural products

The most common class of natural products, based on the 1,4-diazabicycloalkane framework, are proline derived diketopiperazines or derivatives thereof. Marcfortines, brevianamides, paraherquamides, verruculogens, tryprostatins and similar derivatives (a few examples are shown in Figure 2) comprise a structurally interesting group of fungal metabolites.[2]

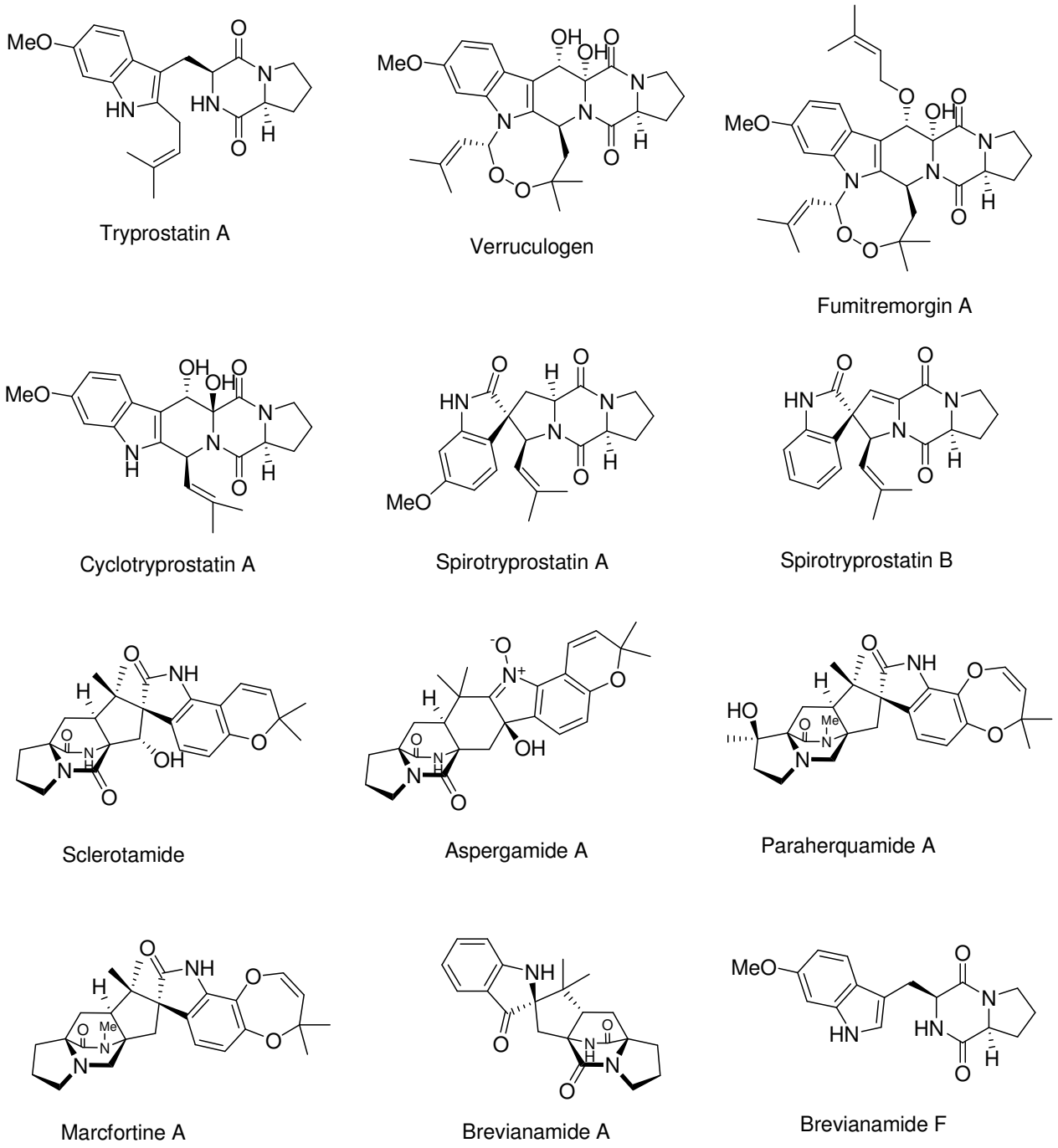


Figure 2

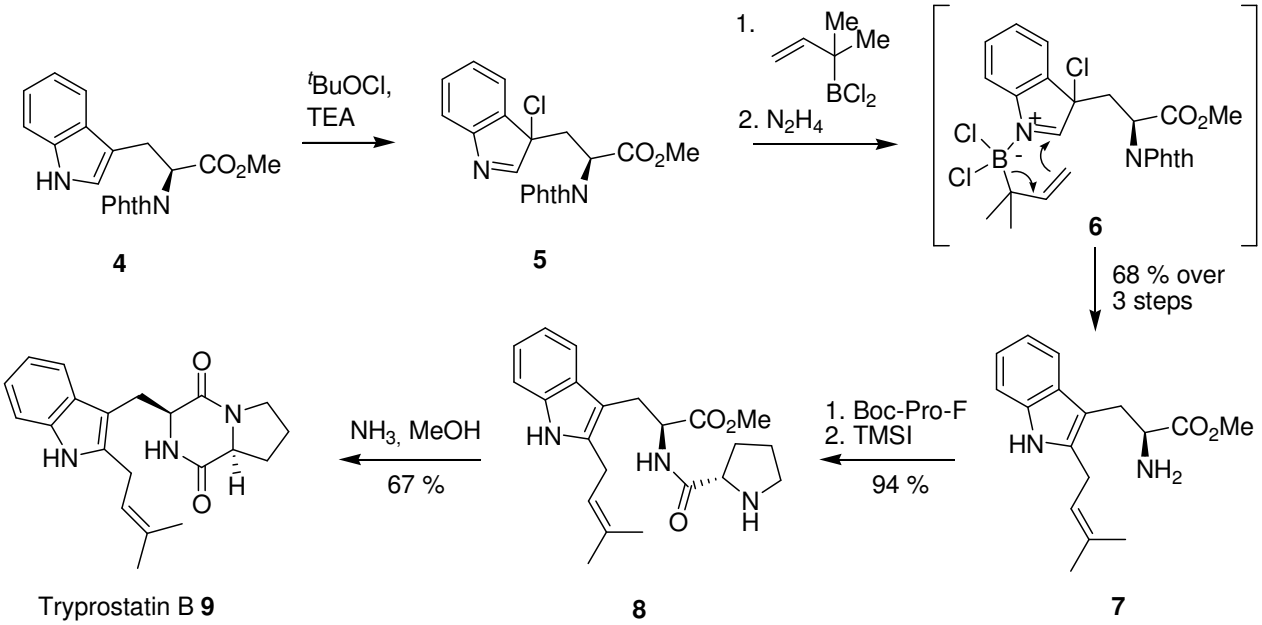
Their scaffolds are derived from proline, tryptophan and prenyl units. The unique bicyclo[2.2.2]diazaoctane core of brevianamides and related structures has been proposed to be derived from a Diels-Alder reaction in nature.[3] However, the complete biogenesis of the compounds in Figure 2 is unclear and their biosynthesis awaits experimental verification.

A number of these natural products have interesting biological properties. In particular tryprostatins,[4] cyclotryprostatins[5] and spirotryprostatins A[6] and B,[7] which have been isolated first by Osada's group in small quantities from *Aspergillus fumigatus*, have attracted considerable interest. They represent a promising class of antimitotic substances, although the precise mechanism of action by which these agents inhibit microtubule assembly is presently unknown.[8]

Earlier comprehensive reviews focusing on the synthesis and biosynthesis of these compounds exist and the reader is referred to the literature.[9] The purpose of this chapter is to highlight recent synthetic developments not covered by the review literature.

2.1. Tryprostatins

Osada reported the isolation, structure und biological activity of tryprostatins A **15** and B **9**.[10] These two compounds have a characteristic diketopiperazine scaffold that is derived from tryptophan and proline with a prenylated indole part. Interestingly, both natural products are cell cycle progression inhibitors at the G_2/M phase barrier with tryprostatin B **9** being more potent than its congener **15**.[11] Furthermore, tryprostatin A was found to reverse breast cancer resistance protein-mediated drug resistance.[8a] Their biological activity has stimulated a number of groups to develop practical syntheses to both natural products as well as structural analogs thereof.



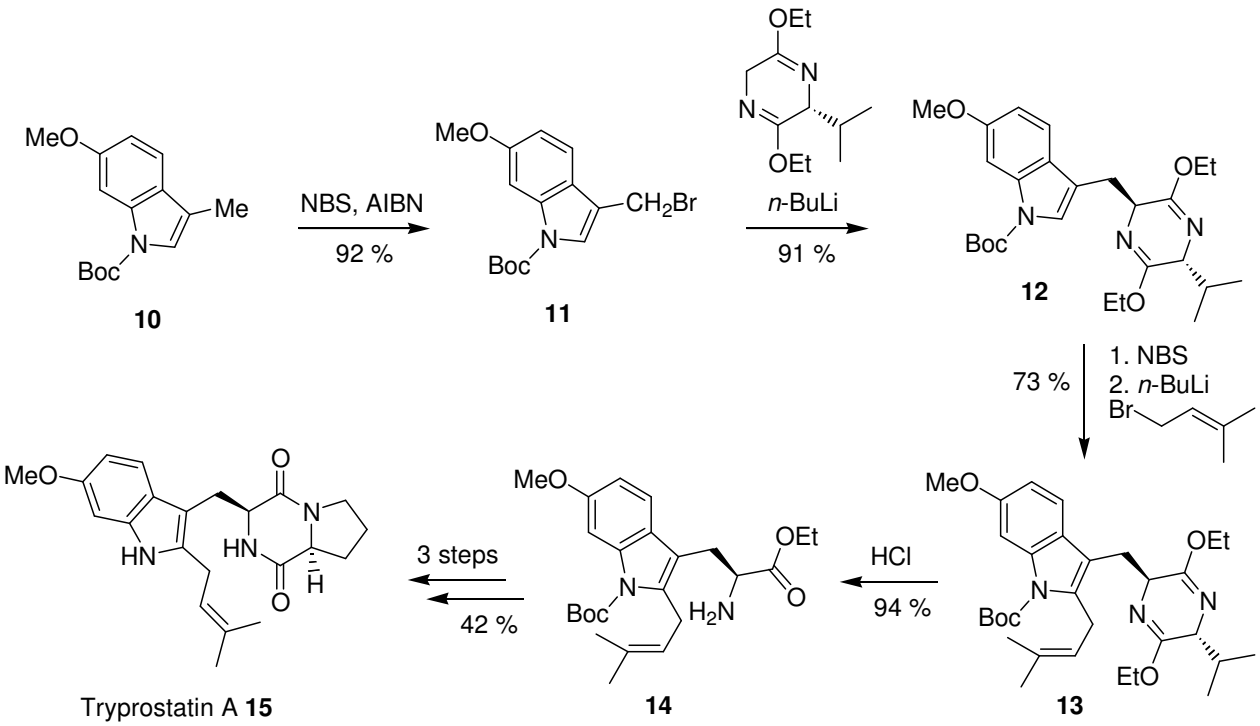
Scheme 1

A key aspect of these syntheses is the implementation of the prenyl side chain. Danishefsky and coworkers solved this problem with a regioselective prenylation of chlorinated indole derivative **5**, which is easily synthesized by chlorination of protected tryptophan **4**.[12] A prenyl boron reagent, which is formed *in*

situ from prenyl stannane and BCl_3, was used for prenylation and intermediate **6** proposed. After phthaloyl deprotection with hydrazine prenylated tryptophan **7** was obtained in good overall yield for the three step sequence. Alternatively, intermediate **7** was prepared by Lobo and Prabhakar by a BF_3-mediated aza-cope rearrangement of *N*-prenylated tryptophan in good yield.[13]

Coupling was performed with Boc-protected proline acid fluoride and subsequent Boc-deprotection with trimethylsilyliodide gave dipeptide **8** in excellent yield. In a final step the diketopiperazine was formed with methanolic ammonia solution to give tryprostatin B **9** (Scheme 1). With reasonable quantities of **9**, Danishefsky and coworkers verified its biological activity. However, they observed that tryprostatin B tends to be oxidized under assay conditions and speculated that these side products may be even more active than the natural product itself.

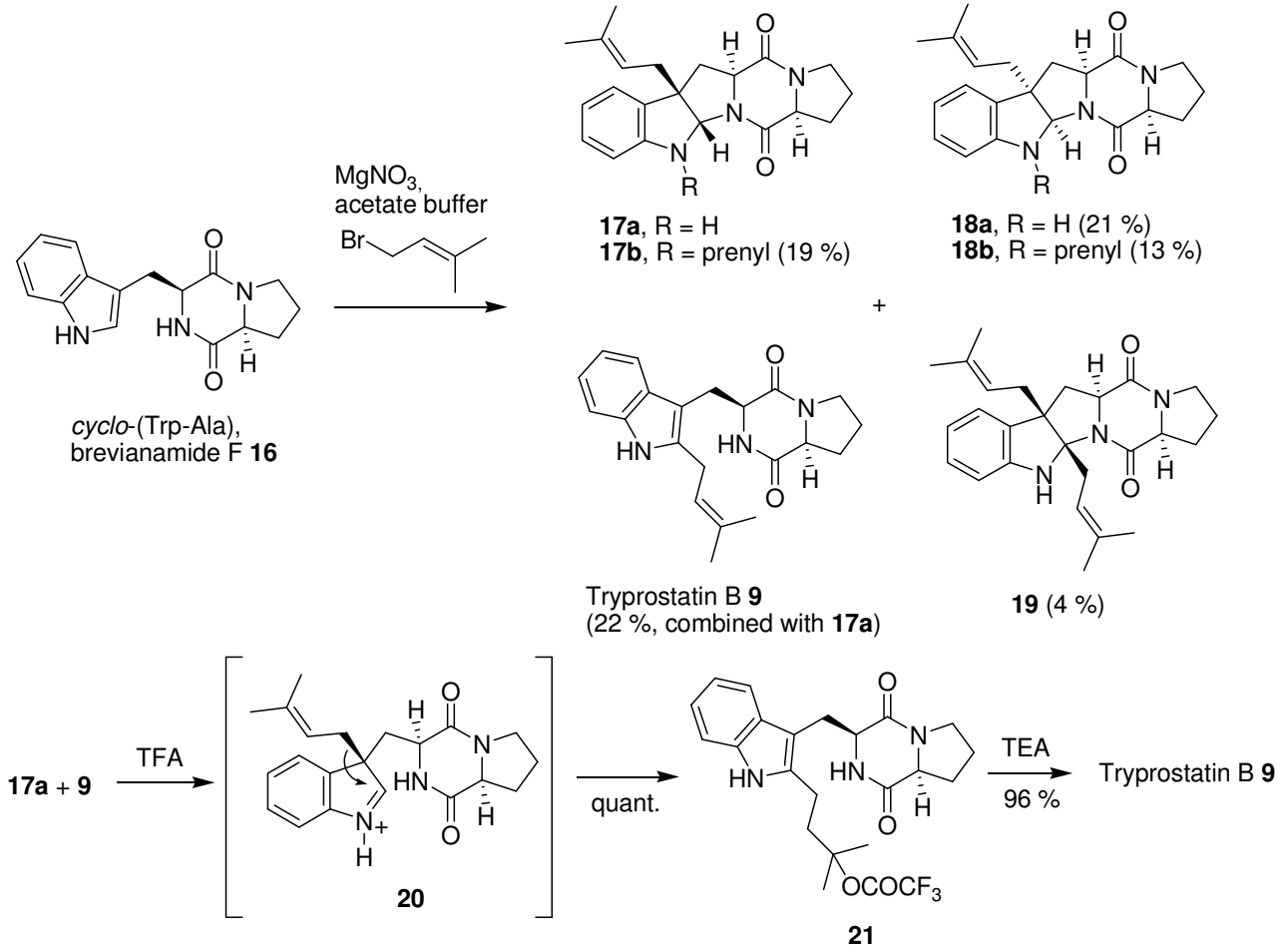
Cook reported a strategy to tryprostatin A starting from indole **10** which can be synthesized over five steps from *m*-anisidine.[14] Although precursors like **10** have to be synthesized in multistep procedures and do thus add a number of steps to the total synthesis in comparison to tryptophan based strategies, the route offers flexibility with respect to different substituents in the indole part of tryprostatins.[15] Indole **10** was brominated with NBS to give **11**, that was treated with a deprotonated Schöllkopf reagent leading to the exclusive formation of the desired *trans*-diastereoisomer **12**. The indole **12** was again brominated with NBS, treated with *n*-butyl lithium and then with prenyl bromide to give **13** in good yield for the two step process. Hydrolysis of the bislactimether was performed in ethanolic HCl providing **14** in excellent yield. Assembly of the diketopiperazine was done in analogy to the above described procedure to give tryprostatin A **15** (Scheme 2). Cook has applied this strategy to the synthesis of both enantiomers of tryprostatins A and B.[16]



Scheme 2

An interesting method for installation of the prenyl group in the indole part of tryprostatins was investigated by Menendez and coworkers.[17] Their synthesis starts from readily available *cyclo*-(Trp-Pro)

which is treated with magnesium nitrate in acetate buffer. A complex product mixture of six compounds **9**, **17a**, **17b**, **18a**, **18b** and **19** was generated. However, large fractions are the desired mono-prenylated compounds **9**, **17a** and **18a** and the undesired diprenylated derivatives **17b**, **18b** and **19** were separable. Installation of the prenyl group at the desired two position of the indole moiety was performed with a trifluoroacetic acid mediated rearrangement of a mixture of **9** and **17a** *via* an iminium intermediate **20** to give the trifluoroacetate **21** in quantitative yield (Scheme 3). It is remarkable that the same rearrangement was not mediated by TFA when **18a** was the substrate. However, tryprostatin B **9** was formed directly *via* an $Yb(OTf)_3$-mediated rearrangement of **18a** in 50 % yield.



Scheme 3

Besides the solution syntheses outlined above, the synthesis of tryprostatin B **9** on solid support has been reported.[18] Although this synthesis is conceptually not new, it might prove useful for the synthesis of unnatural tryprostatin analogs. This is particularly interesting because Williams has recently reported promising biological activities for a number of prenylated *cyclo*-(Trp-Pro) derivatives.[19]

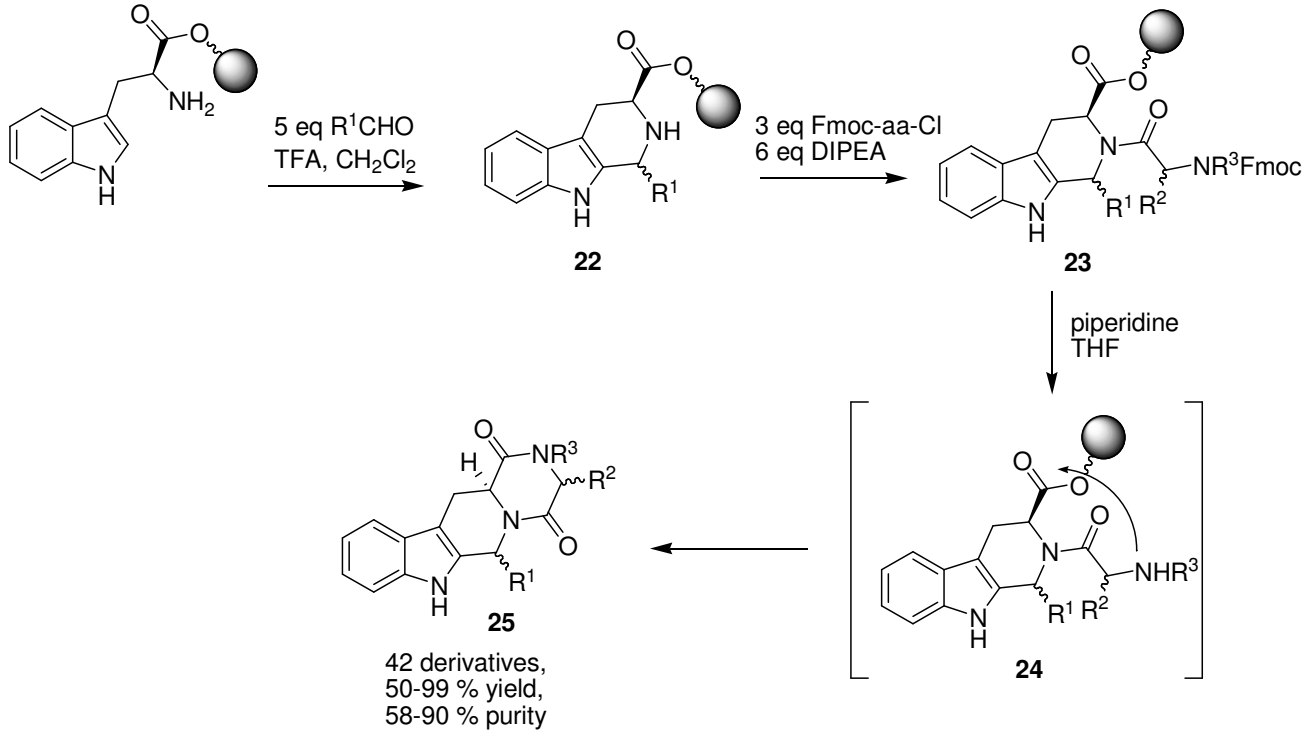
2.2. Verruculogen, fumitremorgins and cyclotryprostatins

Verruculogen, fumitremorgins and cyclotryprostatins belong to a class of indole alkaloids with a proline derived diketopiperazine scaffold and were first isolated from *Penicillium verruculosum*, *Aspergillus fumigatus* and the marine fungal strain BM939, respectively.[20] Members of all three families have shown

inhibitory effects on the mammalian cell cycle.[5] Fumitremorgins and verruculogens were found to be tremorgenic, interfering with mechanisms responsible for the release of neurotransmitters in the CNS.[21] In addition, Fumitremorgin C was found to reverse breast cancer resistance protein (BCRP) mediated drug resistance, a serious clinical problem for chemotherapy of breast cancer.[22] These various biological activities have caused several attempts to find practical syntheses for the above mentioned natural products as well as structural analogs thereof. An excellent review of Nakagawa[9] summarizes the literature up to 1997 and only more recent approaches will be considered here.

Koomen and Ganesan presented a solid phase synthesis of demethoxyfumitremorgin derivatives that is based on a cyclization/cleavage strategy.[23] They started with solid phase-bound tryptophan and subjected it to a TFA-mediated Pictet-Spengler cyclization with excess aldehyde to give tetrahydro-β-carbolines **22**.[24] The subsequent coupling reaction to **23** was found to be problematic with standard coupling reagents like HATU, PyBoP/HOAt or even *via* the corresponding acid fluorides. Coupling was finally achieved with Fmoc-amino acid chlorides. However, this procedure leads to epimerization of the coupled amino acids and products **23** were therefore obtained as mixtures of diastereomers in most cases. Removal of the Fmoc group with piperidine lead to the formation of intermediates **24**, which cyclized spontaneously causing simultaneous cleavage from the solid support to give final products **25** in good to excellent yields and acceptable purities (Scheme 4). The libraries were tested for BCRP inhibition as well as cell cycle arrest and several potent candidates were identified.[25]

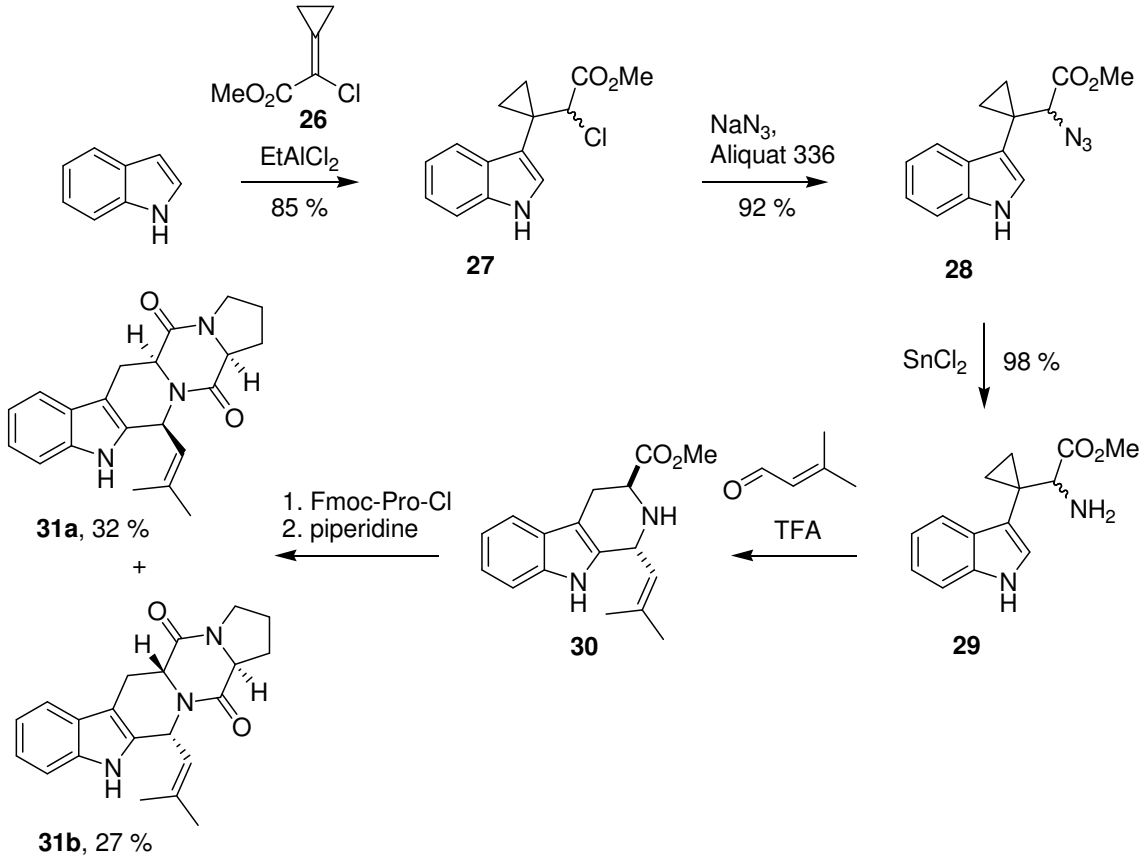
Diastereoselectivities in these solid phase approaches were low. However, Bailey[26] and Ganesan[27] accomplished the diastereoselective synthesis of demethoxyfumitremorgins in solution again *via* Pictet-Spengler approaches.



Scheme 4

A cyclopropyl substituted derivative of demethoxyfumitremorgin, an analog of the Elli Lilly drug Tadalafil, has been synthesized by de Meijere and coworker.[28] The sequence starts with the addition of

indole to a Michael acceptor **26** to give **27** in good yield. Chloride was exchanged for azide and the resulting intermediate **28** was reduced to the amine **29** in excellent overall yield. Pictet-Spengler reaction of the imine derived from **29** and prenyl aldehyde proceeded in moderate yield but excellent diastereoselectivity in favor of the *trans*-configuration (99:1) to give racemic **30**. Coupling with Fmoc-proline chloride and subsequent treatment with piperidine lead to Fmoc-deprotection and spontaneous cyclization to give demethoxyfumitremorgin C analogs **31a** and **31b** (Scheme 5).



Scheme 5

2.3. Spirotryprostatins

To date exist seven reported syntheses of spirotryprostatin B and three of spirotryprostatin A. An excellent review by Carreira[9] summarizes many of these synthetic studies and this chapter is therefore focusing on recent developments not covered by the review literature.

Construction of the spirooxindolpyrrolidine is clearly the most challenging part of spirotryprostatin synthesis and many groups addressed the problem of building an enantiomerically pure spirooxindole with different approaches. A common strategy relies on oxidative rearrangements of β-carbolines **32**, which are easily synthesized *via* Pictet-Spengler chemistry from tryptophan derivatives. Danishefsky and coworkers have used this approach for the synthesis of spirotryprostatin A[29] whereas Ganesan synthesized spirotryprostatin B using the same rearrangement conditions (NBS / AcOH).[27] A Mannich cyclization of **33** was used by Danishefsky for the construction of spirotryprostatin B.[30] Dipolar cycloadditions of chiral azomethine ylide intermediates **34** to oxindoles **35** have been shown to be a powerful approach to the spirooxindole part of spirotryprostatin A and B by Williams.[31] This strategy is well suited for introduction of

chemical diversity into the spirotryprostatin scaffold. Schreiber demonstrated this versatility with the synthesis of a large solid phase attached library of spirooxindoles *via* stereoselective dipolar cycloaddition.[32] Starting from oxindoles **36**, Carreira has synthesized spirotryprostatin B by a ring expansion of cyclopropanes with imine derivatives.[33] A stereoselective nitroolefination of oxindoles **37** with an enantiomerically pure prolinol derivative **38** was the key step in Fuji's synthesis of spirotryprostatin B.[34] While most synthetic concepts started from indole or oxindole precursors, Overman's synthesis is conceptually totally different. From intermediate **39**, he used a very elegant tandem process of intramolecular Heck cyclization and subsequent trapping of the resulting η^3–allylpalladium species for the synthesis of spirotryprostatin B (Figure 3).[35]

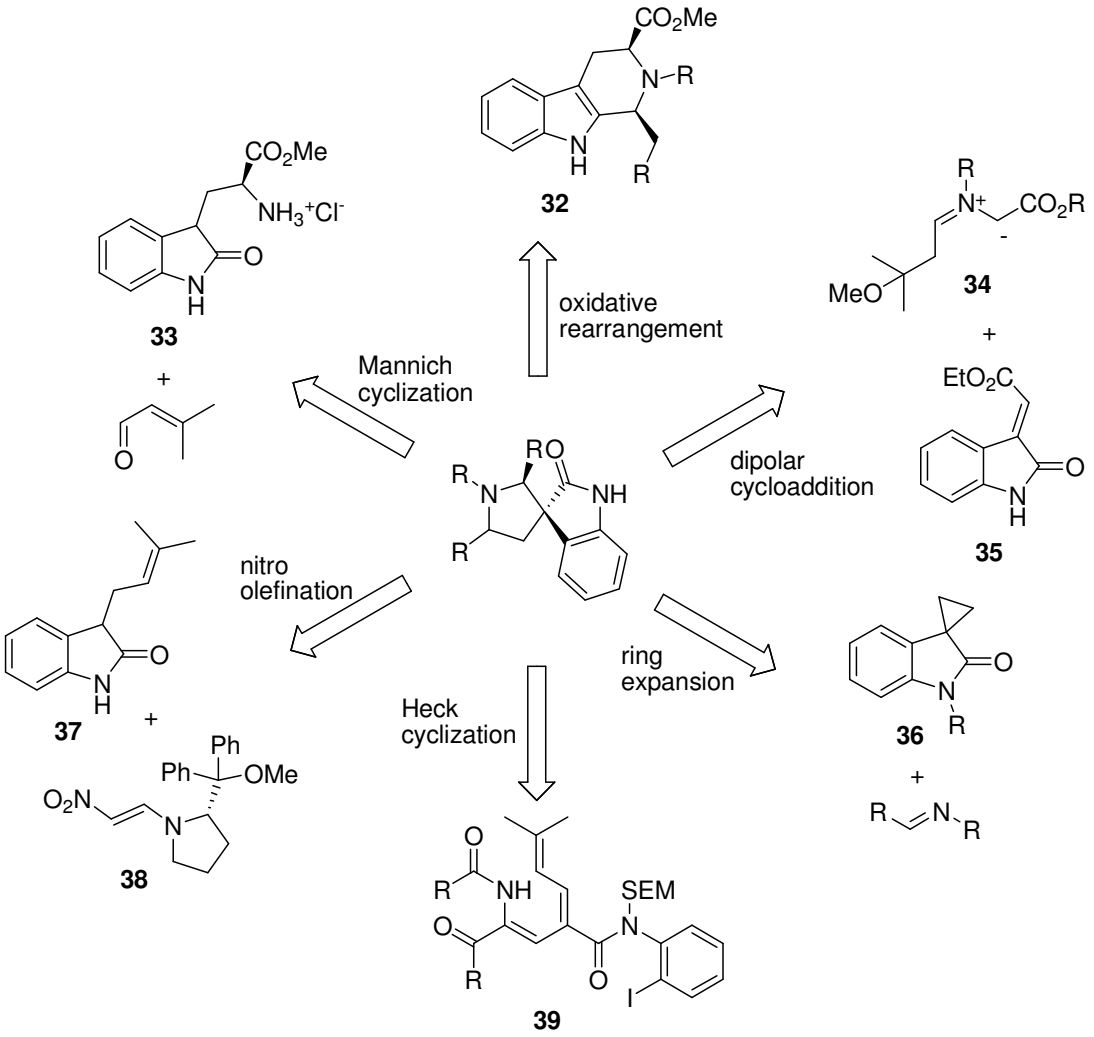
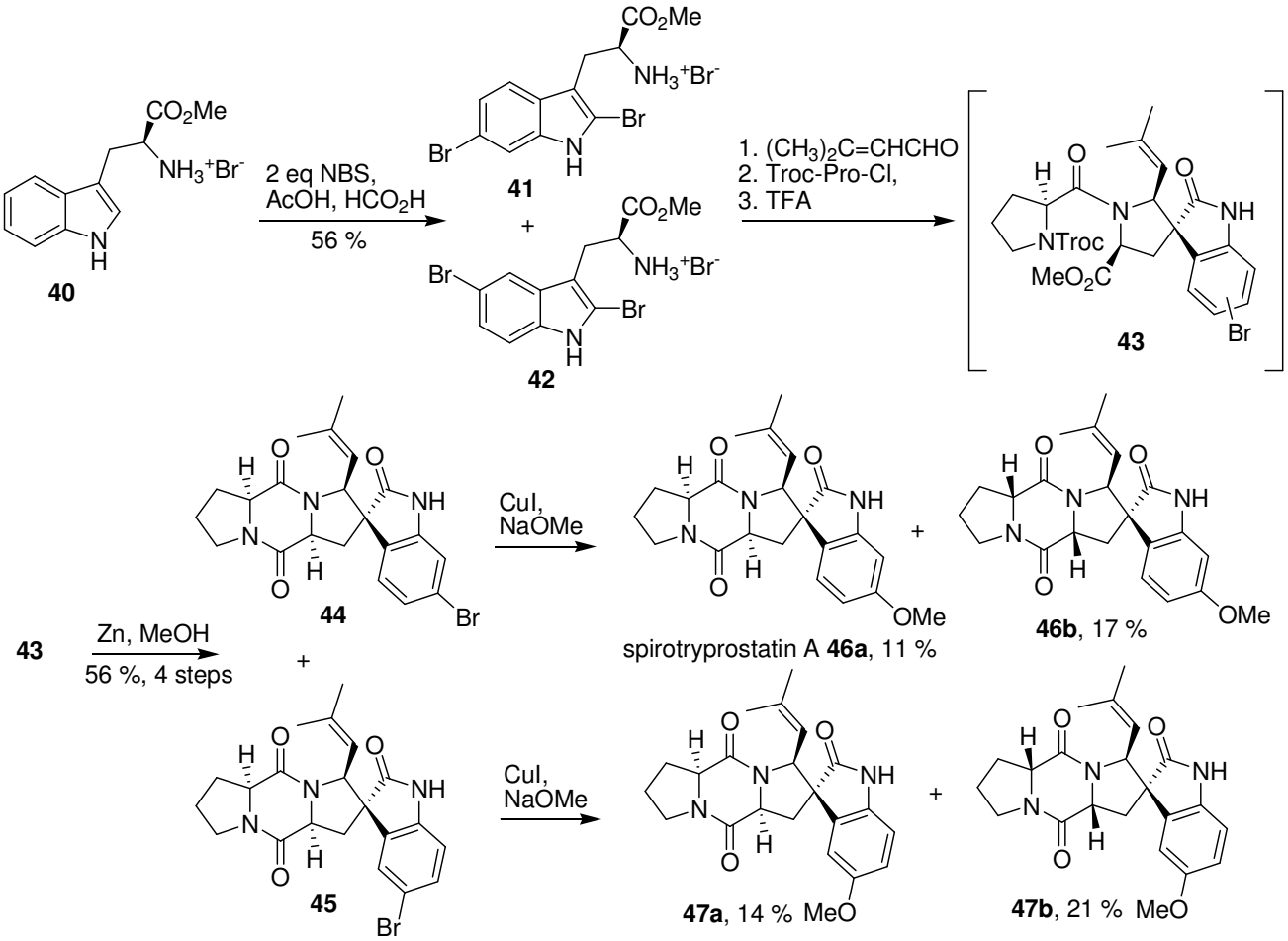


Figure 3

Horne reported recently an *N*-acyliminium cyclization approach to spirooxindoles. The synthesis starts from tryptophan methyl ester **40** which was brominated to dibromo derivatives **41** and **42** with NBS in acidic media. After treatment with prenyl aldehyde, the resulting imine was acylated with Troc protected proline acid chloride to give an intermediate *N*-acyliminium ion which cyclized immediately to form the spiroindole moiety. Treatment with TFA resulted in hydrolysis of the chloroindolenine intermediate giving oxindole **43**

with good stereoselectivity. Crude **43** was then deprotected and cyclized to regioisomeric diketopiperazines **44** and **45** upon heating in methanol with zinc. Exchange of bromine for methoxy can be achieved with CuI and sodium methylate to give spirotryprostatin A **46a** and unnatural derivatives **46b**, **47a** and **47b** (Scheme 6).[36] This strategy was also applied to the synthesis of spirotryprostatin B (Figure 2) in a very similar sequence starting from 2-chloro tryptophan methylester.[37]

Horne's strategy leads to the shortest known syntheses of spirotryprostatin A and B and provides access to some unnatural stereoisomers. A further benefit is the variability with respect to the substitution pattern in the oxindole moiety. Both syntheses have a limited efficiency due to one low yielding step in each sequence and epimerization or low stereoselectivity respectively. However, the low number of steps is impressive.



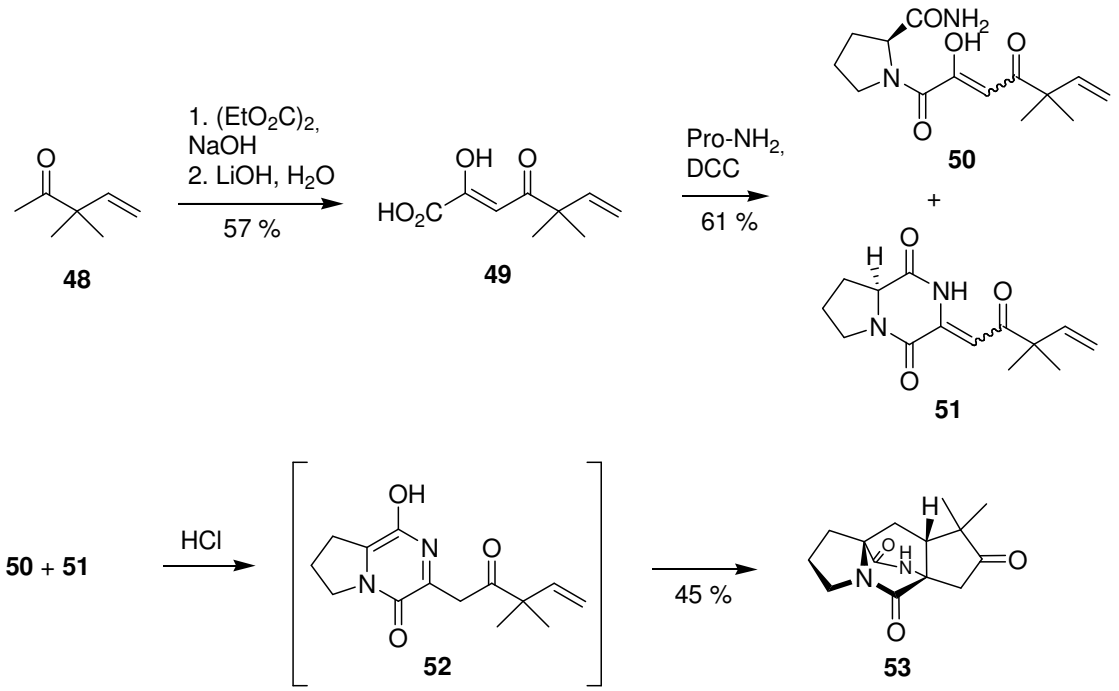
Scheme 6

2.4. Paraherquamides, brevianamides and Asperparalines

These compounds constitute a remarkable family of fungal metabolites that possess a bicyclo[2.2.2]diazaoctane core ring system most likely derived from a Diels-Alder reaction in nature. Brevianamides were originally isolated as the major metabolites from *Penicillium brevicompactum*.[38] The paraherquamides are structurally a little more complex and have interesting antihelminitic and antinematodal activities.[39] Paraherquamides and several related compounds have been isolated from various *Penicillium* and *Aspergillus* species.[40] The asperparalines differ from the brevianamides and paraherquamides in that

they contain a *spiro*-succinimide ring system in place of a *spiro*-oxindole and were isolated from *Aspergillus japonicus* JV-23.[41] An excellent review by Williams covers most of the relevant literature including total syntheses of these natural products up to 2003.[9]

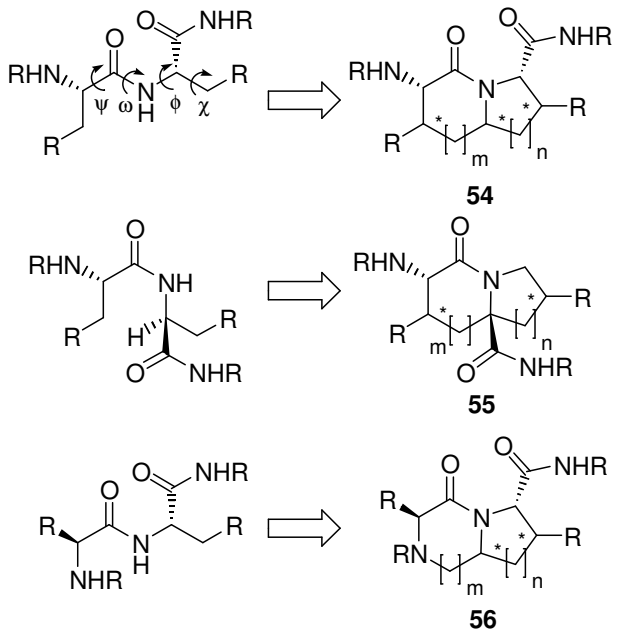
Williams[42] reported recently a short synthesis of the core fragment common to asperparalines, paraherquamides and the structurally related stephacidines.[43] Ketone **48** was treated with sodium ethoxide and diethyl oxalate, yielding the desired pyruvate **49** in good yield after hydrolysis with lithium hydroxide. Synthesis of diketopiperazine **51** proved to be difficult and mixtures of **50** with **51** were obtained upon treatment of pyruvate **49** with DCC and proline amide. However, under acidic conditions this mixture underwent an intramolecular Diels-Alder reaction *via* intermediate **52** to give **53** in moderate yield (Scheme 7).



Scheme 7

3. Diazabicycloalkane dipeptide mimetics

Peptide secondary structure is defined by the backbone torsional angles ω, ϕ and ψ and the side chain torsional angles χ (Figure 1). The different elements of peptide secondary structure are of immense importance for peptide interactions with receptors of various kinds. For example, cytokine receptor interactions[44] and a number of DNA-protein interactions[45] are based on α-helical stretches on the peptide side. In addition, many receptor/ligand and antigen/antibody interactions are mediated through reverse turns[46] and proteases,[47] most Src Homology 2 (SHC) domains[48] and Major Histocompatibility Complex (MHC)[49] recognize their substrates in extended peptide conformations. These receptor/ligand interactions are in many cases mediated by local key elements of secondary structure. Mimicking native peptide ligands with small molecules can thus derive potent receptor binders or modulators of receptor/ligand interactions if the local peptide structure of a ligand is conserved in its (often unnatural) small molecule counterpart.[50] Of course such peptide mimetics must also arrange the right side chain functionalities in a geometry that is suitable for efficient interaction with the receptor.



Parameters χ, ψ, ω and ϕ for peptide secondary structure and bicyclic dipeptide mimetics **54**, **55** and **56**.

Figure 4

Local constraint of peptide geometry has been achieved with different strategies. Peptide cyclization is one of them[51] and the impressive work of Kessler on cyclic RGD-peptides is one of the best examples for the importance of peptide backbone geometry for specificity and affinity to a given receptor, demonstrated by RGD / Integrin interactions.[52] Other strategies for rigidifying the peptide backbone are introduction of double bonds[53] or introduction of bulky or α,α-disubstituted amino acids.[54]

A particularly successful strategy has been bridging different atoms in the peptide backbone or amino acid side chains.[55] In this context, bicyclic ring systems of the aza- and diazabicyclo[X.Y.0]alkane type **54**-**56** are versatile scaffolds mimicking a range of different peptide conformations.[56] Within these bicyclic peptide analogs backbone dihedral angles ω, ϕ and ψ as well as at least the first side chain torsional angle χ_1 can be fixed. In addition, a fine tuning of the imitated dipeptide geometry can be achieved with variation of stereochemistry and ring sizes (n and m in Figure 4). Syntheses of compounds **54**-**56** therefore have to be stereoselective and flexible with respect to different ring sizes and stereochemistry.

A whole set of compounds mimicking a range of different dipeptide geometries is available based on aza- and diazabicycloalkane scaffolds like **54**-**56** or similar structures. These dipeptide mimetics have been used to probe structure activity relationships, as modulators of pharmaceutically relevant receptor functions, as scaffolds for combinatorial chemistry[57] and have been proposed for tumor targeting.[58] In addition, diazabicycloalkane scaffolds (in particular some proline derived diketopiperazines) have been used as templates for peptide secondary structure elements. In consequence, a number of synthetic strategies to bicyclic dipeptide mimetics of structure **54**-**56** have been developed. This chapter focuses on recent synthetic developments for the preparation of diazabicyclo[X.Y.0]alkane peptide mimetics **56**.

In comparison to azabicycloalkanes **54** and **55**, much less effort has been devoted to develop syntheses for diazabicycloalkanes. The diazabicycloalkane core forms the backbone of dipeptide mimetics of the general structure **56** (Figure 4) that are complementary to azabicycloalkanes **54** and **55** in that they mimic dipeptide conformations not accessible by azabicycloalkane scaffolds.

Different cyclization strategies have been used for the assembly of the two diazabicycloalkane core structures **57** and **58** in Figure 5. These can be classified into two groups according to the precursors needed for cyclization. Precursors are either substituted proline derivatives **59** for lactam formation (chapter 3.1.) or *N*-acylated proline derivatives **60**-**64** for lactam formation (chapter 3.1.), ring closing metathesis (RCM, chapter 3.2.), intramolecular reductive amination (chapter 3.3.), *N*-acyliminium cyclization (chapter 3.4.) or tandem cyclization (chapter 3.5.). The efficiency of these different approaches heavily depends on the availability of enantiomerically pure cyclization precursors **59**-**64** which are often synthesized in multistep procedures. With few exceptions, ex-chiral pool strategies starting from amino acids, such as proline, pyroglutamate,[59] aspartate or glutamate have been chosen for this purpose.

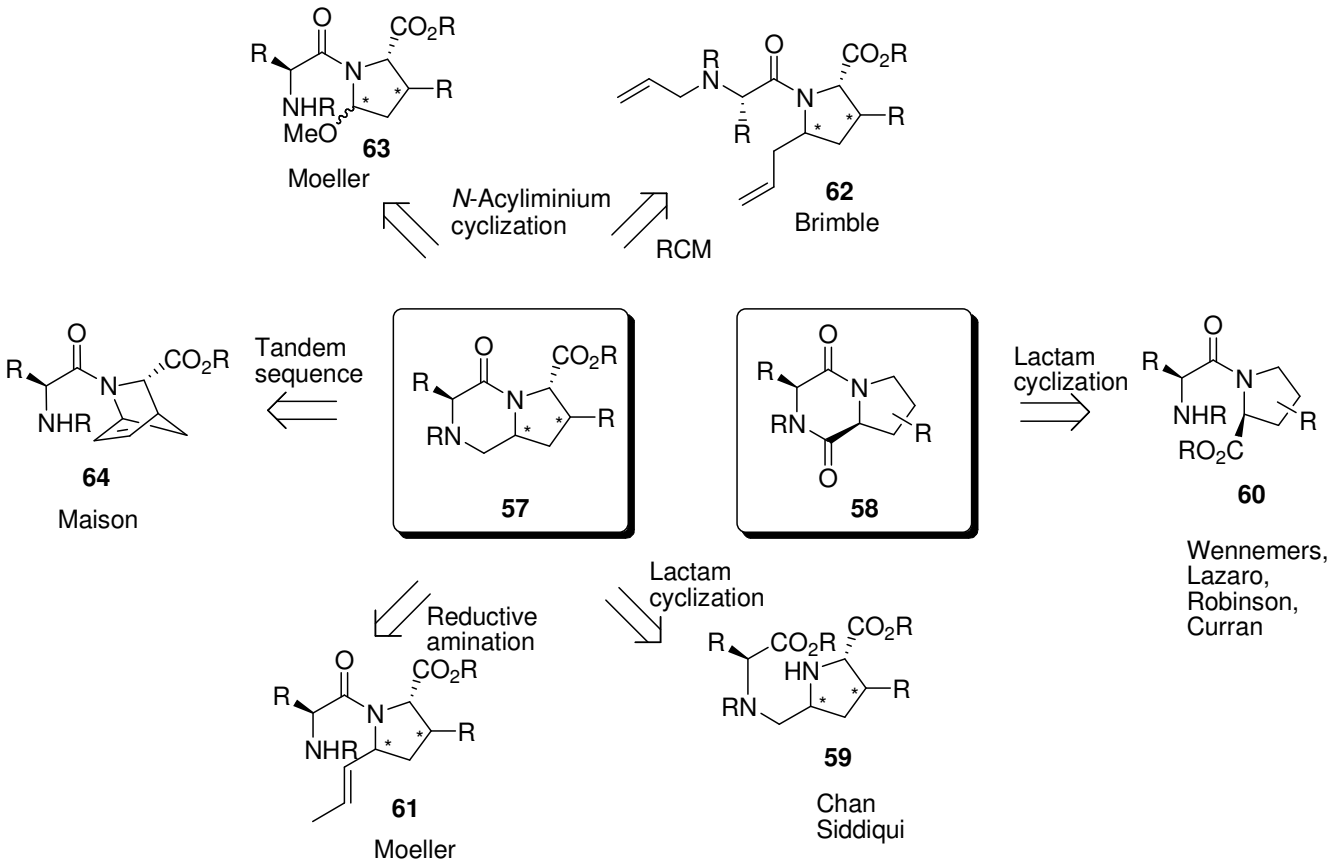


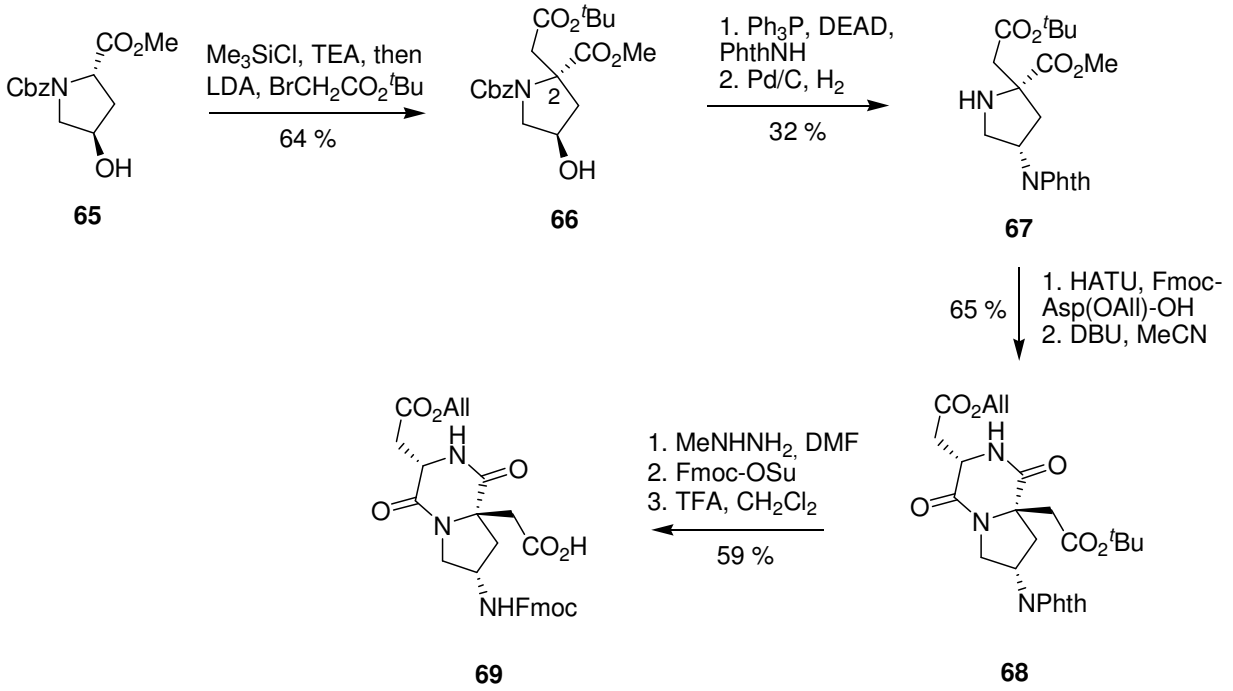
Figure 5

3.1. Lactam formations

Lactam formation is probably the most obvious result of a retrosynthetic analysis of diazabicycloalkanes **57** and **58** and has been used by a number of groups successfully. However, synthesis of the appropriate cyclization precursors **59** and **60** is by no means trivial.

The structure inducing properties of proline derived diketopiperazines have been studied by the Robinson group.[60] In this context, dipeptide diazabicycloalkane **69** was designed as a loop mimetic and incorporated into a hexapeptide model sequence by solid phase methodology.[61] This model system was shown to adopt a stable β-turn conformation in aqueous solution. The synthesis of template **69** started from protected hydroxyproline **65**, which was α-alkylated by *tert*-butyl acetate in the presence of LDA to give **66** as a 2:1 mixture of diastereoisomers in favor of the wanted *2R*-isomer. Conversion of **66** under Mitsunobu

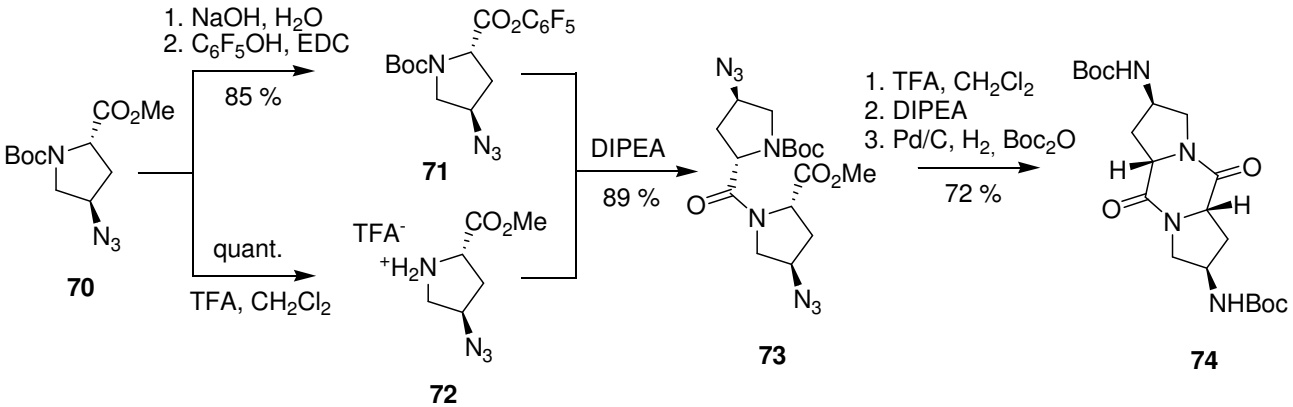
conditions and subsequent hydrogenation gave proline derivative **67**. At this stage the two diastereoisomers were separated by column chromatography. Peptide coupling with an aspartate derivative and cyclization under alkaline conditions gave protected diazabicycloalkane **68** in moderate yield (Scheme 8).



Scheme 8

Manipulation of protecting groups gave finally template **69** with a free carboxylic acid that can be used for attachment to a solid phase.

Diketopiperazines **74** have been synthesized by the Wennemers group from hydroxyproline according to Scheme 9.[62] Starting material **70** was converted to active ester **71** and the TFA salt **72** under standard conditions. These two building blocks were coupled with DIPEA to give **73**. Removal of the Boc-protecting group, cyclization with DIPEA and reduction of the azides in the presence of Boc_2O gave protected diketopiperazine scaffold **74** in five steps and good overall yield.

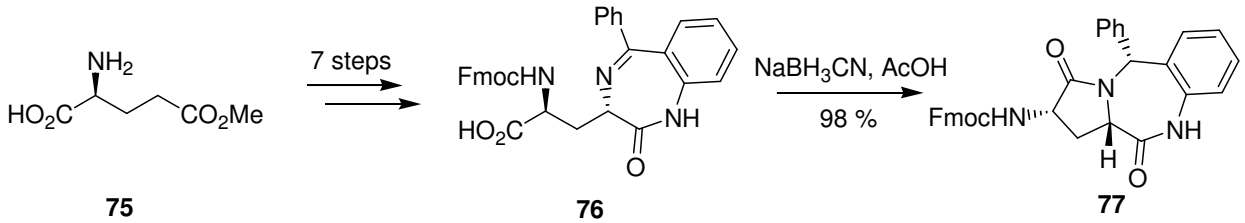


Scheme 9

Scaffolds **74** have been used as templates for artificial peptide receptors, by attachment of peptide arms to the Boc-protected secondary amines.[63] It was shown by the authors that the structure of template **74** has a

profound influence on its ability to function as a peptide receptor. A number of other templates including stereoisomers of **74** showed significantly lower binding affinities to members of a combinatorial tripeptide library (~ 24000 peptides).[64]

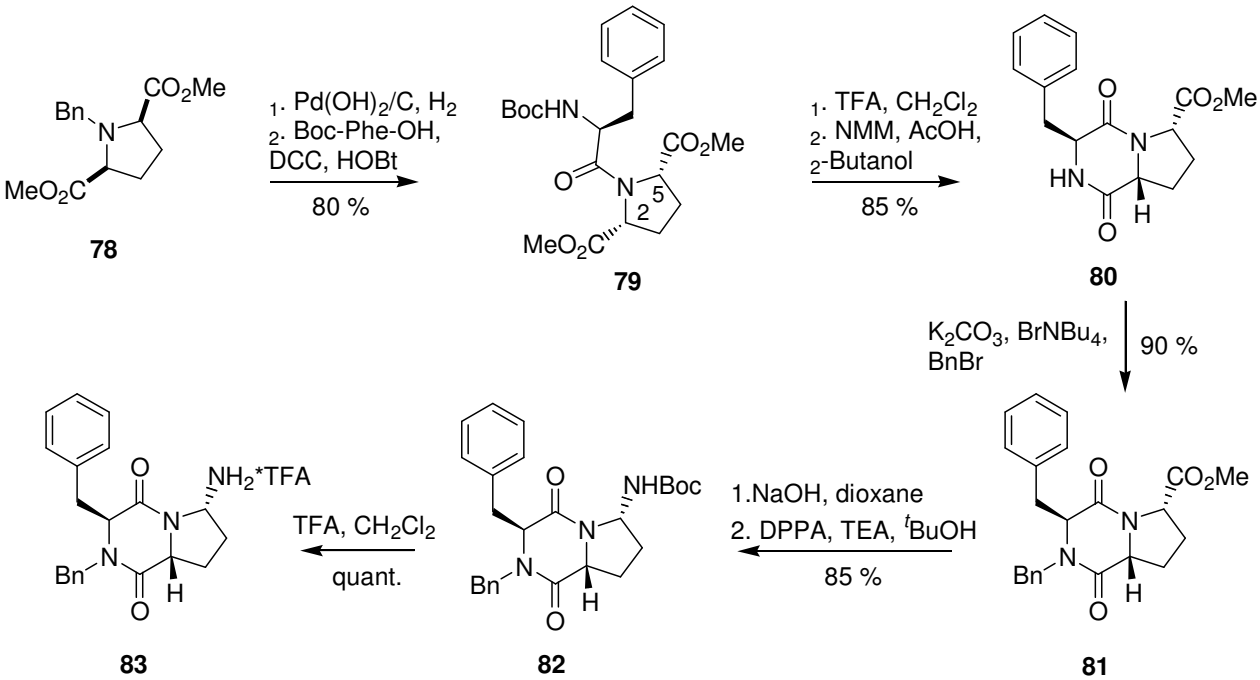
An interesting route to diketopiperazine dipeptide mimetics has also been established by the Mulzer group.[65] Starting from glutamate **75**, *syn*- and *anti*-diaminoglutaric acid derivatives **76** have been prepared in seven steps. These were transformed to diazabicycloalkanes **77** by reduction of the imine double bond and subsequent intramolecular lactamization in acetic acid (Scheme 10). Lactam **77** was formed with good diastereoselectivity (5:1).



75 **76** **77**

Scheme 10

Viallefont and coworkers have used diketopiperazine **83** as a chiral auxiliary in organic transformations such as Mannich reactions.[66] Aminal **83** was synthesized in a short sequence starting from *meso*-*N*-benzyl-dimethoxycarbonyl pyrrolidine **78** which was debenzylated and subsequently desymmetrized by coupling to Boc-protected phenylalanine to give **79** in good yield and diastereoselectivity in favour of the 2R,5S isomer. Boc deprotection and subsequent treatment with NMM gave diazabicycloalkane **80** along with the other minor diastereomer (de = 76 %), which was difficult to separate. The diastereomeric mixture was therefore *N*-benzylated under phase transfer conditions to give **81**, which was saponified to the corresponding carboxylic acid and then submitted to a Curtius transformation to give the protected aminal **82**.



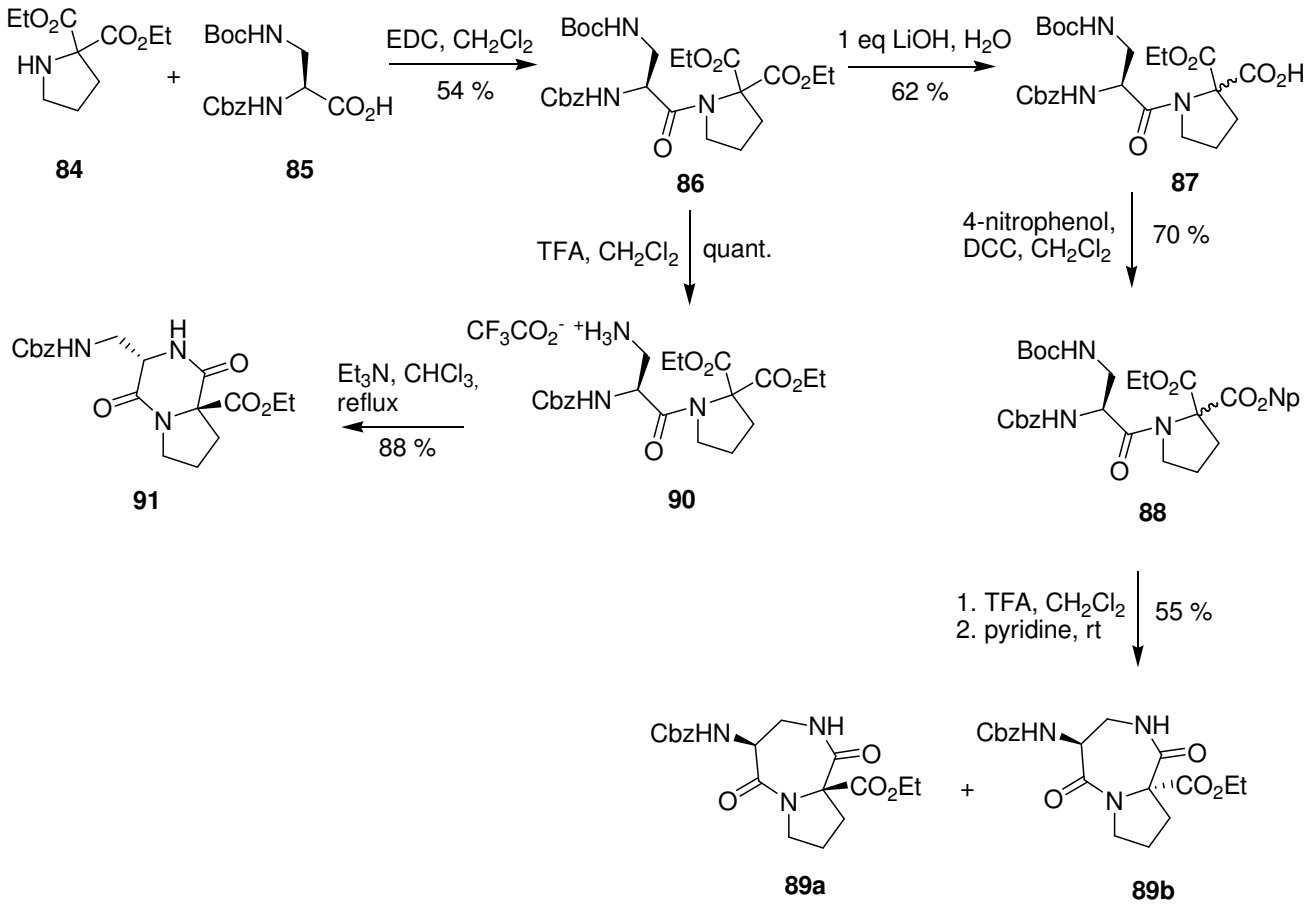
78 **79** **80**

83 **82** **81**

Scheme 11

A final deprotection step gave auxiliary **83** as a configurationally stable *N*-acylated aminal which can easily be converted to imine derivatives for Mannich reactions (Scheme 11). Since the imine is connected to the auxiliary *via* an *N*-acylated aminal, the resulting Mannich product can be cleaved off under acidic conditions and the auxiliary can be recycled in principle.

Diazabicycloalkane dipeptide mimetics **89** and **91** have been synthesized by Curran *via* a short synthesis starting from 2,2-pyrrolidinedicarboxylate **84** (prepared in one step from diethylaminomalonate and 1,3-dibromopropane) and (S)-*N*-α-Cbz-*N*-β-Boc-aminoalanine **85** (commercially available).[67] Pyrrolidine **86** is partly hydrolyzed to the monoacid **87** as a 1:1 diastereomeric mixture. Conversion to an active ester derivative **88** and its subsequent deprotection and cyclization under mild conditions gives two diastereomeric diketopiperazines **89a** and **89b** which were separated by column chromatography (Scheme 12).

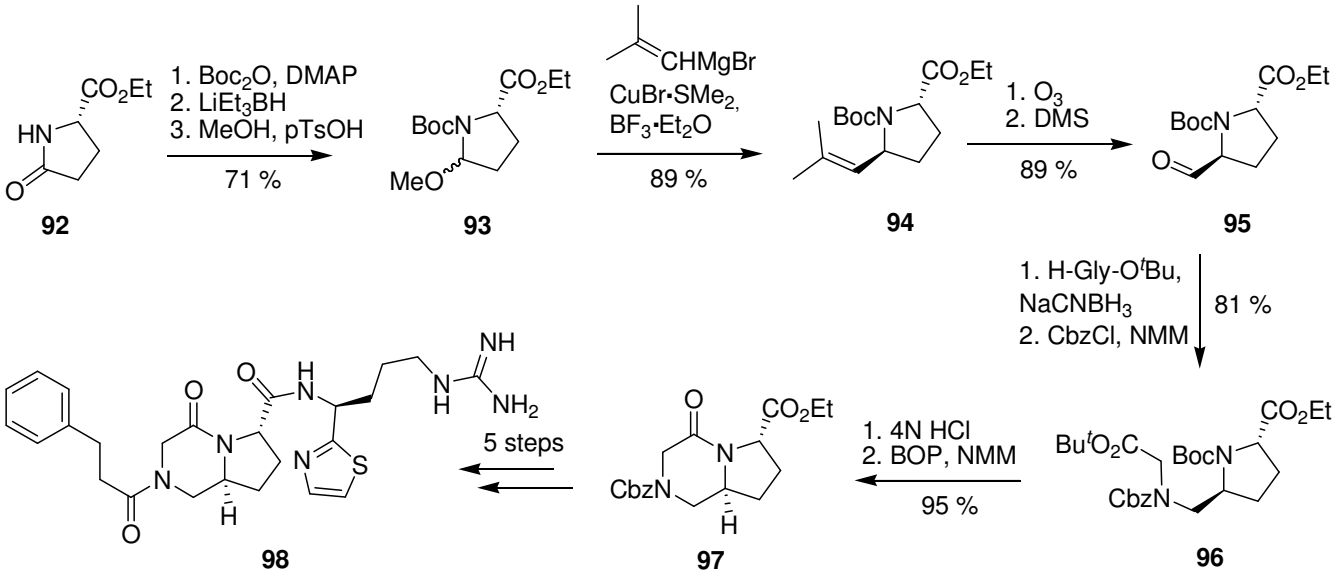


Scheme 12

Curran noted that a direct deprotection of **86** to trifluoroacetate ammonium salt **90** and its subsequent cyclization in refluxing triethylamine / chloroform lead to a transfer of the Cbz-group from the α to the β-amine and yields exclusively the 5,6-fused diketopiperazine **91** (Scheme 12). All three products **89a**, **89b** and **91** are valuable dipeptide mimetics, since they contain a conformationally rigid *cis*-prolyl amide bond.

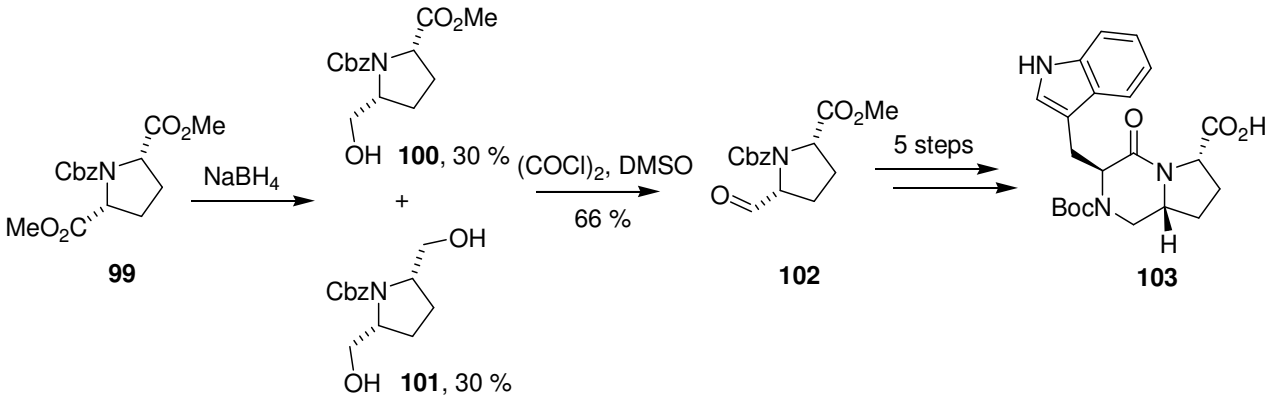
Different starting materials from the chiral pool have been used for the preparation of lactam precursors **59** in Figure 5. Siddiqui and coworkers have used ethyl pyroglutamate **92**, which was Boc-protected, reduced with superhydride and subsequently converted to the *N*-Boc protected aminal **93** in good yield. Cyclic *N*-acylated aminals like **93** have been known for a while to be excellent precursors for stereoselective *N*-acyliminium alkylations. Stereoselectivity in these alkylations can be tuned to give 2,5-*cis*

or 2,5-*trans* configured proline derivatives depending on the choice of organometal compound.[68] Addition of a vinyl cuprate to the *N*-acyliminium ion derived from aminal **93** by treatment with a Lewis acid gave 5-substituted proline **94** in good yield with excellent diastereoselectivity.[69] The alkene in **94** was cleaved by ozonolysis and reductive workup yielded amino aldehyde **95**, which is unstable and was immediately submitted to reductive amination with glycine methyl ester and $NaCNBH_3$. The resulting secondary amine was protected with Cbz to give **96** in very good yield for this two step conversion. The Boc group and the *tert*-butyl ester were removed in one step and subsequent lactamization was performed with Castro's reagent (BOP) and *N*-methyl morpholine (NMM) in excellent yield to give diazabicycloalkane **97**, a mimic of the protected dipeptide Cbz-Gly-Pro-OEt.[70] This dipeptide mimetic was further elaborated in five additional steps (Scheme 13) to a synthetic library of compounds that was tested for thrombin inhibition.[71] This screening identified compound **98** as a potent inhibitor of thrombin (IC_{50} 4 nM).



Scheme 13

A very similar approach was used by Chan and coworkers for the synthesis of endothelin antagonists like **103** (Scheme 14).[72]



Scheme 14

In this case, however, the starting material was *cis*-pyrrolidine-2,5-dicarboxylic acid **99**.[73] Reduction with $NaBH_4$ gave a separable mixture of the racemic mono reduction product **100** and the undesired diol **101**. Due to this unselective reduction yields of the overall sequence are quite low. Alcohol **100** was oxidized to aldehyde **102** which was transferred according to the sequence that is depicted in Scheme 13 to diazabicycloalkane **103**, a mimetic of Boc-Trp-Pro-OH.

3.2. Ring closing metathesis

Olefin metathesis has proven to be extremely valuable for the synthesis of various heterocycles.[74] For metathesis reactions of nitrogen containing substrates, Grubbs' ruthenium catalysts (Figure 6) have been employed most frequently, but Schrock's molybdenum catalyst has also been shown to have a good reactivity and functional group tolerance for these reactions.[75]

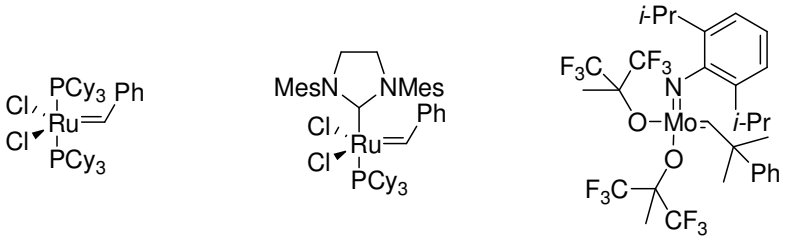
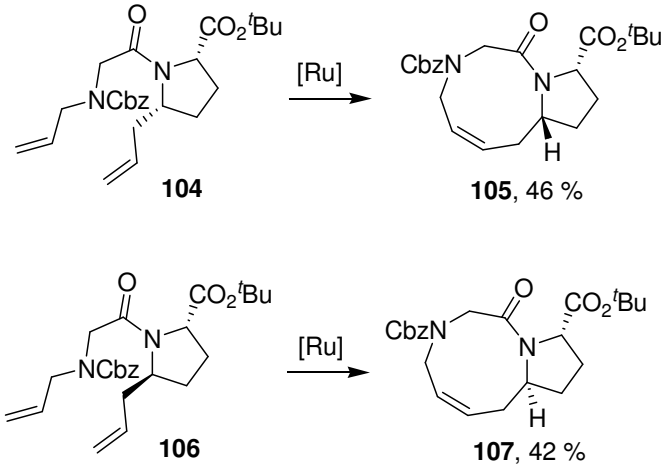


Figure 6

Application of ring closing metathesis (RCM) to the synthesis of peptide mimetics was first described by Grubbs[76] and later extended to the synthesis of dipeptide mimetics by Moeller[77] and Wagner.[78]

So far only one example of diazabicycloalkane formation using a ring closing metathesis is described in the literature.[79]

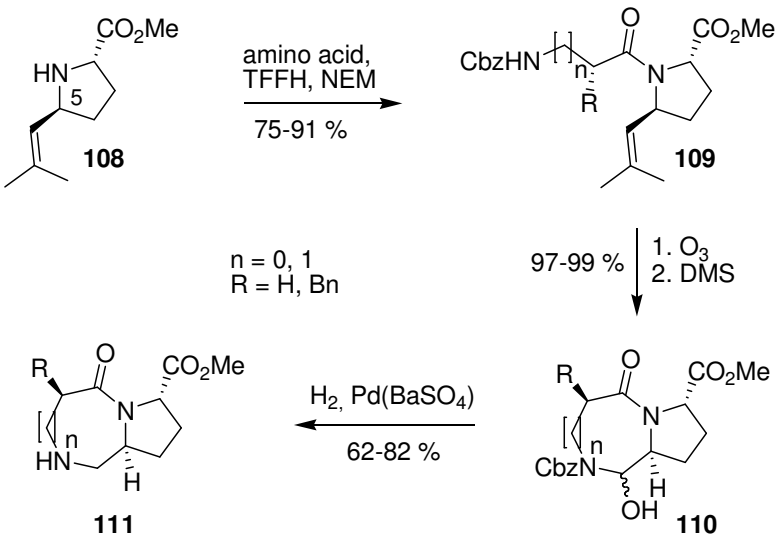


Scheme 15

Bisolefines like **104** and **106** can be prepared from known 5-allylproline and *N*-allyl-Cbz-glycine by standard peptide coupling with EDCI. Ring closing metathesis was achieved with Grubbs catalyst of the first generation (Figure 6) in moderate yield to give the two 9,5-fused diazabicycloalkanes **105** and **107** (Scheme 15).

3.3. Intramolecular reductive amination

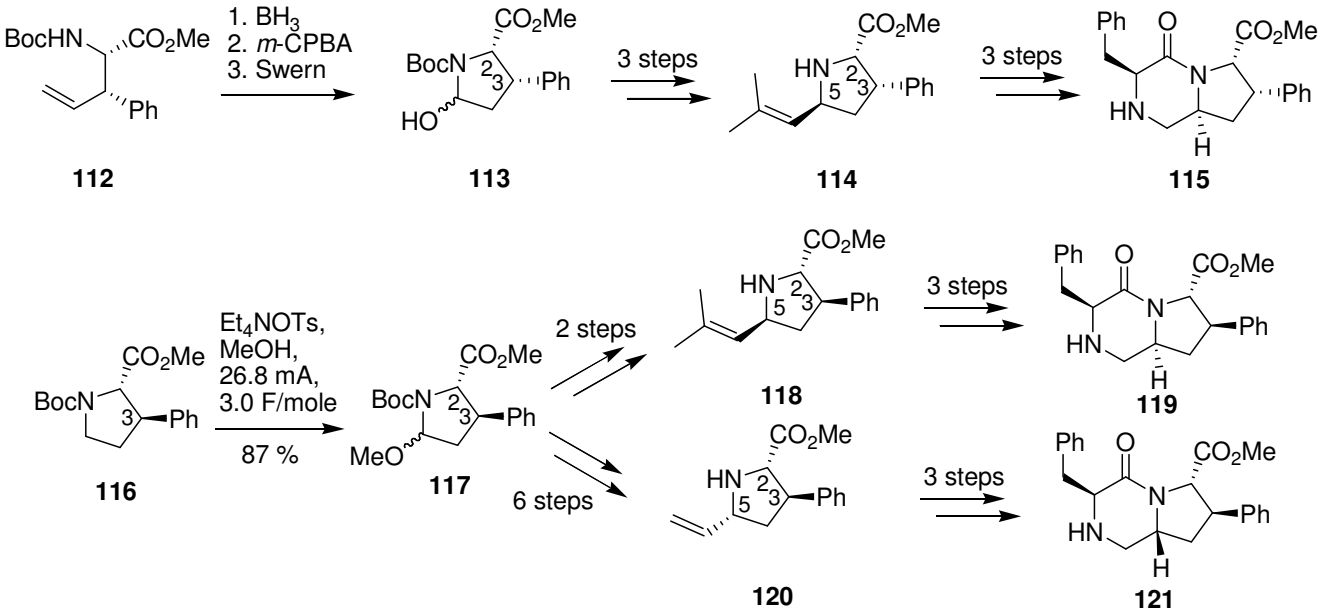
Moeller and coworkers have pioneered cyclizations *via* an intramolecular reductive amination and have synthesized a number of different diazabicycloalkane dipeptide mimetics.[80] Key intermediate in their initial approach was the 5-substituted proline derivative **108** that was synthesized in three steps from Boc-protected proline methylester. Peptide coupling of different α- and β-amino acids to **108** has been performed using Carpino's acid fluoride method with TFFH (Fluoro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate),[81] to give dipeptides **109** in very good yield. Ozonolysis followed by reductive workup gave an aldehyde intermediate, that cyclized with the *N*-terminal carbamate group to give aminals **110** as epimeric mixtures at the aminal position in excellent yields. A final deprotection of the Cbz group was accompanied by the reduction of the resulting imine species to give diazabicycloalkanes **111**, mimetics of the protected dipeptides Cbz-Gly-Pro-OMe and Cbz-Phe-Pro-OMe (Scheme 16). This strategy allows for the synthesis of dipeptide analogs mimicking a *C*-terminal proline unit in only six steps with good overall yield from protected proline. It can, of course, easily be extended to a number of X_{AA}-Pro mimetics with different *N*-terminal amino acids X_{AA}, excluding only those amino acid side chains which are sensitive to ozonolysis or oxidative conditions in general. This excludes, for example, sulphur containing side chains and thus Met and Cys mimetics. Ring sizes in the *N*-terminal portion of the bicyclic systems can be varied by the use of α- and β-amino acids (n = 0, 1 in Scheme 16) for peptide couplings.



Scheme 16

This approach has been extended to the synthesis of dipeptide mimetics for the Phe[7]-Phe[8] region of substance P. Introduction of side chains into the *C*-terminal portion of dipeptide mimetics like **111** can be achieved by the methods outlined in Scheme 17.

Two different intermediates **112** and **116** leading to either a 2,3-*cis* or a 2,3-*trans* configuration in cyclization precursors **114**, **118** and **120** have been prepared. Starting from pentenoic acid **112**, a 2,3-*cis* configuration in **113** can be achieved. A sequence of hydroboration, workup with *m*-chloroperbenzoic acid (MCPBA) and a subsequent Swern oxidation gave aminals **113**, which were converted under acid catalysis to the corresponding methoxy derivatives. These were transformed in five steps to Phe-Phe mimetic **115** according to the method described in Scheme 16.[82]



Scheme 17

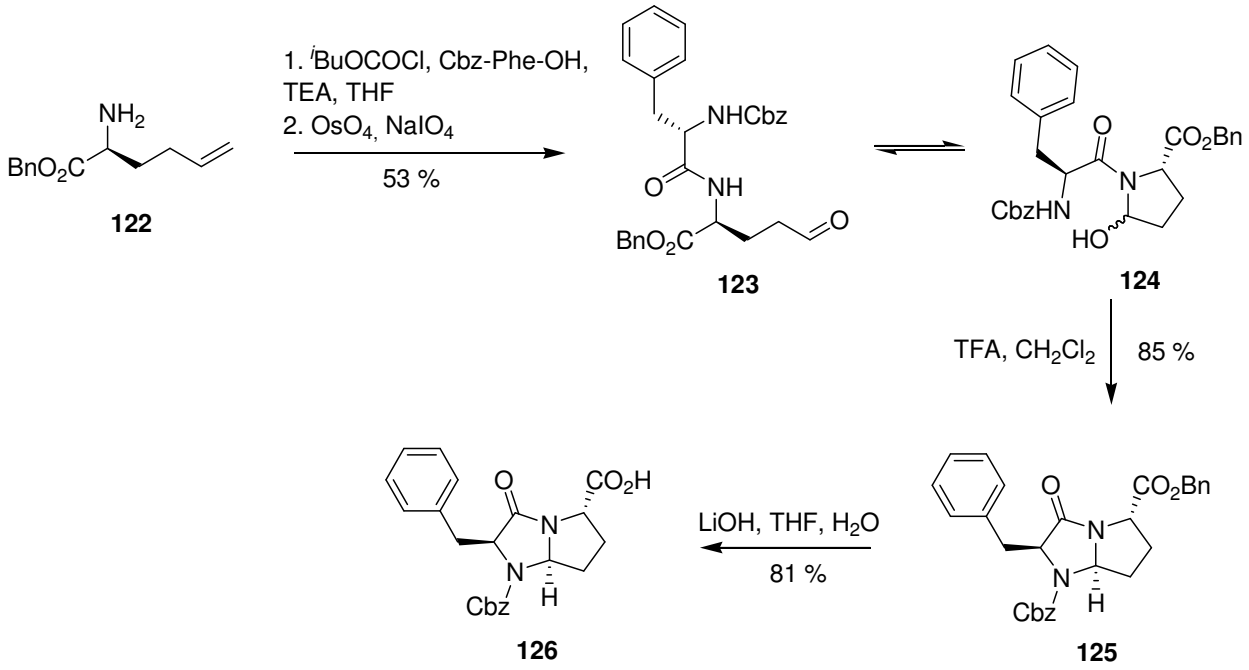
The 2,3-*trans* configured intermediate **117** was synthesized by anodic oxidation of protected 3-phenyl proline **116**. This intermediate provides access to two different series of dipeptide mimetics **119** and **121** in 5 or 9 steps, respectively.[83]

Moellers approach does thus permit the variation of stereochemistry and ring sizes in the *N*-terminal portion of dipeptide mimetics **111**, **115**, **119** and **121**. In addition, introduction of side chains is possible, as demonstrated with the synthesis of Phe-Phe mimetics **115**, **119** and **121**, but comes along with a number of additional synthetic steps.

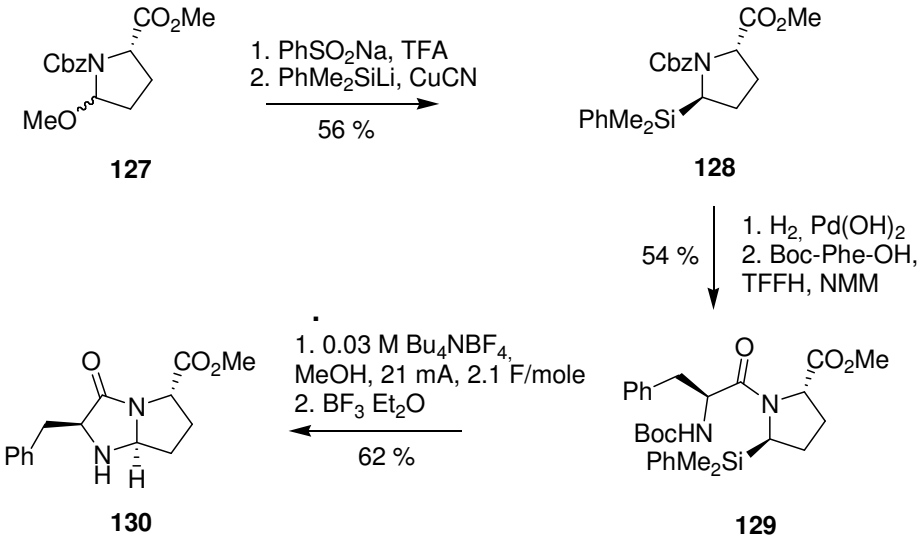
3.4. *N*-Acyliminium cyclization

Baldwin and coworkers have synthesized a bicyclic lactam dipeptide mimetic **126** from homoallylglycine **122**.[84] Peptide coupling and oxidative cleavage of the double bond gave aldehyde **123** that is in equilibrium with the aminal **124**. Cyclization of the diastereomeric mixture of **124** was achieved with TFA *via* an *N*-acyliminium intermediate that is trapped intramolecularly by the NHCbz-group to give diazabicycloalkane **125** as the only detected diastereoisomer. Saponification of the benzyl ester gave the final dipeptide mimetic **126** in good yield (Scheme 18).

Cyclization *via N*-acyliminium intermediates have also been reported by Moeller and coworkers.[85] The synthesis of cyclization precursor **127** has been performed by anodic oxidation of a protected proline derivative. Aminal **127** was converted to the corresponding sulfonyl proline derivative and a silyl cuprate was then used to introduce the silyl moiety to give **128**. The Cbz-group was removed hydrogenolytically and the free amine was then coupled to Boc-protected phenylalanine *via* its acid fluoride to give dipeptide **129**. In contrast to the methoxy aminal **127**, the silyl substituted proline **128** is stable to peptide coupling conditions. In addition, the silyl group lowers the oxidation potential of the neighbouring amide significantly, enabling a regioselective anodic oxidation of the proline amide in **129**. The resulting aminal was treated with $BF_3 \cdot Et_2O$ to generate the *N*-acyliminium ion which was trapped intramolecularly by the *N*-terminal free amine function to give diazabicycloalkane **130**, a constrained mimic of H-Phe-Pro-OMe (Scheme 19).



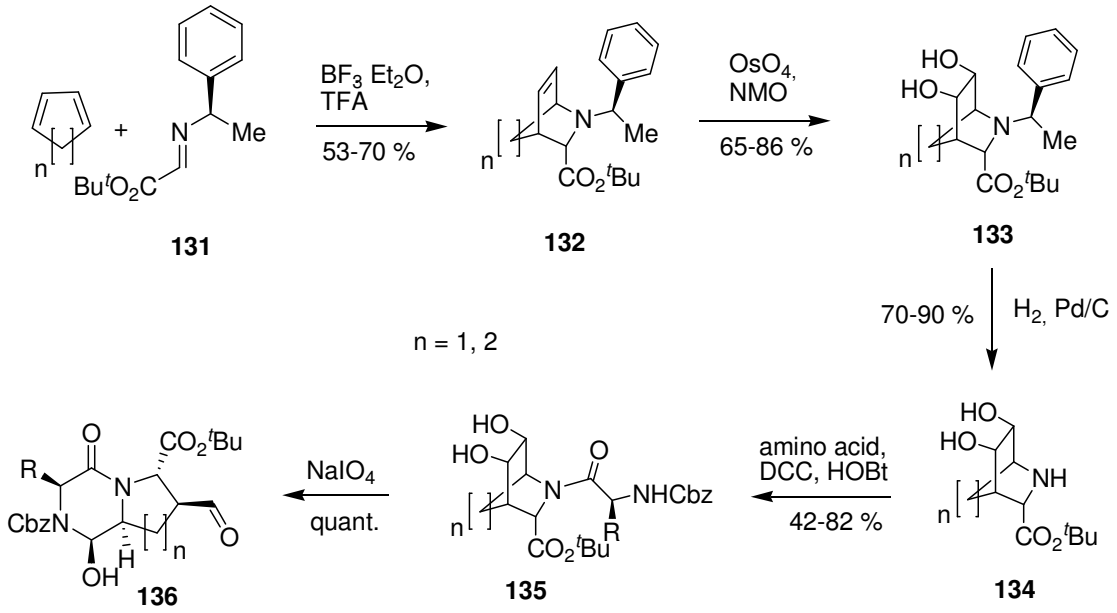
Scheme 18



Scheme 19

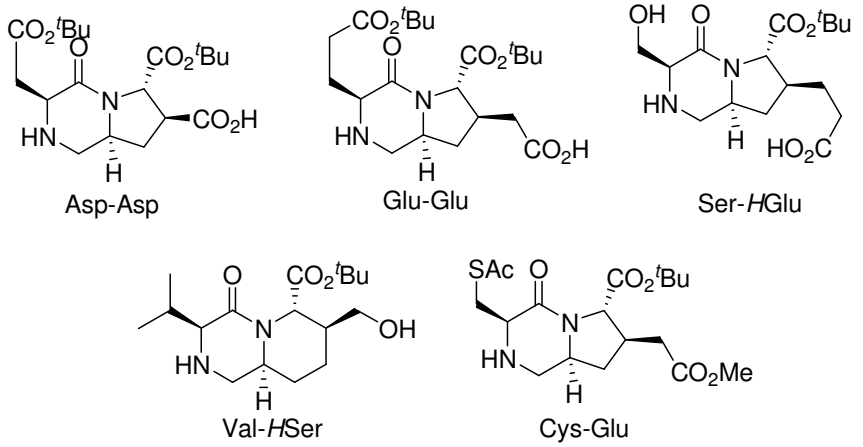
3.5. Tandem cyclization

Central intermediates of all syntheses reported so far are substituted derivatives of proline or pipecolic acid. These compounds are difficult to synthesize if functional groups suitable for later modifications to amino acid side chains are introduced. Derivatives of pipecolic acid are especially problematic since starting materials are expensive and especially 2,6-*trans* substituted derivatives are difficult to couple to an *N*-terminal second amino acid.[86] Synthesis of aza- and diazabicycloalkanes has therefore mostly been restricted to the preparation of X_{AA}-Pro mimetics and very few strategies hold the potential for an introduction of side chains and variation of ring sizes in the *C*-terminal amino acid of the dipeptide mimetic. We have therefore used azabicycloalkenes like **132** (Scheme 20) or bishydroxylated derivatives **134** as masked substitutes of 3,5-substituted prolines or 3,6-substituted pipecolic acids.[87] This strategy has been pioneered in a different context by Steglich for on-site modifications of oligopeptides at serine residues.[88]



Scheme 20

Our sequence starts with a diastereoselective *imino*-Diels-Alder reaction of chiral imine **131** and cyclopentadiene or cyclohexadiene.[89] The imine **131** was preformed in the same reaction vessel by treating (*R*)-phenyl ethylamine with *tert*-butyl glyoxylate in the presence of molecular sieves. Azabicycloalkenes **132** are obtained in good yields and stereoselectivity with a strong preference for the *exo*-product. Alkenes **132** were bishydroxylated with catalytic osmium tetraoxide and *N*-methyl morpholine (NMO) as cooxidant giving diols **133** as single diastereoisomers.[90] Hydrogenation gave aminodiols **134** which are coupled to a second amino acid under standard coupling conditions to give dipeptides **135**. Periodate cleavage of the diol bridge and subsequent intramolecular trapping of the resulting bisaldehyde by the *N*-terminal carbamate NH-group gives diazabicycloalkanes **136** in only five steps from readily available educts. Starting from diazabicycloalkanes **136** almost any dipeptide mimetic can be synthesized, because the aldehyde function can be easily transformed into a number of different amino acid side chains. This has been demonstrated for a number of different structures and a selection is presented in Figure 7.[91]

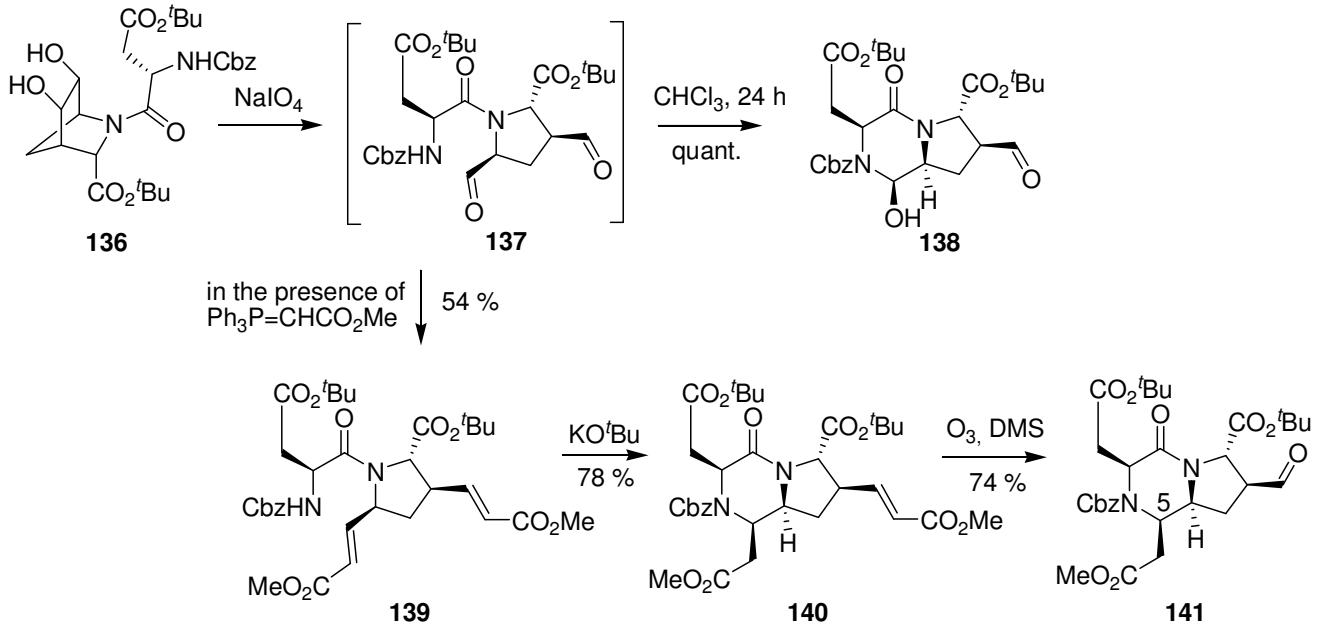


A selection of diazabicycloalkane dipeptide mimetics.

Figure 7

Some of these polar dipeptide mimetics have been tested for their affinity to the prostate specific membrane antigen and proven to be potent ligands (an *N*-acylated Asp-HGlu mimetic, for example, inhibits PSMA with IC_{50} 2 μM). These ligands might be useful lead structures for development of modular ligands for prostate cancer diagnostics.[92]

Further functionality can be introduced by performing the oxidative cleavage of diols **136** in the presence of a *C*-nucleophile such as a Wittig ylide.[93] Diols **136** can thus serve as intermediates for two different series of diazabicycloalkanes **138** and **141** (Scheme 21). Routine periodate cleavage and stirring for 24 hours gives diazabicycloalkanes **138** in quantitative yields. If the oxidation is in contrast performed in the presence of a Wittig ylide, the initially formed bisaldehyde **137** can be trapped to give bisolefine **139**. Upon treatment with a base, this bisolefine undergoes regioselective intramolecular addition of the *N*-terminal carbamate to the α,β-unsaturated methyl ester in **139** to give diazabicycloalkane **140**. The remaining double bond can be cleaved oxidatively to give aldehyde **141** which is again a versatile precursor for the synthesis of dipeptide mimetics. It should be noted that dipeptide mimetics **141** are functionalized with an additional orthogonally protected carboxymethyl group in 5-position, that is useful for conjugation to other functional molecules such as markers for tumour diagnostics or a solid phase for combinatorial applications.



Scheme 21

4. Conclusions

Efficient syntheses of a range of different and in some cases highly complex compounds with diazabicycloalkane cores have been developed. These synthetic advances have provided chemists and biologists with sufficient quantities of a number of natural products with extremely interesting biological properties. In addition, efficient methodologies for unnatural analogs and combinatorial libraries have been developed. Detailed studies of structure activity relationship are therefore possible and have already been performed for some scaffolds.

In addition, diazabicycloalkane dipeptide mimetics have evolved to be extremely useful tools for studies of receptor ligand interactions and drug design. This development is due to several efficient synthetic

strategies which have been developed by a number of research groups. Most of these strategies are ex-chiral pool syntheses that are based on proline or pyroglutamate derivatives. Only very few catalytic, enantioselective approaches have been reported so far and more catalytic approaches may be expected in the future. This might also add some further structural diversity to up to now mostly proline based scaffolds.

Acknowledgments

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List of abbreviations:

AIBN: azobisisobutyronitrile
m-CPBA: *m*-chloroperoxybenzoic acid
DBU: 1,8-diazabicyclo[5,4,0]undec-7-ene
DCC: *N*,*N'*-dicyclohexylcarbodiimide
DEAD: diethyl azodicarboxylate
DIPEA: *N*-ethyldiisoproylamine
DMAP: 4-dimethylaminopyridine
DMS: dimethylsulfide
DPPA: diphenylphosphoryl azide
EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
HATU: *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
HOAt: 1-hydroxy-7-azabenzotriazol
HOBt: 1-hydroxy-1*H*-benzotriazol
LDA: lithium diisopropylamide
NBS: *N*-bromosuccinimide
NEM: *N*-ethylmorpholine
NMM: *N*-methylmorpholine
PyBoP: benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
TEA: triethylamine
TFA: trifluoroaetic acid
TFFH: tetramethylfluoroformamidinium hexafluorophosphate
TMSI: trimethylsilyliodide

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5,6-DIHYDROINDOLIZINE CORE FORMATION UNDER RHODIUM-CATALYZED HYDROFORMYLATION OF N-ALLYLPYRROLES

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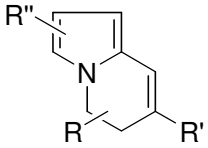
Abstract. *We describe a new access to the 5,6-dihydroindolizine core based on the rhodium-catalyzed hydroformylation of N-allylpyrroles. This nucleus is a building block of natural and synthetic target compounds. The construction of the indolizine moiety occurs via C7-C8 or C8-C9 bond generation involving two different intramolecular cyclodehydrations of the 4-pyrrolylbutanal intermediates.*

Contents

1. Introduction

This account is focused on the use of the homogeneous rhodium-catalyzed hydroformylation of N-allylpyrroles in the synthesis of 5,6-dihydroindolizines (Figure 1), which are intermediates of target indolizine derivatives.



R, R', R"= H, CH_3, C_2H_5, C_6H_5, CHO, CH_3CHO

Figure 1

The described application constitutes one of the few examples of the hydroformylation as a synthetic instrument for the fine chemistry. In fact, contrary to its industrial importance, the hydroformylation has not been of frequent use in organic synthesis yet, the control of the selectivity throughout the course of the reaction being the main difficulty. Nevertheless the reaction shows many advantages: the addition of CO and H_2 to an alkene function provides a new carbon-carbon and a new carbon-hydrogen bond and simultaneously introduces the synthetically useful aldehyde function, which prepares the product for additional carbon skeleton expanding operations. In particular, in the synthesis of the 5,6-dihydroindolizines treated here, the carbonyl group of a 4-pyrrolylbutanal, the *oxo* product (Figure 2), becomes the starting point for cyclization/dehydration reactions sequences giving pyrrole fused structures (Figure 2) in a very economic process.

R,R',R",R'"= H, CH_3, C_2H_5, C_6H_5, CHO, CH_3CHO

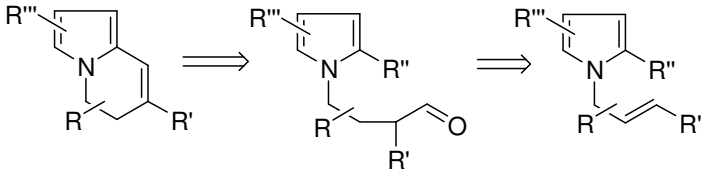
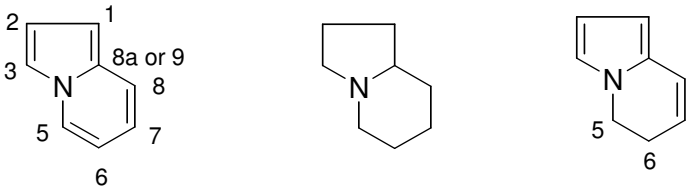


Figure 2

1.1. Indolizines family

The indolizine building block is a very common skeleton for many types of active compounds. The complete unsaturated system is named indolizine and it is a very important target in organic synthesis because of its wide range of biological activity.[1] The complete saturated bicyclic core instead is named indolizidine (or octahydroindolizine) and is widely diffused in nature, bearing many different substituents (Figure 3).[2]



Indolizine, indolizidine and 5,6-dihydroindolizine

Figure 3

One of the most interesting classes of indolizidine is formed by the polyhydroxylated derivatives, which have been deeply investigated because of their activity as inhibitors of glicosidase enzyme,[3] but also 5- or 3,5-alkyl-substituted indolizidines are quite important derivatives. Partial hydrogenated systems have been prepared and characterized. Often they are used as intermediates in the synthesis of indolizines or indolizidines, because the peculiar reactivity of the unsaturated derivative can be exploited in further functionalisation of the different positions of the bicyclic core.[4] On the other hand partial hydrogenated indolizines constitute also target molecules for themselves, as illustrated by the wide literature concerning the 5,6,7,8-tetrahydroindolizines.[5]

Few publications are reported in the literature concerning the class of the 5,6-dihydroindolizines. Only single examples are reported, so it`s difficult to list in a general scheme the methods used for their preparation. With the exception of patents,[6] Table 1 summarizes the literature covering the articles came out for the synthesis of 5,6-dihydroindolizines, unifying the reaction types according to the bond formed in the cyclization process.

Table 1.

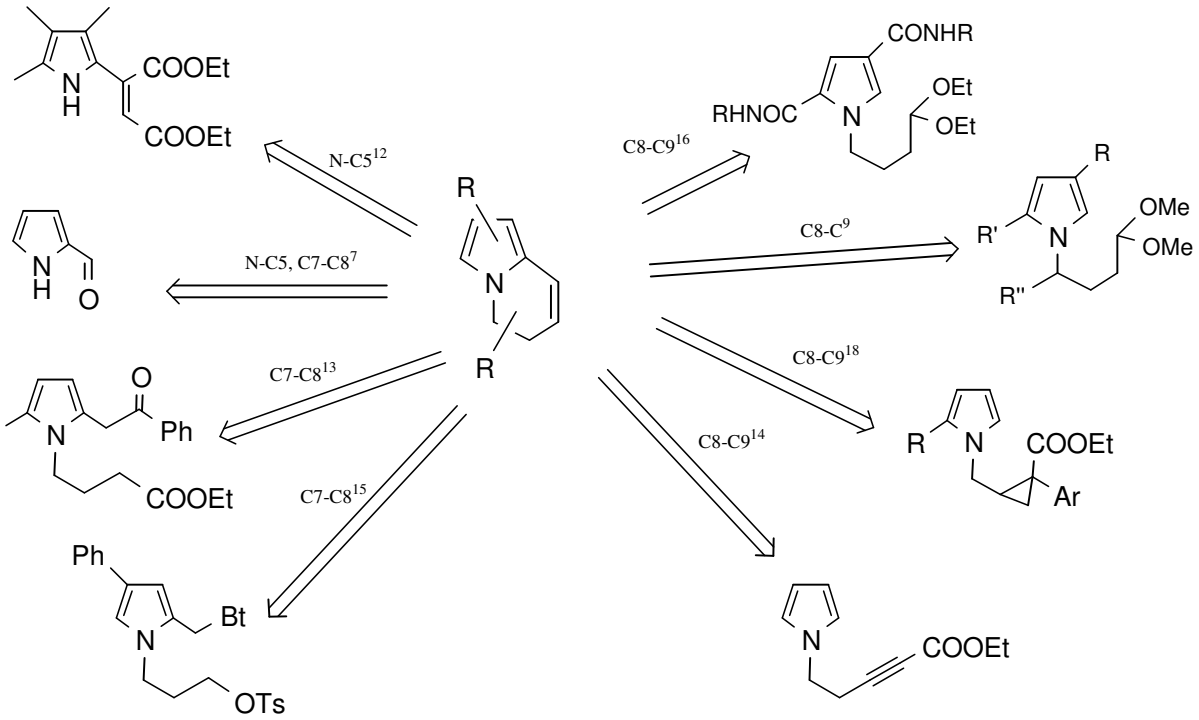
Bond	*Reaction type*	*References*
C1-C2	-	Not found
C2-C3	-	Not found
C3-N	nucleophilic substitution	10
N-C5	Wittig[a]	7
	cycloaddition[b]	12
C5-C6	-	Not found
C6-C7	cycloaddition[b]	12
C7-C8	Dieckmann condensation	13
	nucleophilic substitution	15
	Wittig	7
	Pt(IV) catalyzed hydroarylation	14
C8-C9	Hydroformylation	19, 20
	Nucleophilic substitution	9, 16, 18
C9-C1	-	Not found
N-C9	-	Not found
Others	Reduction, pyrolisis	8, 11, 17

[a]N-C5 and C7-C8 simultaneously formed; [b]N-C5 and C6-C7 simultaneously formed.

5,6-Dihydroindolizines have been prepared for the first time in 1971 by Cliff and coll.[8] by reducing indolizines with metals. The use of sodium in ethanol as well as sodium in liquid ammonia gives generally a mixture of dihydro- and tetrahydroindolizine derivatives. The Birch reduction of indolizines has been very recently improved towards the synthesis of only one product, by carrying out the reaction at very low temperatures.[9] The reaction resulted completely chemo- and stereoselective in the preparation of 5-substituted-5,6-dihydroindolizines, when an ester group is present in position 5. The only example of cyclization involving a pyridine derivative as starting material also gives a mixture of indolizine and

5,6-dihydroindolizine as byproduct,[10] while only traces of 5,6-dihydroindolizines have been found in the pyrolisis of pyrrolyl substituted furans,[11] as described in 1993.

Methodologies of synthetical usefulness have been reported from time to time. The 6-membered ring have been generally built up starting with pyrrolyl derivatives, where the intramolecular cyclisation occurs at different positions, as reported in Scheme 1. In all cases, the 5,6-dihydroindolizine structure is not a target molecule but one product among many, reported as one example for a synthetic methodology.



Scheme 1
Different disconnections in the synthesis of 5,6-dihydroindolizines.

Different types of reaction have been explored in the construction of the indolizine core, *i.e.* electrochemically induced cycloaddition[12] of enamines (N-C5 and C6-C7 bond formation), Dieckmann type condensation (C7-C8 bond formation),[13] or Pt(IV)-catalyzed hydroarylation (C8-C9 bond formation).[14] A C7-C8 bond forming nucleophilic substitution instead has been exploited in the work of Katritzky and coll.:[15] in this case the formation of the double bond occurs *via* an elimination reaction of the benzotriazole substituent.

In other cases the nucleophilic character of the carbon atom in position 2 of the pyrrole moiety has been exploited for the intramolecular cyclization. A masked aldehydic group is involved in the acid catalyzed cyclization of a tripyrrole peptide[16] and in the synthesis of highly substituted 5,6-dihydroindolizines, used as precursors of natural myrmicarins,[17] where the cyclization and the double bond are formed in the same step. A 5,6-diydroindolizine has been obtained by an intramolecular nucleophilic substitution also by exploring the reactivity of indolizin-9-ones bearing a cyclopropane group,[18] where the insaturation between C7 and C8 is performed only after the cyclization.

We first obtained the compounds under rhodium-catalyzed hydroformylation of N-allylpyrroles,[19,20] building up the indolizine core from the produced 4-pyrrolylbutanals *via* formation of C7-C8 or C8-C9 bond respectively.

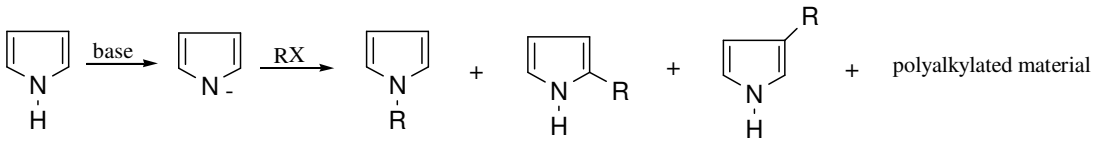
2. Synthesis of N-allylpyrroles

Two are the synthetic approaches to N-substituted pyrroles:

- Synthetic methods starting from pyrrole: the allyl moiety is transferred on the simple pyrrole or functionalized pyrrole *via* a nucleophilic substitution.
- Synthetic methods *via* building of the pyrrole ring: the pyrrole ring is constructed *via* a condensation reaction on the nitrogen of a proper derivative, usually a primary amine, as a source of the pyrrole nitrogen atom.

2.1. Methods from pyrrole: synthesis of racemic N-allylpyrroles

The N-substituted pyrroles are usually obtained by the treatment of pyrrole with an appropriate base followed by the reaction of the resulting salt with an alkylating agent (Scheme 2).



Scheme 2

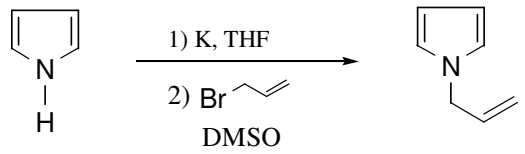
However, since the pyrrolyl anions exhibit ambident behavior as nucleophiles, alkylation can occur at carbon as well as at nitrogen.[21,22] Thus, substantial quantities of 2- and 3-alkylpyrrole may contaminate the N-alkylated product along with some polyalkylated material (Scheme 2). The amount of N-alkylation relative to C-alkylation depends upon a number of factors, including the base employed for the deprotonation of the heterocycle, the solvent, and the alkylating agent. Although nitrogen alkylation generally prodominates when the cation is a sodium or potassium ion, carbon alkylation usually is the favoured product with harder[23] cations like lithium or magnesium which are tightly bonded to the nitrogen.[24] The solvent can dramatically influence the ratio of N to C alkylation[22b-d,22g,25] and dipolar aprotic solvents can give rise to predominant N-alkylation of salts derived from pyrrole even when magnesium is the counterion.[22b,d,g] Finally, the alkylating agent can influence the ratio of N to C alkylation. For example, when compared to other alkylating agents, allylic or benzylic halides generally afford a greater proportion of C-alkylated material.[22b,g,26] More recently, several new procedures have been developed in which the N-alkylation of pyrrole can be accomplished with little or no interference from C-alkylation. [22g,25,27] Included in these procedures are those which rely on the use of dipolar aprotic solvents [25,27] and several others which rely on phase-transfer catalysis[28] by quaternary ammonium salts[21g,26,27c,29] or crown ethers.[22e,30] The phase-transfer methods appear to be the most useful in terms of mildness of conditions and convenience.

2.1.1. Procedures which rely on the use of dipolar aprotic solvent

The synthesis of the simple 1-(2-propenyl)pyrrole starting from pyrrole and metallic kalium[31] is a significant example (Scheme 3).

The two reagents were mixed and heated in THF to form the pyrrole kalium salt. The solvent was substituted with DMSO and the resulted hot mixture was added of a solution of allylbromide. After hydrolysis and solvent extraction, the product was obtained *via* distillation at reduced pressure. Although the

yield was convenient, the use of pirophoric kalium makes this approach not useful for preparation on a large scale.

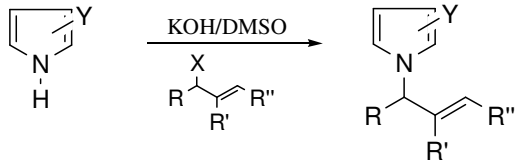


Scheme 3

In the last years Trofimov *et al.*[32] developed a simpler and more effective procedure for the preparation of 1-(2-propenyl)pyrrole. These authors showed that pyrrole reacts with allyl chloride in the superbasic system KOH-DMSO (molar ratio pyrrole-allyl chloride-KOH-DMSO 1:2:2.5:14) at 20-25 °C, yielding in 11.5 h 1-(2-propenyl)pyrrole in 88% yield. However, despite the mild conditions, the reaction mixture contained about 18% of other products, among which 1,2- and 1,3-bis(2-propenyl)pyrroles and isomerized product 1-(1-propenyl)pyrrole.

In 2004 Chen *et al.*[33] examined the reactions of pyrrole with some electrophilic reagents in ionic liquid. The authors found that in the presence of KOH, the reaction of pyrrole with allyl bromide proceeds at 70 °C in the ionic liquid 1-butyl-3-methylimidazoliumhexafluorophosphate[Bmim][PF_6] giving N-allylpyrrole in 100% yield.

Among the above reported methods, we adopted the KOH/DMSO conditions to prepare the following N-allylpyrroles, wich are unsubstituted on the pyrrole ring or bear on it an electrondonor group[34] (Scheme 4).



1

Y=2-Et, 3-Et X=Cl, Br

a: R=R'=R"=Y=H
b: R=R"=Y=H, R'=Me
c: R=R"=H, R'=Me, Y=2-Et
d: R=R"=H, R'=Me, Y=3-Et
e: R=Me, R'=R"=Y=H
f: R=R'=Y=H, R"=Ph

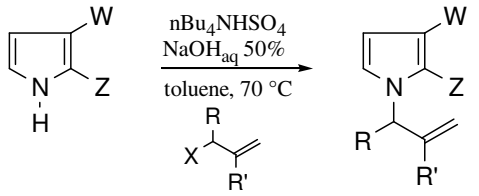
Scheme 4

The products were obtained with medium to good yield (40-68%). In the case of **1e** a double molar amount of alkylating agent was necessary in order to convert all starting pyrrole, the dehydroalogenation of the allylic halide to the corresponding diene being a concurrent step. Only traces of the isomerized internal olefin were found, oligomers being the current by-products.

2.1.2. Procedures which rely on the use of phase-transfer catalysis by quaternary ammonium salts

By using the phase-transfer approach, we recently prepared some N-allylpyrroles bearing an electronwithdrawing group on the pyrrole ring (Scheme 5).[19,35]

The tetrabutylammonium hydrogen sulphate generates the deprotonation of the annular nitrogen *via* ionic exchange with the dissolved sodium hydroxide.



Z=CHO, $COCH_3$ X=Cl, Br
W=$COCH_3$ R, R'=CH_3, H

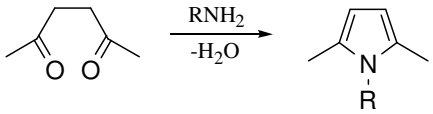
g: R=R'=W=H, Z=CHO
h: R=CH_3, R'=W=H, Z=CHO
i: R=W=H, R'=CH_3, Z=CHO
l: R=W=H, R'=CH_3, Z=$COCH_3$
m: R=R'=Z=H, R'=CH_3, W=$COCH_3$

Scheme 5

This anion, forming an ionic couple with the tetrabutylammonium, is soluble in the organic phase and it can give nucleophilic substitution on allylic alogenide, forming the final N-allylated product. During the experimental procedure the acylpyrrole dissolved in toluene was mixed to 50% aqueous NaOH containing tetrabutylammonium hydrogen sulphate. Then the allylic alogenide was added and the resulting mixture heated at 70 °C. The separation of the organic phase from the aqueous one was the sole difficulty: dilution of the organic phase and repeated extraction with methylene chloride resulted a convenient approach. Analogously to what observed in dipolar solvents, traces of the corresponding internal olefin were observed, due to the isomerizing basic conditions. It is to remark that whereas the phase-transfer conditions allow the preparation of the above compounds in good yield, they cannot be used for the synthesis of N-allylpyrroles unsubstituted or bearing an electrondonor group on the pyrrole ring: the formation of the corresponding pyrrolylanion is not favoured in the mild phase-transfer by quaternary ammonium salts conditions.

2.2. Methods *via* building of the pyrrole ring: synthesis of racemic and optically active N-allylpyrroles

The Paal-Knorr synthesis, starting from primary amines and 1,4-dicarbonyl compounds and their masked equivalents such as 2,5-dimethoxytetrahydrofuran, is often used for the construction of the pyrrole ring[36] (Scheme 6).

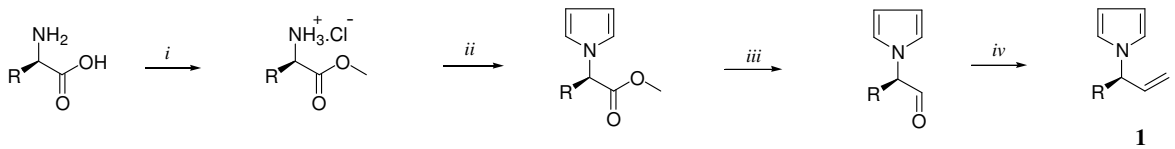


Scheme 6

The formation of the pyrrole derivative likely occurs *via* nucleophilic attack of the amine on the carbonyl group and successive elimination of two equivalents of water. The interest for this procedure is demonstred also by the recent modifications reported in the literature such as clay-mediated[37] organic reaction and microwave irradiation method.[36,38,39]

In addition to simple amines, polyfunctional substrates such as aminoacids,[40] aminoesters,[40] aminoalcohol[41] and aminoolefins[42] have been also used.

Patterson and coll.[42] prepared 1-allylpyrrole and 1-(1-methylprop-2-enyl)pyrrole *via* condensation of the proper allylammine with 2,5-dimethoxytetrahydrofuran in 45% and 34% yield respectively. We recently pointed out an original synthetic method of the differently substituted 1-allylpyrroles **1** in optically active form[43] utilizing the nitrogen atom of an amino group as source of the pyrrole nitrogen (Scheme 7)**.**



n: R=Me; o: R=*i*-Pr; p: *n*-Pr

Reagents and conditions: (*i*) R=*i*-Pr, $SOCl_2$, MeOH at reflux, 90 min., 97% yield; R=*n*-Pr, HCl, MeOH at reflux, 60 min., 98% yield; (*ii*) 2,5-dimethoxytetrahydrofuran, AcOH/AcONa, 80 °C, 30-120 min; (*iii*) 1M DIBAH in hexane (1.8 equiv.), -78 °C, 15-40 min.; (*iv*) Ph_3PCH_3Br, $NaNH_2$, THF, -30 °C, 30 min..

Scheme 7

We chose the D-α-amino acids methyl esters hydrochloride to introduce both the stereogenic center and the useful ester functionality.[43] These compounds were submitted under condensation with 2,5-dimethoxytetrahydrofuran,[40,43]giving its 1*H*-pyrrole derivatives in good yield (70-92%) and excellent enantiomeric excess (>99%).

Reduction of the pyrrolylesters to pyrrolylaldehydes, the crucial step of the process, was chemoselectively carried out by treatment with 1.0 M DIBAH in hexane (1.8 equiv.) at –78 °C; the excess of the reducing agent was destroyed with methanol and the resulting solution hydrolyzed with Rochelle salt, at the same temperature. In the adopted experimental conditions the substrate conversion was complete (use of lesser amounts of DIBAH resulted in recovery of unreacted starting material) and neither overreduction to the respective alcohols nor significant racemization of the produced aldehydes were observed. We found that the hydrolysis temperature is a critical parameter for the configurational stability of the aldehydes. When Rochelle salt solution was added at room temperature, the enantiomeric excess for (2R)-2-(pyrrol-1-yl)pentanal was the lowest observed (70%) and an intermediate value was found (81%) when the hydrolysis was carried out at –30 °C (at –78 °C the e.e. was 95%) (Table 2).

Table 2. Reduction of methyl (2R)-2-(pyrrol-1-yl)pentanoate to (2R)-2-(pyrrol-1-yl)pentanal with DIBAH in hexane: influence of the hydrolisis temperature on enantiomeric excess.

entry	**T (°C)**	**e.e. (%)[a]**
1	r.t.	70
2	-30	81
3	-78	95

[a] Determined by gas chromatography with the chiral capillary column CHIRALDEX G-TA (γ Cyclodextrin trifluoroacetyl, 50 m x 0.25 mm)

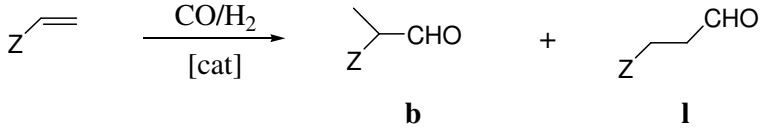
The aldehyde enolization is prevented under these conditions, probably because the intermediate aluminoxy acetal, species thermally labile, is long lived at –78 °C only.[43] The aldehydes resulted both chemically and configurationally stable during their purification by vacuum distillation and storage at 0 °C (three weeks). The produced (2R)-2-(pyrrol-1-yl)propanal,[43] (2R)-3-methyl-2-(pyrrol-1-yl)butanal, (2R)-2-(pyrrol-1-yl)pentanal were obtained in high yield (> 78%) and with almost complete retention of chiral integrity (e.e.> 92%).

The Wittig reaction, a useful tool for simultaneous elongation of the chain and introduction of the desired terminal double bond, was carried out with Shlosser-Schaub instant ylid reagent at –30 °C in THF. The olefins (3R)-3-(pyrrol-1-yl)but-1-ene (**1n**), (3R)-4-methyl-3-(pyrrol-1-yl)pent-1-ene (**1o**), (3R)-3-(pyrrol-1-yl)hex-1-ene (**1p**) were obtained in good yield (65-75%) and high e.e. (>92-98%). Few examples of Wittig olefination on N-protected amino aldehydes are reported in literature and the question of the racemization in this reaction has not been addressed.[43] In the experimental conditions here described, aldehydes enolization does not occur and the corresponding olefins are obtained with retention of optical integrity.

3. Rhodium catalyzed hydroformylation of N-allylpyrroles: synthesis of indolizines

3.1. Rhodium catalyzed hydroformylation of olefins: general remarks

The hydroformylation reaction or "oxo" synthesis provides the formal addition of CO and H_2 to an olefinic double bond catalyzed by transition metals-based precursors. In the case of vinyl groups, two aldehydic isomers are obtained, the branched (**b**) and the linear (**l**) ones (Scheme 8).



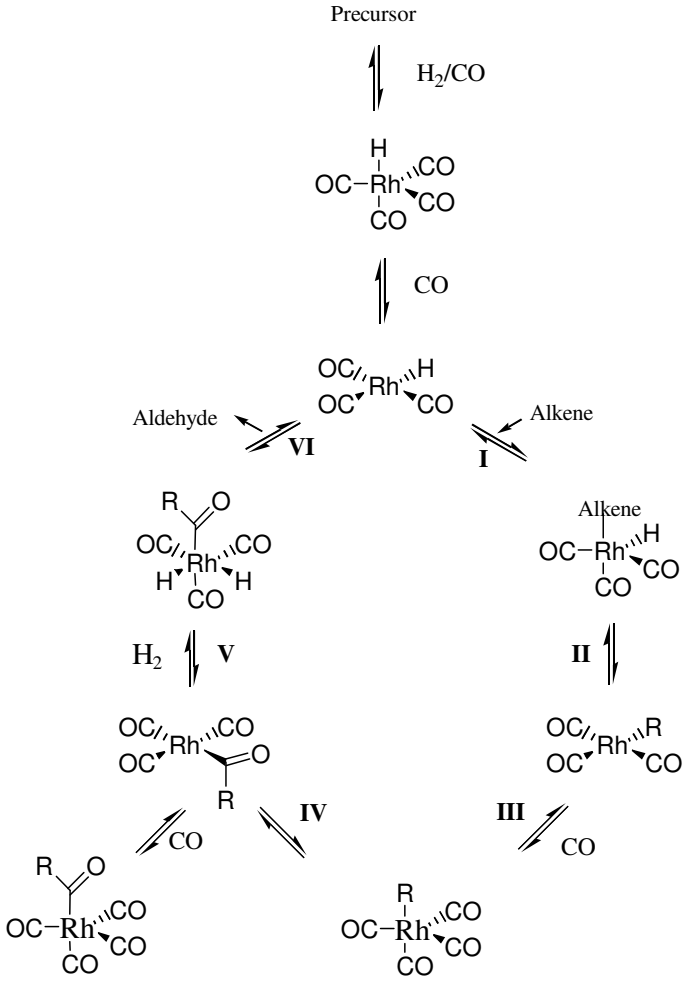
b **l**

[cat]= [Rh], [Co], [Ru], [Pt/Sn]

Scheme 8

The first investigations on the rhodium-catalyzed hydroformylation were carried out at the end of 1950's,[44] about 20 years after the discovery by Roelen of the cobalt-catalyzed "oxo" reaction.[45] After more than sixty-eight years, it still constitutes the most important way of producing aldehydic products for industrial purposes, above all for the functionalization of the simple olefins derived from the treatment of petroleum. On this light the most used catalyst precursors are the cobalt-based ones, being the best compromise between economic advantage and activity. The rhodium-based catalysts are in general much more active (even 10^5 times) than the cobalt based ones and much more tolerant of the presence of other functional groups in the unsaturated substrates.[46] Indeed there has been an enormous amount of research on the synthesis and use of phosphorus- and sulfur-containing ligands with various steric and electronic characteristics,[47] including optically active ones for the use in enantioselective processes.[48] Nevertheless, unmodified Rh catalyst precursors such as $Rh(CO)_2(acac)$, $[Rh(COD)(OAc)]_2$ and $Rh_4(CO)_{12}$ are still the subject of detailed investigations. This is due to their easy availability, their well-known properties and their rather unproblematic handling.[49] A simplified scheme for the generally accepted mechanism for the

hydroformylation processes catalyzed by unmodified rhodium precursors is reported in Scheme 9 and proposes the rhodium-carbonyl hydride [$HRh(CO)_3$] as the catalytic active species of the reaction.[50,51]



Scheme 9

In the first stadium (**I**) the alkene coordinates to a free site in the rhodium metal, giving rise to a π complex. In stadium **II** the alkene inserts into the Rh-H bond, giving rise to the alkyl-rhodium intermediates. These ones, after the coordination of a fourth CO molecule to the metal center (stadium **III**) give rise to the migratory insertion on a carbon monoxide in cis position, leading to the formation of an acyl-rhodium species (stadium **IV**). The oxidative addition of H_2 on the latter intermediates produces an hexacoordinated Rh (III) complex (stadium **V**), and the subsequent reductive elimination (stadium **VI**), which gives the final aldehydes and regenerates the catalytic species, concludes the whole cycle.

The main goal in the rhodium-catalyzed hydroformylation of unsaturated substrates concerns the control of the reaction regioselectivity, *i.e.* the branched aldehyde (**b)/**linear aldehyde **(l)** ratio.

The substrate structure as well as the experimental parameters can play a crucial role in determining the reaction regioselectivity.

As far as the influence of the substrate nature is concerned, the hydroformylation of vinyl aromatic substrates (*i.e.* styrene),[52] vinylfurans,[53] vinylthiophenes,[54] vinilpyrroles[55] and vinylpyridines,[56,57] under mild temperature always provides a large predominance of the branched isomer over the linear one. Under the same conditions, alkenes with α hydrogens (*i.e.* linear 1-alkenes) give the two regioisomers in almost 1:1

molar ratio.[58] The linear isomer largely predominates over the branched ones in the hydroformylation of 3-alkyl substituted allyl alkenes (*i.e.* 3-methylbut-1-ene).[59]

In the case of vinylidenic substrates, whatever kind of Z substituent is present (dialkyl, arylalkyl, diaryl) the linear isomer is almost exclusively produced.[60]

These results can be rationalized taking into account that under mild conditions the aldehydes regioselectivity reflects the regioselectivity of the formation of the branched and linear rhodium-alkyl intermediate (Figure 4): the same electronic and steric effects determining a prevalence of a single rhodium alkyl, will also favour the corresponding aldehyde.

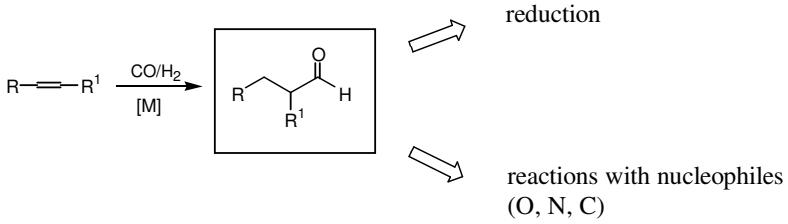
Figure 4

As far as the influence of the reaction conditions on the regioselectivity is concerned, in the case of vinyl and vinylidenic alkenes, the amount of linear aldehydes increases by raising the reaction temperature, and decreasing the CO and H_2 partial pressures. Indeed, this is a general trend in the hydroformylation of different substrates and constitutes a fundamental starting point for a rationalization of the influence of experimental parameters on the reaction selectivity.[61]

3.2. Rhodium catalyzed hydroformylation of olefins: an instrument for the fine chemistry

Although the process introduces the preparatively useful aldehyde functionality, in terms of synthetic efficiency the reaction suffers from the fact that it provides only a one carbon chain elongation (Scheme 10).

One way to overcome this deficiency could be to incorporate this reaction as a key step in a domino-type process[62] (Scheme 10), the aldehydic group being a well-known versatile functionality in organic chemistry.[63]



Scheme 10

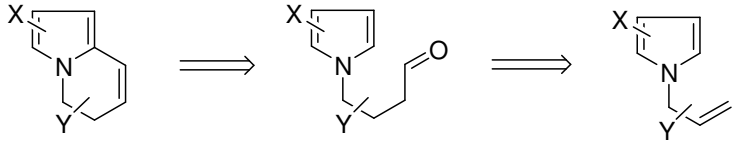
The most widespread domino process is the one pot hydroformylation-reduction to obtain alcohols. In addition the formation of acetals can be achieved under oxo conditions by using suitable alcohols or diols, which react with the just formed aldehydes.[64] Similar processes are observed with nitrogen containing substrates. In this case the hydroformylation reaction usually proceeds with a N,O[65] or N,N[66] acetal cyclization. Anyway the most frequent reaction, which takes place in these experimental conditions, is the formation of an imine, which can be further hydrogenated to amine, usually the main byproduct. In this way it is possible to build several heterocyclic nuclei, such as quinolines[67] and indoles.[68] Another interesting

reaction is the alkylamination under oxo conditions, which occurs by carrying out the reaction in the presence of the suitable amine compound. This reaction has been used to prepare various compounds of pharmaceutical interest, starting from the commmercially available 1,1-diphenylethene.[60b,69] Both intra- and intermolecular aldol reactions following hydroformylation have been reported.[70] An example with both partners generated under oxo conditions is the hydroformylation of 1,3-butadienes, which gives monoaldehydes containing a five membered ring.[71] In conclusion, it is possible to state that the hydroformylation reaction, alone or in sequence with cyclization processes, constitutes a valid tool for the formation of C-C, C-N and C-O bonds. However all references cited in literature always report the domino oxo-cyclization reactions in the presence of a suitable functionality, such as hydroxy- or amino-groups. No examples have been reported until now about the possibility of having a cyclization process in the absence of such moieties.

3.3. Hydroformylation of N-allylpyrroles as key step into two new domino-type processes to 5,6-dihydroindolizines

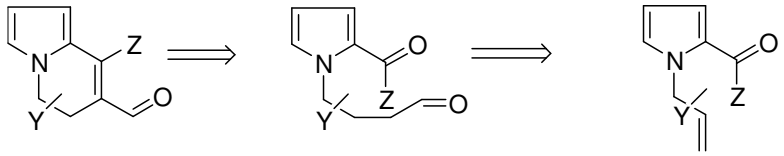
The hydroformylation of 1-allylpyrroles, carried out by us for the first time, resulted to be the key step of two new domino-type processes. In fact, contrary to the branched aldehyde which remains unchanged under hydroformylation conditions, the linear 4-pyrrolylbutanal can be involved in an intramolecular cyclodehydration *via*:

-electrophilic substitution on the α pyrrole position, followed by water elimination (C8-C9 indolizine bond formation) (Scheme 11);



Scheme 11

-aldol addition of the carbon atom adjacent to the carbonyl group in the chain onto a carbonyl group on the α pyrrole position, followed by water elimination (C7-C8 indolizine bond formation) (Scheme 12).



Scheme 12

3.3.1. Experimental conditions

In a typical procedure, a toluene solution of the proper N-allylpyrrole and $Rh_4(CO)_{12}$, as the catalyst precursor (substrate/Rh = 100-500), was introduced by suction into an evacuated 25 ml stainless autoclave under magnetic stirring. Carbon monoxide was introduced, the autoclave was heated at the desired temperature (20-140 °C) and hydrogen was rapidly introduced up to the final total pressure [CO/H_2 = 30-120

atm (1:1)]. When the reaction started the drop in pressure was compensated by injection of a carbon monoxide-hydrogen mixture (1:1) from a high pressure container. When the gas absorption reached the value corresponding to the desired conversion, the reaction vessel was rapidly cooled, the reaction mixture was siphoned out and GLC was used to determine the isomeric composition. The degree of conversion was measured by GLC by using acetophenone as internal standard.

Stainless autoclave: sampling

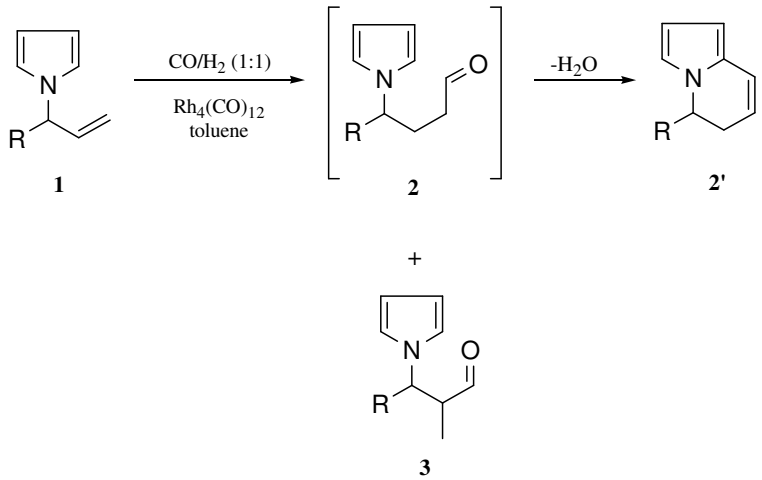
Components of the stainless autoclave

3.4. Construction of the indolizine moiety *via* C8-C9 bond formation

3.4.1. Synthesis of racemic 5,6-dihydroindolizines

a) Case of 1-allylpyrrole (**1a**) and 1-(α-methallyl)pyrrole (**1e**).

The hydroformylation experiments on 1-allylpyrrole (**1a**) were carried out in toluene at 20 and 100 °C, at 120 atm total pressure (CO/H_2=1:1), using a 250:1 and 500:1 substrate-rhodium ratio, respectively[34] (Scheme 13).

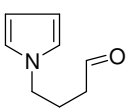
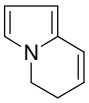
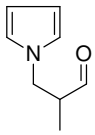


a: R=H; e: R=Me

Scheme 13

As far as the branched/linear aldehyde ratio is concerned, it ranged from 80:20 at 20 °C to 59:38 at 100 °C. These values, characterized by a prevalence of the branched aldehyde at both temperatures, were similar to the ones reported for the hydroformylation of allylbenzene with rhodium-based catalyst precursors.[72] The influence of the temperature on the regioselectivity was in agreement with the well-documented increase of the linear aldehyde content with temperature increase in the hydroformylation of other vinylsubstrates.[73,74] At 20 °C and partial substrate conversion (16%), an almost complete chemoselectivity into the expected aldehydes was observed, the 5,6-dihydroindolizine (**2′a**) being present in a very low amount (<1%). After 36 h, **2′a** was 20% of the total products, while the linear aldehyde was present in traces only (Table 3). At 100 °C the hydroformylation process was much faster, the substrate conversion reaching 90% after 0.25 h only. Also in this case, the chemoselectivity into the aldehyde isomers was very high, the (**3**+**2**)/**2**' molar ratio being 97:3. At total substrate conversion (> 99%) the linear aldehyde **2a** disappeared and **2′a** was 40% of the total products, the branched aldehyde staying unreacted during all reaction time (Table 3).

Table 3. Composition of the crude reaction mixtures resulting from the hydroformylation of 1-allylpyrrole (**1a**) with $Rh_4(CO)_{12}$ at 20 and 100 °C.[a]

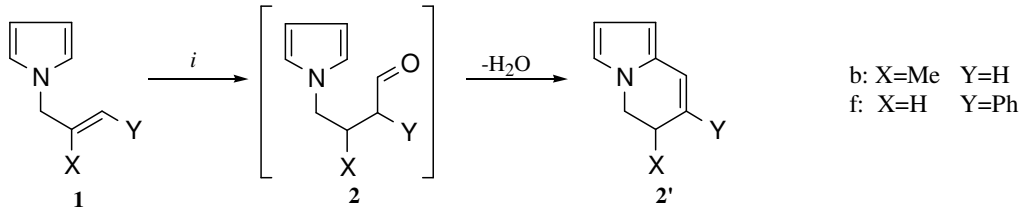
Entry	Temperature (°C)	Reaction time (h)	Conversion (%)[b]	Products (%)[b]		
				 **2a**	 **2′a**	 **3a**
1	20	4	16	20	<1	80
2	20	36	99	-	20	80
3	100	0.25	95	38	3	59
4	100	3	99	-	40	60

[a] Reaction conditions: 0.2 g 1-allylpyrrole (**1a**), 6 ml toluene, substrate/Rh = 250:1 at 20 °C, 500:1 at 100 °C; autoclave volume 25 ml; 120 atm total pressure (CO/H_2 = 1:1).[b] Determined by GLC using acetophenone as internal standard.

The hydroformylation of the vinyl substrate 1-(α-methallyl)pyrrole (**1e**), under the same experimental conditions, gives 5-methyl-5,6-dihydroindolizine (**2'e**) in addition to 2-methyl-3-(pyrrol-1-yl)butanal (**3e**), in a **2′e/3e** = 59/41 molar ratio (Scheme 13). The linear aldehyde **2e**, the precursor to **2'e**, was present only in traces in the reaction mixture both at partial and complete substrate conversion. On carrying out the hydroformylation of **1e** at a higher temperature (120 °C) and lower pressure (30 atm CO/H_2=1:1), the molar ratio **2′e/3e** conveniently increased to 78/22, according to the well documented behavior of vinyl and allyl substrates.[20,55a]

b) Case of 1-(β-methallyl)pyrrole (**1b**) and 1-(3-phenyl-2-propenyl)pyrrole (**1f**).

When we submitted 1-(β-methallyl)pyrrole (**1b**) and 1-(3-phenyl-2-propenyl)pyrrole (**1f**) under hydroformylation conditions, the 5,6-dihydroindolizines **2'b** and **2'f** substituted at C6 and C7 respectively were obtained as the exclusive products[20] (Scheme 14).



i: CO/H_2 100 atm (1:1), $Rh_4(CO)_{12}$, toluene, 100 °C

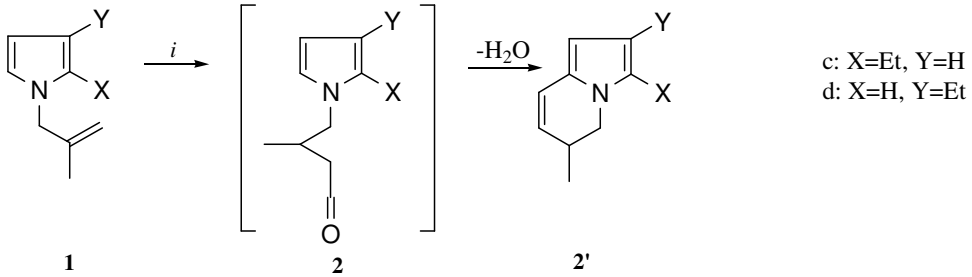
Scheme 14

By using a Rh/substrate ratio of 1:100, the olefin **1b** was totally converted into 6-methyl-5,6-dihydroindolizine (**2'b**) in a short time (0.5 h). In order to slow down the reaction, a Rh/substrate ratio of 1:1000 was employed: at 10% conversion, a small amount of aldehyde **2b** was detected in the reaction mixture, the indolizine formation still being a fast process with respect to the *ox*o one. On the other hand, attempts to carry out the reaction at lower temperatures were unsuccessful, **1b** remaining unreacted.

The hydroformylation of **1f** under the same conditions as for **1b**, gave 7-phenyl-5,6-dihydroindolizine **2'f** with almost complete selectivity (Scheme 14). In this case no traces of 2-phenyl-4-(pyrrol-1-yl)butanal (**2f**), the precursor to **2'f**, were observed even at very low conversions, the cyclization/dehydration being very fast with respect to the hydroformylation reaction. It is to note that in both cases the hydroformylation occurs with complete regioselectivity. In the presence of **1b**, the addition of the formyl group exclusively takes place to the terminal carbon atom, according to the behavior typical of disubstituted terminal olefins.[60a,75] In the case of **1f**, instead, exclusive addition of the formyl group to the carbon atom directly bonded to the phenyl group occurs, the pyrrolyl olefin **1f** showing a very similar behavior to styrene.[52]

c) Case of 1-(β-methallyl)pyrrole bearing an electrondonor group on the pyrrole ring.

In order to explore the possibility to obtain dihydroindolizines selectively functionalized on the pyrrole ring, we submitted to hydroformylation 2- and 3-ethyl-1-(β-methallyl)pyrroles **1c-d**[20] (Scheme 15).



i: $Rh_4(CO)_{12}$, CO/H_2 (1:1) 100 atm, toluene

Scheme 15

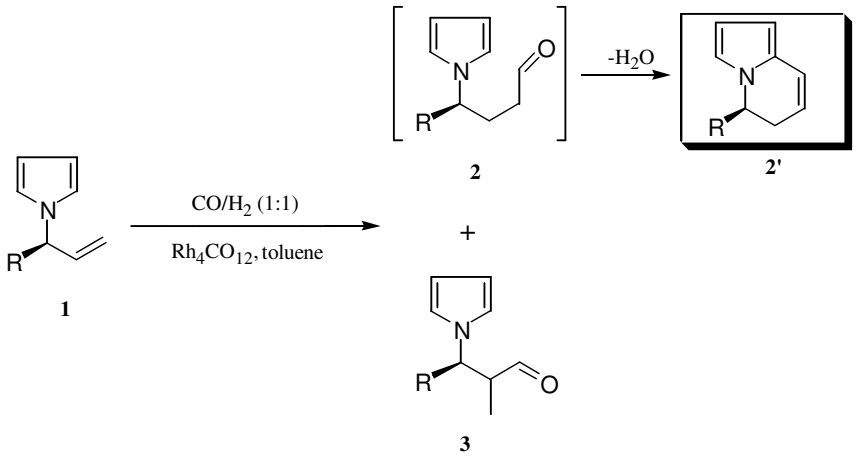
With these substrates, the 5,6-dihydroindolizines **2'c** and **2'd** were also obtained in very high chemo- and regioselectivity. The oxo of **1c** gave 3-ethyl-6-methyl-5,6-dihydroindolizine (**2'c**) as the sole reaction

product. In the case of **1d**, both the 2 and 5 positions of the pyrrole ring were involved in the cyclization process but the 2-ethyl-6-methyl-5,6-dihydroindolizine **2'd**, coming from annulation on the pyrrole C5 carbon atom, was largely prevalent (90:10) with respect to 1-ethyl-6-methyl-5,6-dihydroindolizine, derived from the annulation on the pyrrole C2 carbon atom. It is worth noting that no traces of the expected pyrrolylbutanals, precursors to the dihydroindolizines **2'c** and **2'd**, were found in the crude reaction mixtures at any degree of conversion: these aldehydes, as they form, immediately give the cyclization process.

3.4.2. Synthesis of optically active 5,6-dihydroindolizines

a) Case of (3R)-3-(pyrrol-1-yl)alk-1-enes.

We hydroformylated the highly enantiomerically enriched (3R)-3-(pyrrol-1-yl)alk-1-enes (**1n-p**), synthesized starting from α-aminoacids as previously described (see section **2.2.**).[43] The (5R)-5-alkylindolizidines **2'n-p** having the same optical purity (> 92%) as the starting olefins were obtained *via* a highly regioselective and stereospecific domino transformation[76] (Scheme 16).



n: R = Me; **o**: R = *iso*-Pr; **p**: R = *n*-Pr

Scheme 16

When **1n** was submitted under the same experimental hydroformylation conditions adopted for the corresponding racemic substrate, after 0.2 h the conversion was 25% and the reaction mixture was constituted by 5-methyl-5,6-dihydroindolizine (**2'n)** and branched aldehyde **3n** in a 57/43 molar ratio. This value resulted unchanged also at total conversion (after 1.5 h, 59/41 regioisomeric ratio)(Table 4). The linear aldehyde **2n**, the precursor of **2'n**, was present only in traces in the reaction mixture both at partial and complete substrate conversion, the cyclization reaction being faster than hydroformylation. An evaluation of the optical purity of both unconverted **1n** and produced **2'n** was carried out in order to test the configurational stability of these structures under hydroformylation conditions. Interestingly **1n** showed, at all conversions, pratically the same e.e., *i.e.* the starting e.e. value (98 %). A similar behavior occurred for the dihydroindolizine **2'n,** its e.e. value resulting the same as the corresponding olefin **1n** (98%) at all reaction times (Table 4).

According to the well documented behavior of vinyl and allyl substrates under rhodium-catalyzed hydroformylation,[20,52] a marked improvement was obtained on carrying out the hydroformylation of **1n** at 120 °C and lower pressure (30 atm; CO/H_2=1:1): the molar ratio **2'n/3n** conveniently increased to 85/15. It is

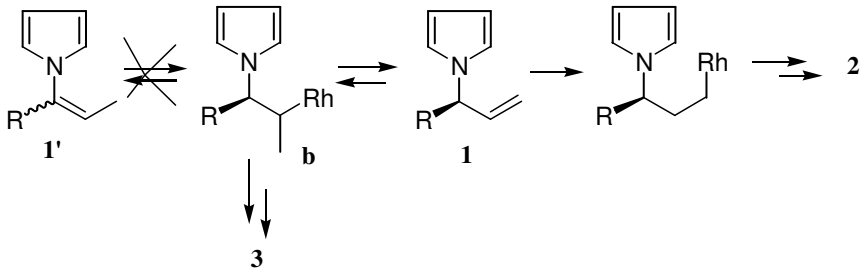
to note that these forcing conditions do not affect the optical purity of **2'n** (e.e. 98%). On this light the other olefins **1o-p** were submitted under the same hydroformylation conditions. In particular the olefin **1o** gave 5-*i*-propyl-5,6-dihydroindolizine (**2'o**) in **2'o/3o** = 87/13 regioisomeric ratio. In a similar manner 5-*n*-propyl-5,6-dihydroindolizine (**2'p**) was obtained from **1p** in a high percent (**2'p/3p** = 84/16). No traces of the linear aldehydes **2o-p**, the precursors to **2'o-p**, were observed in the reaction mixture both at partial and complete substrate conversion.

Table 4. Hydroformylation of (3R)-3-(pyrrol-1-yl)alk-1-enes **1n-p** in the presence of $Rh_4(CO)_{12}$ at 100 °C and 125 °C.

1		**T (°C)**	**P (atm)**	**Reaction time (h)**	**Conversion (%)**	**Products**		
entry	**e.e.(%)[a]**					**2'/3 (%)**	**2' yield(%)[b]**	**2' e.e(%)[a]**
n	98	100	100	0.2	25	57/43	-	98
n	98	100	100	1.5	99	59/41	55	98
n	98	125	30	0.5	97	85/15	73	98
o	92	125	30	0.5	99	87/13	70	92
p	92	125	30	0.5	99	84/16	75	92

[a] Determined by gas chromatography with the chiral capillary column CHIRALDEX G-TA (γ-Cyclodextrin trifluoroacetyl, 50 m x 0.25 mm)[b] Isolated pure product.

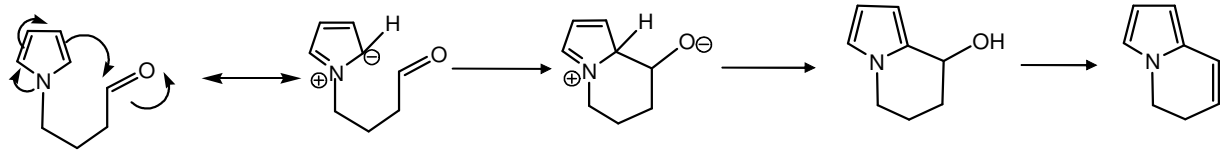
The very high e.e. values obtained for **2'** indicate that the hydroformylation conditions are perfectly compatible with the optically active pyrrolylolefins employed, allowing a complete configurational stability also under stressed isomerizing conditions (high temperature and low pressure). Taking into account the general accepted mechanism of hydroformylation,[63] we can affirm that, under the above conditions, the branched alkyl-rhodium intermediate **b** undergoes a β-hydride elimination process not involving the chiral center, which generates the olefin **1** again and not **1'** (Scheme 17).



Scheme 17

In fact no traces of the internal olefin **1'** were observed in the crude reaction mixture at both partial or total conversion. Due to the influence of the electronwithdrawing heteroaromatic effect, the methinic hydrogen bonded to the carbon vicinal to the annular nitrogen into **b** could not have hydruric character enough to give β-hydride elimination.

The above findings indicate that the rhodium-catalyzed hydroformylation of N-allylpyrroles provides a concise synthesis of substituted 5,6-dihydroindolizines from easily available starting material, *via* a one pot 4-(pyrrol-1-yl)butanal formation and intramolecular cyclization. The key step of the sequence likely consists in an intramolecular electrophilic aromatic substitution promoted by the carbon atom of the carbonyl group on the electronrich C2 (C5) carbon atom of the pyrrole ring. Then a bicyclic alcohol should form, which undergoes water elimination very easily to give a double bond conjugated with the pyrrole ring (Scheme 18).



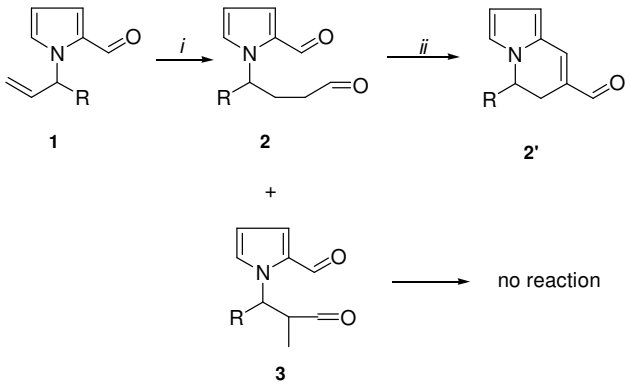
Scheme 18

All dihydroindolizines obtained are stable enough to be handled easily at room temperature without any decomposition and can be stored at 0 °C for long periods.

3.5. Construction of indolizine moiety *via* C7-C8 bond formation: synthesis of racemic 7-formyl-5,6-dihydroindolizines

a) Case of 1-allyl-2-formylpyrrole (**1g**) and 1-(α-methallyl)-2-formylpyrrole (**1h**).

1-Allyl-2-formylpyrrole (**1g**) was submitted to hydroformylation in the presence of $Rh_4(CO)_{12}$ as catalyst precursor, at 100 °C and 100 atm total pressure (CO/H_2 = 1:1), using a 100/1 substrate/rhodium ratio[19,35a] (Scheme 19).



g: R=H; **h**: R=Me

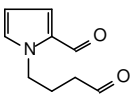
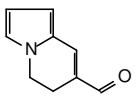
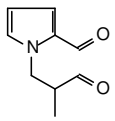
Reagents and conditions: (*i*) $Rh_4(CO)_{12}$, 100 atm $CO:H_2$ (1:1), 100 °C, toluene, 0.5-2 h. (*ii*) The same conditions as (*i*), 70 h under N_2 atmosphere, after CO and H_2 removal.

Scheme 19

The regioisomeric **3g/2g** ratio was 54/46 at partial conversion (Table 5, entry 1).This value was very similar to that observed in the case of unsubstituted 1-allylpyrrole (59/41 at the same temperature),[34] the presence of a formyl group on the aromatic ring weakly affecting the regioselectivity of the reaction. After

1 h at 100 °C (Table 5, entry 2), the conversion was complete and the *oxo*-dialdehydes 4-(2-formylpyrrol-1-yl)butanal (**2g**) and 2-methyl-3-(2-formylpyrrol-1-yl)propanal (**3g)** were the almost exclusive isomeric products (97%). A low amount of 7-formyl-5,6-dihydroindolizine (**2'g**) (<3%) was also observed. When the crude reaction mixture was allowed to stand under CO/H_2 pressure for longer reaction times, an increase of the dihydroindolizine **2'g** was observed together with the reduction of the carbonyl group of both the branched and the linear dialdehydes **3g** and **2g** to the corresponding hydroxyl group. At complete substrate conversion, the CO/H_2 gas mixture was removed and the autoclave was heated at 100 °C for additional 72 h (Table 5, entry 3c); the dialdehyde **2g** disappeared and **2'g** was 46% of the total products, the branched dialdehyde **3g** (54%) staying unreacted during all reaction time. After 0.5 h at 100 °C, the starting olefin **1h** was completely converted into the isomeric dialdehydes 4-(2-formylpyrrol-1-yl)pentanal (**2h**) and 2-methyl-3-(2-formylpyrrol-1-yl)butanal (**3h**) (**2h/3h**=68/32; **2h+3h**=98%) (Scheme 19). A very low amount of 5-methyl-7-formyl-5,6-dihydroindolizine (**2'h**) (<2%) was also found. For longer reaction times, an increase of the dihydroindolizine **2'h** was observed together with the reduction of the carbonyl group of both branched and linear dialdehydes **3h** and **2h** to the corresponding hydroxyl group (GC-MS control). In absence of gas, the dialdehyde **2h** totally evolved into **2'h** (Scheme 19), the branched dialdehyde **3h** staying unreacted during all reaction time.

Table 5. Composition of the crude reaction mixtures resulting from 1-allyl-2-formylpyrrole (**1g**)[a] in the presence of $Rh_4(CO)_{12}$, at 100 °C, with or without CO/H_2 gas pressure.

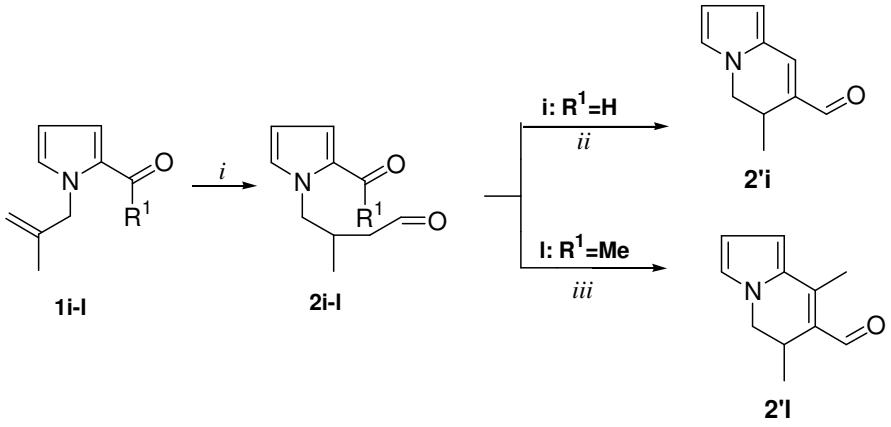
Entry	CO (atm)	H_2 (atm)	Reaction Time (h)	Conversion (%)[b]	Products		
					 **2g** (%)[b]	 **2′g** (%)[b]	 **3g** (%)[b]
1	50	50	0.5	58	46	-	54
2	50	50	1.0	100	43	<3	54
3	a) -	-	1.2	100	39	<7	54
	b) -	-	24	100	37	9	54
	c)		72	100	-	46	54

[a]Reaction conditions: 0.5 g of 1-allyl-2-formylpyrrole (**1g**), 10 ml toluene, 7 mg $Rh_4(CO)_{12}$ (substrate/Rh=100/1); autoclave volume 25 ml. [b]Determined by GLC using acetophenone as internal standard.

b) Case of 1-(β-methallyl)-2-formylpyrrole (**1i**) and 1-(β-methallyl)-2-acetylpyrrole (**1l**).[35a]

The vinylidenic olefin 2-formyl-1-(2-methylprop-2-enyl)pyrrole (**1i**) was selectively converted into 7-formyl-6-methyl-5,6-dihydroindolizine (**2'i**) (Scheme 20) *via* formation of the sole aldehyde 3-methyl-4-(2-formylpyrrol-1-yl)butanal (**2i)**. 2-Acetyl-1-(2-methylprop-2-enyl)pyrrole (**2l**) was submitted to the same

hydroformylation conditions adopted for 2-formylderivatives **1g-h**; the aldehyde 3-methyl-4-(2-acetylpyrrol-1-yl)butanal (**2l**) was obtained as the exclusive product (Scheme 20.). This compound does not cyclize under the above conditions even for long heating time. However by treating the crude oxo-mixture with EtONa/EtOH for few minutes, the corresponding 7-formyl-6,8-dimetyl-5,6-dihydroindolizine (**2'l**) was selectively obtained (Scheme 20). Under these last experimental conditions the dihydroindolizines **2'h** and **2'i** were also obtained from **2h** and **2i** respectively.



Reagents and conditions: (*i*) $Rh_4(CO)_{12}$, 100 atm CO:H_2 (1:1), 100 °C, toluene, 0.5-2 h. (*ii*) The same conditions as (*i*), 70 h under N_2 atmosphere, after CO and H_2 removal. (*iii*) The same conditions as (*i*), EtONa/EtOH, 5 min., after CO and H_2 removal.

Scheme 20

The above findings suggest that the indolizine structure **2'** comes from **2** (Figure 5) likely *via* an intramolecular aldol addition between the carbon atom adjacent to the formyl group in the alkyl chain and the carbonyl group directly bonded to the pyrrole ring.

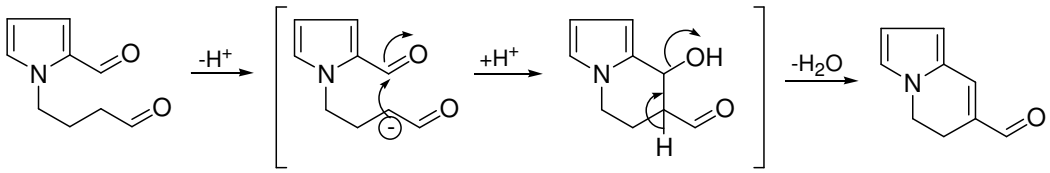
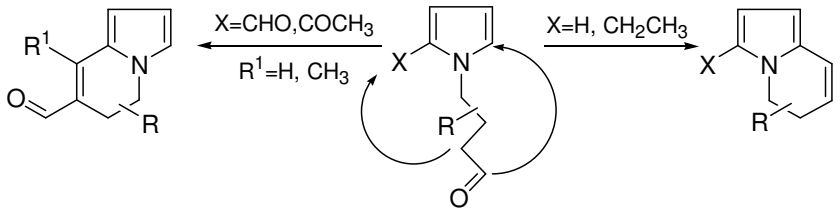


Figure 5

A bicyclic hydroxyaldehyde should form, which very easily undergoes water elimination to give a double bond conjugated with both the pyrrole and the formyl group.

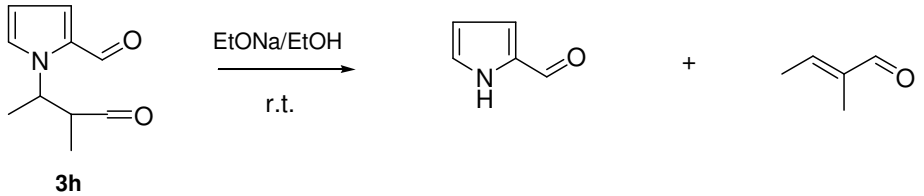
Aldol condensations of oxo aldehydes under hydroformylation conditions have been often observed.[73,74,77] Recently several efforts have been reported in the literature to combine hydroformylation with a consecutive aldol reaction in a one pot sequence.[70a,71a,78,79] As far as we know, the process here described constitutes the first example of sequential hydroformylation/aldol condensation sequence devoted to the synthesis of the indolizine moiety. Whereas in the first three cases a rhodium carbonyl species likely plays a catalytic role in the annulation, although at a very low rate, in the last example the butanal **2l** is not sufficiently active to overcome the electrondonor effect of the methyl group bonded to the carbonyl in

position two of the pyrrole ring. It is to note that, unlike what observed by us for 1-allylpyrroles characterized by an unsubstituted pyrrole ring or an alkyl substituted one, the annulation of **2g-l** on C5 pyrrole carbon atom does not occur, the above described aldol condensation being the exclusive process. In fact no traces of 3-formyl or 3-acetyl-5,6-dihydroindolizines, isomers of **2′g-l**, were detected. Because of the presence of an electron-withdrawing group on the pyrrole C2 carbon atom, the C5 carbon atom is not nucleophilic enough to bear the electrophilic attack of the carbonyl moiety (Scheme 21).



Scheme 21

It is to note that under aldol condensation conditions the branched aldehydes **3h** is not stable, giving rise to the corresponding 2-formylpyrrole and the unsaturated aldehydes 2-methylbut-2-enal respectively *via* a N-dealkylation promoted by the basic conditions adopted (Scheme 22).



Scheme 22

The formyl indolizines obtained are stable enough to be handled easily at room temperature without any decomposition and can be stored at 0 °C for long periods.

3.6. Construction of indolizine moiety *via* C8-C9 bond formation: synthesis of racemic 8-hydroxytetrahydroindolizines

a) Case of N-allylpyrrole bearing an acetyl group on position 3.

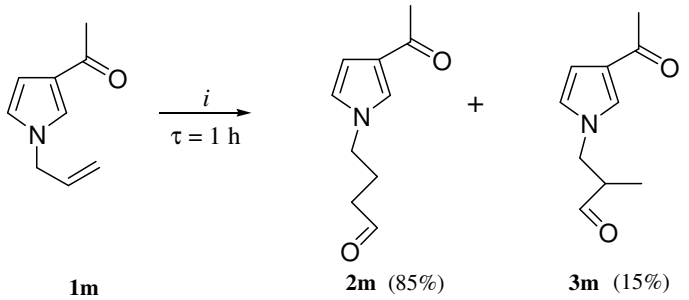
The hydroformylation experiments on 1-allyl-3-acetylpyrrole (**1m**) were carried out at 30 atm total pressure (CO/H_2=1:1) and 140 °C, using a 200 : 1 substrate : Rh ratio.

After one hour the starting olefin **1m** was completely converted into the corresponding aldehydes, the linear isomer **2m** being strongly favoured with respect to the branched one **3m** (regioisomeric **2**:**3** molar ratio 85:15)[35b] (Scheme 23).

This value was very similar to that observed for other 1-allylpyrroles:[34] under these conditions (high temperature, low pressure), no trace of the isomeric olefin 1-(3-acetylpyrrol-1-yl)propene was found in the crude reaction mixture, at any conversion percentage.

For long reaction times (τ = 48 hours) (Table 6, entry 3), the linear aldehyde was completely transformed into two products, *i.e.* 2-acetyl-5,6,7,8-tetrahydroindolizine **4′m** and 1-acetyl-5,6,7,8-

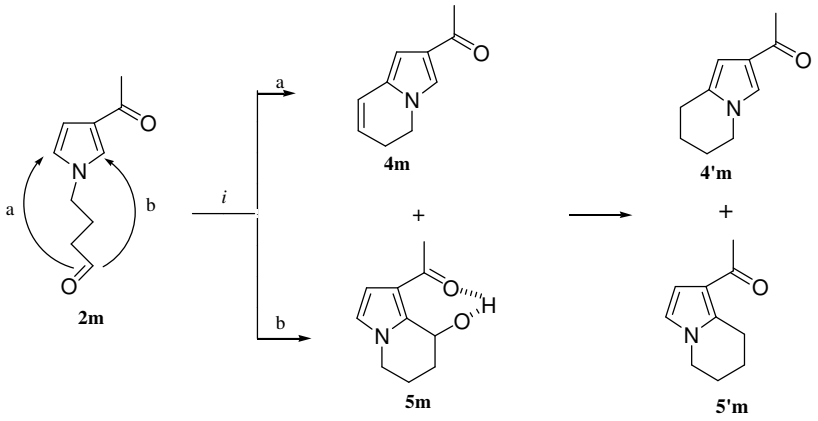
tetrahydroindolizine **5′m** in a 1:1 molar ratio. In contrast, the branched aldehyde **3m**, which was present in a very small amount, did not give cyclization products but only reduction to the corresponding alcohol.



Reagents and conditions: *i* = $Rh_4(CO)_{12}$, CO/H_2 1:1, 30 atm, 140 °C, toluene

Scheme 23

According to the previous report,[34] the formation of **4′m** is explainable by an electrophilic attack of the carbonyl group of **2m** on the C5 pyrrole carbon atom (route **a**, Scheme 24) *via* the conjugated dihydroindolizine **4m**, which was identified in the crude reaction mixture at intermediate times (Table 6, entry 1).

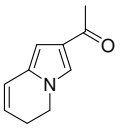
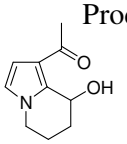
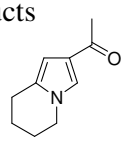
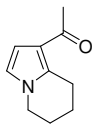


Reagents and conditions: *i* = $Rh_4(CO)_{12}$, CO/H_2 1:1, 30 atm, 140 °C, toluene

Scheme 24

An analogous attack on the pyrrole carbon atom C2 (route **b**, Scheme 24) instead of C5 occurs for the formation of **5′m**: in this case the bicyclic alcohol **5** was found as a transient species (Table 6, entry 1 and 2). Note that **5m** does not undergo water elimination but it is converted into the tetrahydroindolizine **5′m** *via* a direct reduction of the hydroxyl group (Table 6, entry 3). Indeed the corresponding dihydroindolizine has never been found in the crude reaction mixture. It is to be pointed out that the reduction of **4m** to **4′m** is faster than the transformation of tetrahydroindolizine **5m** into the corresponding compound **5′m**. However, it is possible to stop the reaction at the stage of formation of **4m** and **5m** by removing the CO/H_2 gas mixture after the complete conversion of **1m** to **2m** and by pressuring the reactor with CO only. In this way after 48 hours the aldehyde **2m** was quantitatively converted into an equimolar mixture of **4m** and **5m** (Table 6, entry 5), while the reduction products **4′m** and **5′m** could not be detected; **4m** and **5m** were easily separated by column chromatography and characterized.

Table 6. Distribution of the cyclization products resulting from 4-(3-acetylpyrrol-1-yl)butanal (**2m**)[a] in the presence of $Rh_4(CO)_{12}$, at 140 °C, with CO/H_2 or CO only gas pressure.

Entry	CO (atm)	H_2 (atm)	Reaction Time (h)	Conv. (%)[b]	Products			
					 **4m** (%)[b]	 **5m** (%)[b]	 **4'm** (%)[b]	 **5'm** (%)[b]
1	15	15	11	58	16	15	5	6
2	15	15	24	100	-	30	45	25
3	15	15	48	100	-	-	45	55
4	30	-	23	50	25	25	-	-
5	30	-	48	100	50	50	-	-

[a]Reaction conditions: 10 ml toluene, 7 mg $Rh_4(CO)_{12}$, autoclave volume 25 ml. [b]Determined by GLC using acetophenone as internal standard.

5 is likely to be stabilized by an intramolecular hydrogen bond between the hydroxylic hydrogen and the carbonyl oxygen atom with consequent formation of a tricyclic structure. This factor could be the driving force for the formation of **5m** in an amount (1:1 molar ratio with respect **4m**) that would not be expected on the basis of otherwise unfavourable steric and electronic effects. In accord with this structural hypothesis, the IR spectrum showed a band due to OH stretching at an unexpectedly low frequency (3037 cm^{-1}). This value was independent of concentration (10^{-2}, 10^{-3}, 10^{-4} M solution in CCl_4) as expected for an intramolecular, rather than intermolecular, hydrogen bond.

In conclusion, the hydroformylation of 3-acetyl-1-allylpyrrole constitutes an interesting extension of the reactivity of 1-allylpyrroles substituted with electron-withdrawing groups. Unlike the analogous 2-acetyl-1-allylpyrrole,[35a] which undergoes no electrophilic substitution but only aldol condensation (Scheme 21), the presence of the acetyl group on the β pyrrole position makes the α pyrrole positions still available for the electrophilic attack of the carbonyl moiety. Interestingly, the cyclization is much slower than the hydroformylation, thus allowing either the aldehydes or the corresponding cyclization products to be recovered as required. Starting from the latter derivatives, tetrahydroindolizines can be obtained at long reaction times under a CO/H_2 gas mixture, dihydroindolizine or 8-hydroxy-tetrahydroindolizine being the exclusive products under CO pressure only. The hydroxylated indolizidines have attracted special interest by virtue of their useful biological actions as potential antiviral, antitumor, and immunomodulating agents.[80] Moreover, tetrahydroindolizines bearing both an acetyl group at C1 and a hydroxyl group at C8 are intermediates for the preparation of antithrombotic derivatives or are antithrombotic compounds themselves, and they also show anti-TNF activity.[6b] Because of the interest in the hydroxylated indolizines, the rhodium-catalyzed hydroformylation of appropriate 3-carbonylsubstituted-1-allylpyrroles could be a convenient protocol for the synthesis of this class of compounds.

4. Conclusions

A new general and versatile access to 5,6-dihydroindolizines based on the rhodium-catalyzed hydroformylation of N-allylpyrroles has been described. The construction of the indolizine moiety occurs *via* C7-C8 or C8-C9 bond generation in dependence on an intramolecular

i) electrophilic substitution at the α pyrrole position followed by water elimination
ii) aldol addition followed by water elimination

The different processes can be selected by moduling the nature and the position of the functional substituents on the pyrrole ring.

Both processes are one-pot domino-type transformations in which the hydroformylation is the crucial step. The adopted experimental conditions are perfectly compatible with many functional groups and assure a complete configurational stability also under stressed isomerizing conditions (high temperature and pressure). Accordingly, 5,6-dihydroindolizines having the same e.e. as the starting olefins have been obtained, indicating that the oxo process applied to the N-allylpyrroles is a stereospecific synthetic instrument. With respect to the few earlier routes reported in the literature (see Cap. **1.1.**), the approach here described employs inexpensive both starting material (it is α-amino acids) and reagents (CO and H_2), does not generate byproducts and provides pure products after a simple purification process. Domino reaction sequences are of great interest because they enable the atom-economic formation of C-C bonds, thus providing relatively easy access to complex molecular architectures. On this light, the oxo process as a step promoting new domino sequences confirms to be a very powerful instrument for the fine chemistry.

Acknowledgments

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SYNTHESIS OF SULFUR HETEROCYCLES FROM AROMATIC THIOKETONES. PART I: THREE- AND FOUR-MEMBERED RINGS

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Abstract. *The methods applied for the preparation of aromatic thioketones are summarized. Their conversions to give three-membered heterocycles with one (thiiranes) and two sulfur atoms (dithiiranes) are reviewed as well as thermal and photochemical reactions leading to four-membered thiaheterocycles (thietanes, thietes, and dithietes).*

Contents

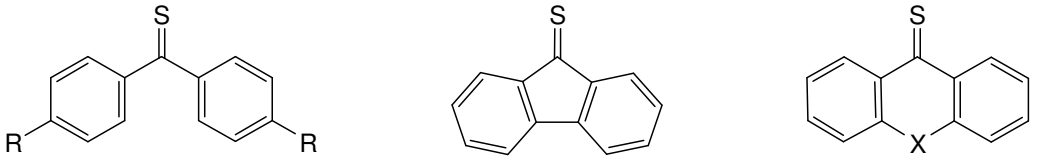
1. Introduction

The first reports on aromatic thioketones originate from the end of the 19th century.[1] In spite of this fact, this class of compounds was much less explored for synthetic purposes in comparison with analogous carbonyl compounds. The main reason was their notorious instability and the difficulty in their handling. One of the frequently emphasized properties of thioketones is their unpleasant odor and that of products of their decomposition. In contrast to aliphatic thioketones, bis-aromatic thioketones cannot enolize and, therefore, are preferred as starting materials in organic synthesis. The chemistry of thioketones has been summarized periodically,[2-10] but none of these reviews focused on the application of aromatic thioketones in the preparation of sulfur heterocycles.

New horizons for the application of thioketones were opened by the works of *Huisgen* and *Sauer* who established this class of compounds as 'superdipolarophiles' and 'superdienophiles', respectively.[11,12] Although cycloaddition reactions offer a general and convenient method for the preparation of sulfur heterocycles, other approaches based on nucleophilic as well as electrophilic additions onto the C=S group are also known. The present article is aimed at describing the applications of thioketones, containing at least one aromatic residue, towards the synthesis of sulfur heterocycles containing three- and four-membered rings.

Thiobenzophenone (diphenylmethane thione, **1a**) and its 4,4'-disubstituted derivatives **1b-g**, bearing methyl, methoxy, dimethylamino, chloro, fluoro and nitro groups, are the most well-known and frequently used representatives. The presence of electron-donating groups such as MeO and Me_2N results in enhanced

stability of these derivatives. Along with thiobenzophenones **1**, 9*H*-fluorene-9-thione (**2**), 9*H*-xanthene-9-thione (**3a**), and 9*H*-thiaxanthene-9-thione (**3b**) are often used as examples of aromatic thioketones (Figure 1).



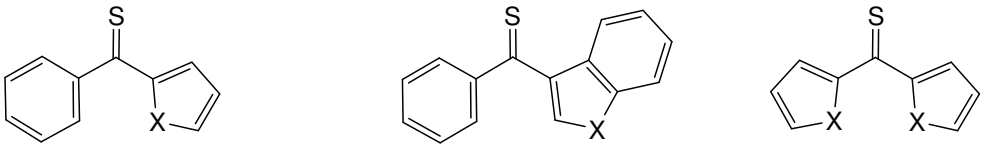
1a R = H
b R = Me
c R = MeO
d R = Me_2N
e R = Cl
f R = F
g R = NO_2

2

3a X = O
b X = S

Figure 1

Another group of diaryl thioketones is depicted by formulae **4** and **5**, where one of the aromatic residues is a furane, a thiophene, a 1-methylpyrrole ring or a benzoanalogue. Diheteroaryl thioketones of type **6** are also known. The replacement of one aromatic ring by an aliphatic residue may lead to either non-enolizable or enolizable thioketones (Figure 2).



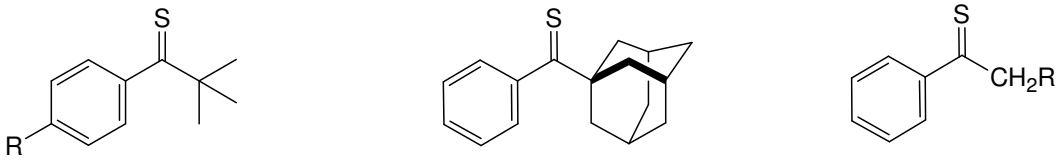
4a X = O
b X = S
c X = MeN

5a X = S
b X = MeN

6a X = O
b X = S

Figure 2

Whereas non-enolizable representatives of type **7** and **8** are relatively stable and, therefore, have been used for the preparation of sulfur heterocycles, enolizable thioketones like **9** have found little application in organic synthesis due to their instability (Figure 3).



7a R = H
b R = Me
c R = MeO
d R = PhO

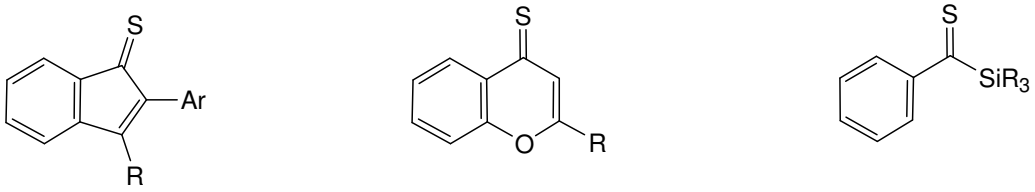
8

9

Figure 3

Thioketones derived from indan-1-one and chromen-4-ones of type **10** and **11**, respectively, were also used as starting materials in heterocyclic synthesis. As a special class of monoaryl thioketones,

(phenyl)(silyl)thioketones **12**, which are related to the sterically crowded thioketones **7**, will also be included in this review (Figure 4).



10a R = Cl
b R = R_2N
c R = RO

11a R = Me
b R = Ph
c R = PhCH=CH

12a R = Me
b R = Ph

Figure 4

2. Preparation of aromatic thioketones

Historically, thiobenzophenone (**1a**) was the first aromatic thioketone prepared by the replacement of the O-atom of benzophenone (diphenylmethanone) using P_4S_{10} in benzene in a sealed tube at 130 ºC.[1a] The analogous conversion can be achieved by using other thionation reagents. In recent years, the most frequently applied procedures involve along with P_4S_{10},[13] sometimes in the presence of additives,[14] a mixture of H_2S and HCl in ethanolic solution[15] and *Lawesson's* reagent in boiling toluene or xylene.[16,17] These procedures are also suitable for the preparation of the thiobenzophenone derivatives **1b-e**[6] and **1f**.[18] The 4-nitro derivative **1g** has been prepared using P_4S_{10}.[19] Several other known procedures have been presented in previous reviews.[6-10,20] A very promising procedure is the rapid and solvent-free thionation with *Lawesson's* reagent under microwave irradiation.[21] The easily available and relatively stable thiobenzophenones **1** are most frequently used in reactions leading to sulfur heterocycles.

The first synthesis of 9*H*-fluorene-9-thione ('thiofluorenone', **2**) was reported in 1946. It was achieved by treatment of the parent carbonyl compound with a mixture of H_2S and HCl in ethanol.[22,23] In a modified procedure, the addition of an equimolar amount of trimethyl orthoformate is recommended.[17a] Heating of 9*H*-fluoren-9-one with *Lawesson's* reagent in benzene/toluene to 80 °C followed by immediate workup gave **2** in high yield.[24] An improved procedure uses microwave irradiation.[21] Alternatively, thionation with bis(trimethylsilyl)sulfide in acetonitrile solution containing trimethylsilyl triflate at room temperature can be applied.[25]

For the preparation of thioketones **3a** and **3b** ('xanthione' and 'thioxanthione') thionation with *Lawesson's* reagent is recommended as an efficient procedure.[17f,21,24] The same method is applicable for the synthesis of the heteroaromatic analogues of thiobenzophenone **4**-**6**,[26] but thionation with P_4S_{10} is also known (*e.g.* **4a**, **4c** and **6b**[27]).

The stable (aryl)(*tert*-butyl)thioketones of type **7** have been prepared by heating of the corresponding thioketones with P_4S_{10}.[28,29] In contrast, the structurally related adamantyl analogue **8** was obtained from the reaction of (1-adamantyl)(phenyl)ketone hydrazone with S_2Cl_2 in dichloromethane at -78 °C in 49% yield.[30]

Enolizable thioketones of type **9**, when prepared by treatment of the corresponding ketones with a mixture of H_2S and HCl, easily undergo trimerization to give 1,3,5-trithianes.[2] Thermolysis of the trimers allows the isolation of the thioketone (*e.g.* thioacetophenone **9**, R = H) in pure form.[31] Recently, thionation

of enolizable ketones with P_4S_{10} in carbon disulfide,[32a] or with *Lawesson's* reagent in boiling toluene[32b] has been reported as a method for the preparation of thioketones **9** (R = Me, $PhCH_2$).

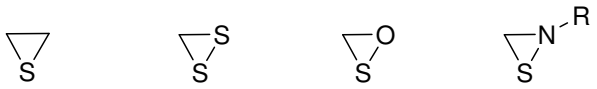
The thionation with a mixture of H_2S and HCl gas in acetonitrile at -40 to -50 ºC was also applied to convert 3-chloroinden-1-ones into the corresponding thioketones of type **10a**. The 3-amino and 3-alkoxy derivatives **10** have been obtained by nucleophilic substitution of chloride by primary or secondary amines or sodium methanolate.[33,34]

Thioketones of type **11** with the chromen-4-one skeleton have been prepared by treatment of the parent ketones with P_4S_{10}[35] or with *Lawesson's* reagent.[36] The solvent-free method using *Lawesson's* reagent leads to these products in high yields.[21]

The silylated thioketones **12** are available by O/S exchange in the silyl ketones using a H_2S/HCl mixture[37]or by treatment with hexamethyldisilathiane in acetonitrile in the presence of $CoCl_2 \cdot H_2O$.[38]

3. Synthesis of three-membered rings

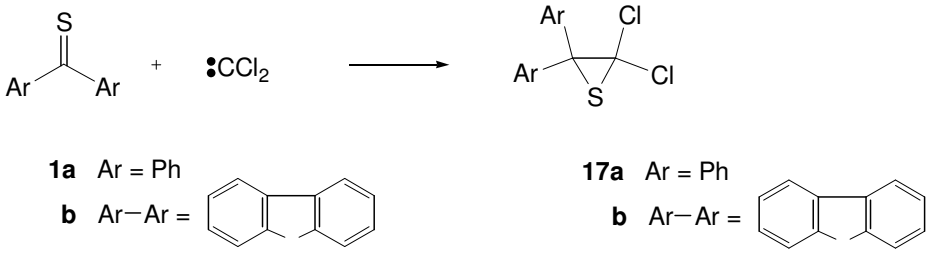
Different reactions with aromatic thioketones leading to three-membered sulfur heterocycles are known.[39] Whereas thiiranes **13** can be obtained as stable products, the derivatives with two heteroatoms in the ring, *i.e.* dithiiranes **14**, oxathiiranes **15** and thiaziridines **16** have been reported as reactive intermediates (Figure 5).



13 **14** **15** **16**

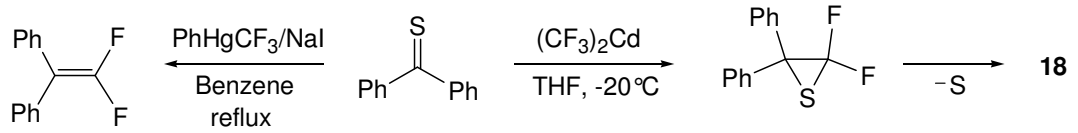
Figure 5

The addition of carbenes to the C,S double bond is the most direct access to thiiranes. Aromatic thioketones such as thiobenzophenone (**1a**) and thiofluorenone (**2**) react smoothly with dichlorocarbene generated in a two-phase system under phase-transfer-catalysis (PTC) yielding 2,2-dichlorothiiranes **17**[17a] as relatively stable compounds (Scheme 1).



Scheme 1

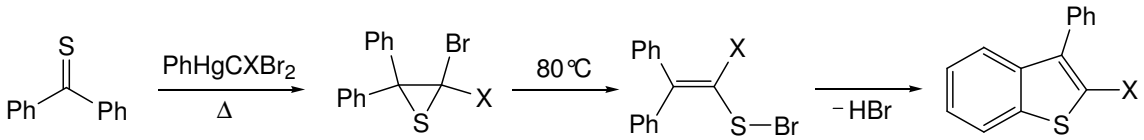
On the other hand, the reactions of **1a** and **1c** with difluorocarbene, generated *in situ* by thermal decomposition of phenyl trifluoromethyl mercury, led to *gem*-difluorinated ethylenes of type **18** as the products of the spontaneous desulfurization of intermediate 2,2-difluorothiiranes.[40] Immediate desulfurization of the thiirane **19a** to yield **18**[41] also occurred, when treating **1a** with difluorocarbene generated from bis(trifluoromethyl)cadmium at -20 ºC (Scheme 2).



18 **1a** **19a**

Scheme 2

The reaction of dibromo- or bromochlorocarbene, generated from the corresponding mercury precursors (*Seyferth's* reagents), with **1a** in boiling benzene afforded benzothiophenes **21** (Scheme 3). Thiiranes **19b** (X = Br or Cl) are believed to be formed as intermediate products, which undergo further conversion *via* ring opening, probably to give vinylsulfanyl bromides **20**, and subsequent ring closure accompanied by HBr elimination.[42]

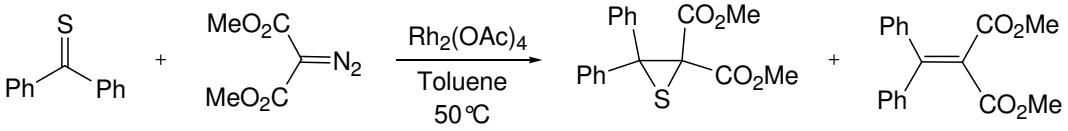


1a **19b** **20** **21**

Scheme 3

Photochemical, thermal and metal-catalyzed decompositions of diazo compounds are most frequently used for the generation of carbenes and carbenoids.[43] A classical example of the use of this method is the photochemical reaction of diethyl diazomalonate in the presence of **1a**, which yielded diethyl benzhydrylidene malonate in 60% yield.[44] The intermediate thiirane could not be detected but eliminated spontaneously sulfur. The rhodium-catalyzed reaction of dimethyl diazomalonate (**22**) with **1a** in toluene at 50 ºC gave the expected thiirane **23** in 46% yield along with the desulfurized product **24**[45] (Scheme 4).

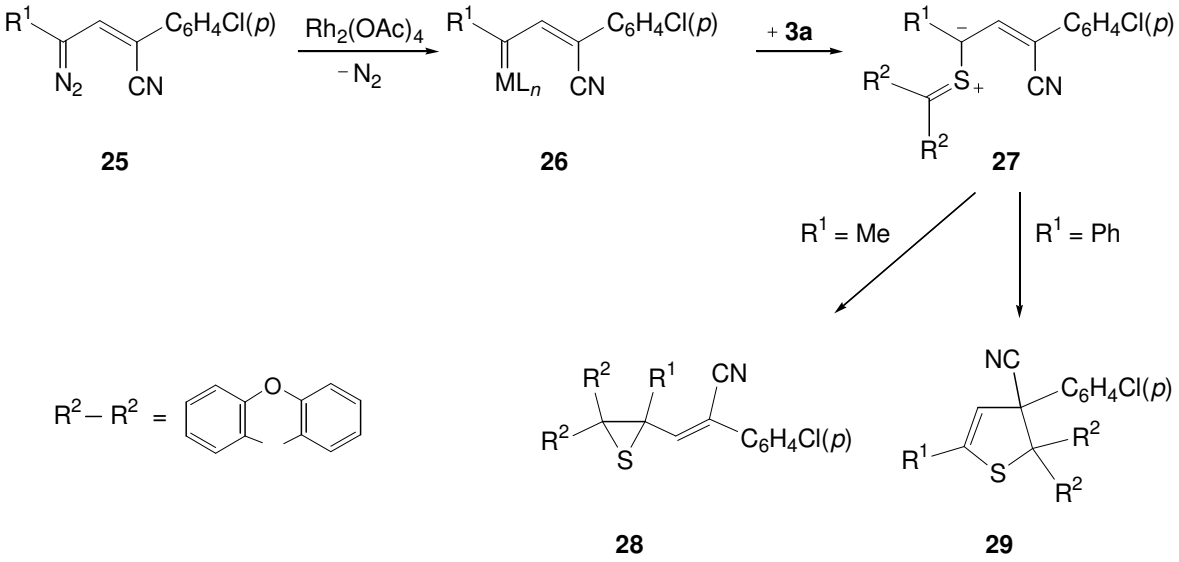
A similar result was obtained when xanthione (**3a**) was used instead of **1a**, although a five-membered 1,3-dithiolane-2,2,4,4-tetracarboxylate was also found in the reaction mixture.[45]



1a **22** **23** **24**

Scheme 4

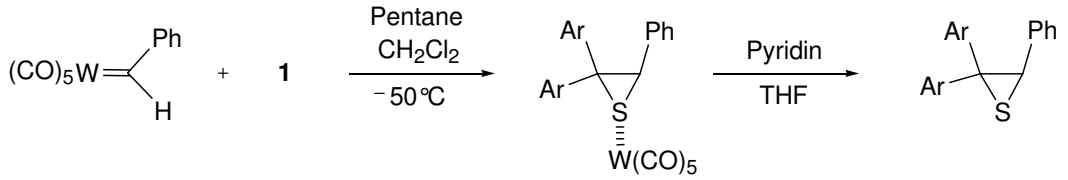
The rhodium-catalyzed decomposition of α,β-unsaturated diazo compounds **25** afforded carbenoids **26**, which add in a thiophilic manner to the C,S-double bond of aromatic thioketones, *e.g.* **3a**, to give a thiocarbonyl ylide **27**. Depending on the substituent R^1, a 1,3-dipolar electrocyclization to give thiirane **28** or the alternative 1,5-dipolar electrocyclization to yield 2,3-dihydrothiophenone **29** took place.[46] In the case of R^1 = Me, the thiirane **28** was obtained in 74% yield, whereas with R^1 = Ph the yield of **29** was 66% (Scheme 5). When R^1 = H, the corresponding conjugated diene was formed by spontaneous desulfurization of thiirane **28** (R^1 = H).



Scheme 5

The benzylidene complex **30** transfers phenyl carbene onto the C=S bond of thiobenzophenones **1** yielding thiirane complexes **31**, which upon treatment with pyridin in THF release triaryl thiiranes **32**[47] (Scheme 6).

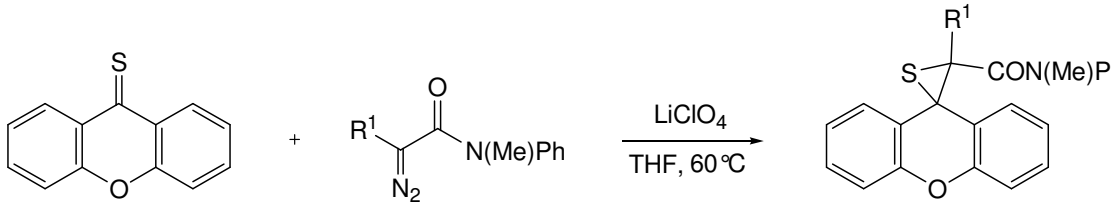
The mechanistic explanation of the conversion of aromatic thioketones with carbenes and carbenoids into thiiranes is based on the assumption that reactive thiocarbonyl ylides (*e.g.* **27**) are the initially formed intermediates, which then undergo the electrocyclic 1,3-ring closure. Similar intermediates are believed to be involved when 2,5-dihydro-1,3,4-thiadiazoles, formed preferentially by [2+3] cycloaddition of diazo compounds with thiocarbonyl compounds, extrude nitrogen.[48]



Scheme 6

In some cases, reactions of aromatic thioketones with less reactive diazo compounds, *e.g.* α-diazoketones or α-diazoamides, require catalysis or must be performed at elevated temperature. For example, thioxanthione (**3a**) reacted with diazoamides **33** in the presence of $LiClO_4$ at 60 ºC yielding thiiranes **34** as sole products[49] (Scheme 7).

The analogous reaction with thiofluorenone (**2**) occurred already at room temperature in the absence of a catalyst.[49] The same pair of thioketones was used for the reactions with α-diazo-1,2-diphenylethanone ('azibenzil'), which showed enhanced reactivity compared with **33**. Also in this case, the reaction with **2** occurred already at room temperature to give exclusively the corresponding thiirane.[50] On the other hand, the reaction with **3a** in THF required heating to 60 ºC, and a mixture of thiirane and corresponding alkene resulting from its desulfurization was obtained.[51]

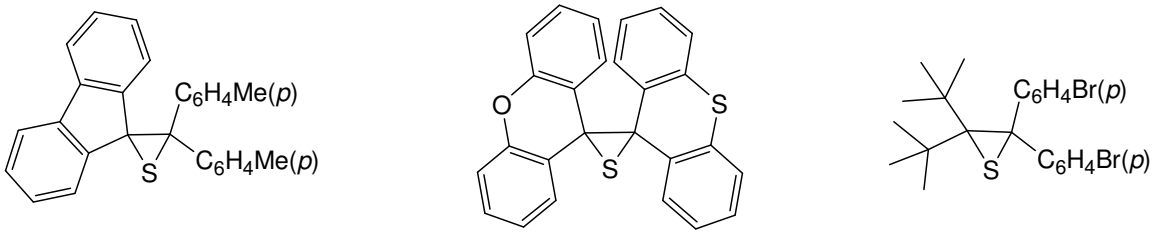


3a **33** (R^1 = Ph, *t*-Bu) **34** (R^1 = Ph, *t*-Bu)

Scheme 7

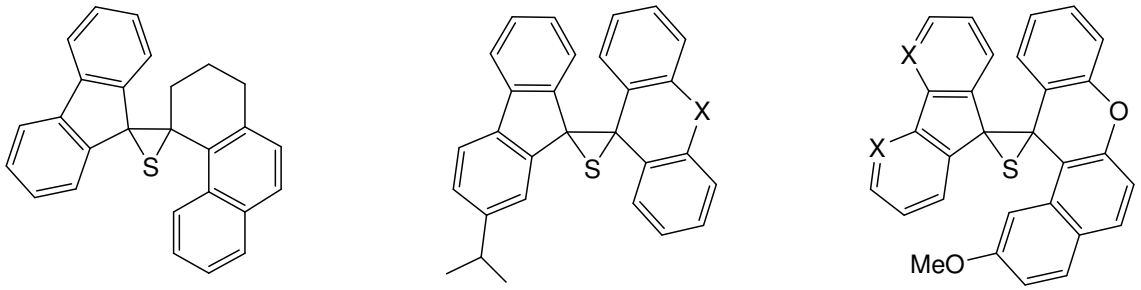
These results demonstrate that the reactivity of aromatic thioketones differs significantly. A kinetic study carried out with diphenyldiazomethane and different dipolarophiles showed that thioketones are superior dipolarophiles ('superdipolarophiles') in comparison with activated alkenes and acetylenes.[52] In all reactions with thioketones, the corresponding 2,2-diphenylthiiranes are the exlusive products. It's worth mentioning that thiofluorenone (**2**) and thiobenzophenone (**1a**), followed by thioxanthone (**3a**) are the most reactive substrates.

Numerous reports show that the reaction of aromatic thioketones with disubstituted diazomethanes offers a convenient access to tetrasubstituted thiiranes (*e.g.* **35-37**[53-58]), which by subsequent desulfurization yield sterically congested tetrasubstituted ethenes. This reaction sequence has been exploited as a straightforward and general method for the preparation of materials with special properties, a proper selection of the reactants opening access to dispiro-thiiranes containing fused polycyclic or heterocyclic residues (*e.g.* **36**[54], **38-40**[59-61]) (Figures 6 and 7).



35[53] **36**[54] **37**[55]

Figure 6

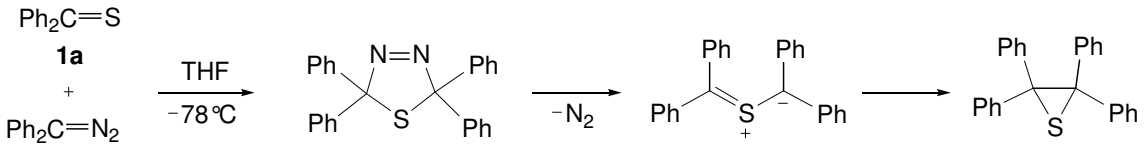


38[59] **39** (X = Se, Te)[60] **40** (X = CH, N)[61]

Figure 7

Recently, this type of conversion has been used for the preparation of a series of helicene-like molecules, which are considered as potential 'chirochromatic optical switches'[62] or show the properties of 'light-driven molecular motors'.[63]

The mechanistic explanation of thiirane formation is based on the assumption that a [2+3] cycloaddition of thioketone and diazo compound leads to the corresponding tetrasubstituted 2,5-dihydro-1,3,4-thiadiazole derivative of type **41**, which spontaneously eliminates nitrogen to give thiocarbonyl ylides of type **42**, stabilized by aromatic substituents (Scheme 8). The formation of **41** could be proved in the reaction of thiobenzophenone with diphenyl diazomethane.[58] The colorless crystals obtained at -78 ºC decomposed with vigorous elimination of nitrogen already at ca. -50 ºC yielding tetraphenylthiirane (**43**) in quantitative yield.

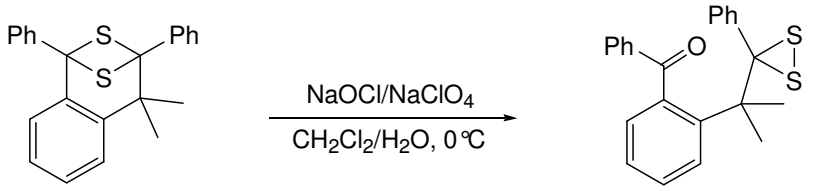


Scheme 8

The formation of tetraarylthiiranes was also observed when diarylthioketones were treated with an equimolar amount of magnesium and iodine in a boiling mixture of benzene and ether.[64] In this case, radical processes are proposed to explain the reaction. Similarly, aromatic thioketones (two equivalents) upon treatment with phenyl magnesium bromide (one equivalent) in ether under reflux are converted into tetraaryl-substituted thiiranes.[65] It is worth mentioning that the *Grignard* reagent induces the conversion but is not incorporated in the structure of the final product. The possibility that this type of reactions may occur *via* single electron transfer (SET) processes has been discussed recently.[66]

Tetraphenylthiirane (**43**) was obtained as the main product when **1a** was reacted with trifluoromethyl trimethyl silane (*Ruppert's* reagent) in the presence of tetrabutylammonium fluoride under rigorously anhydrous conditions.[67] However, treatment of **1a** with 'naked' fluoride leads to dibenzhydryl disulfide exclusively.

Recently, a Japanese group described an efficient route to isolable dithiiranes **45** *via* oxidation of sterically crowded 1,3-dithianes **44**[68,69] (Scheme 9), obtained by thionation of the corresponding diketones using *Lawesson's* reagent (see Chapter 4).



Scheme 9

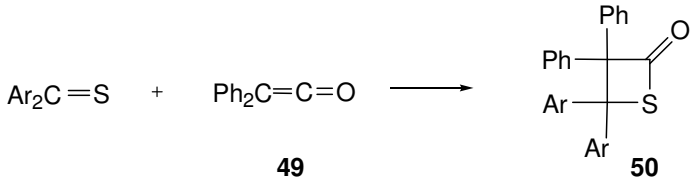
4. Synthesis of four-membered rings

Aromatic tioketones found application in the synthesis of four-membered heterocycles such as thietanes **46**, thietes **47**, and 1,3-dithietanes **48** (Figure 8). In all cases, the formation of the heterocycle occurs *via* a formal [2+2] cycloaddition with the C=S group. This process can be performed thermally or photochemically depending on the structure of the reaction partner.

46 **47** **48**

Figure 8

In the case of heterocumulenes, *i.e.* ketenes and ketenimines, the reaction occurs thermally under mild conditions. For example, thiobenzophenone (**1a**) and 4,4′-dimethoxythiobenzophenone (**1c**) react with diphenylketene (**49**) to give thietan-2-ones **50** in a regioselective manner[70] (Scheme 10). The same reactions with **1a** had been studied previously by *Staudinger*[71] as well as by *Rioult* and *Vialle*,[72] but in both papers the wrong structure of a thietan-3-one was proposed for the cycloadduct.

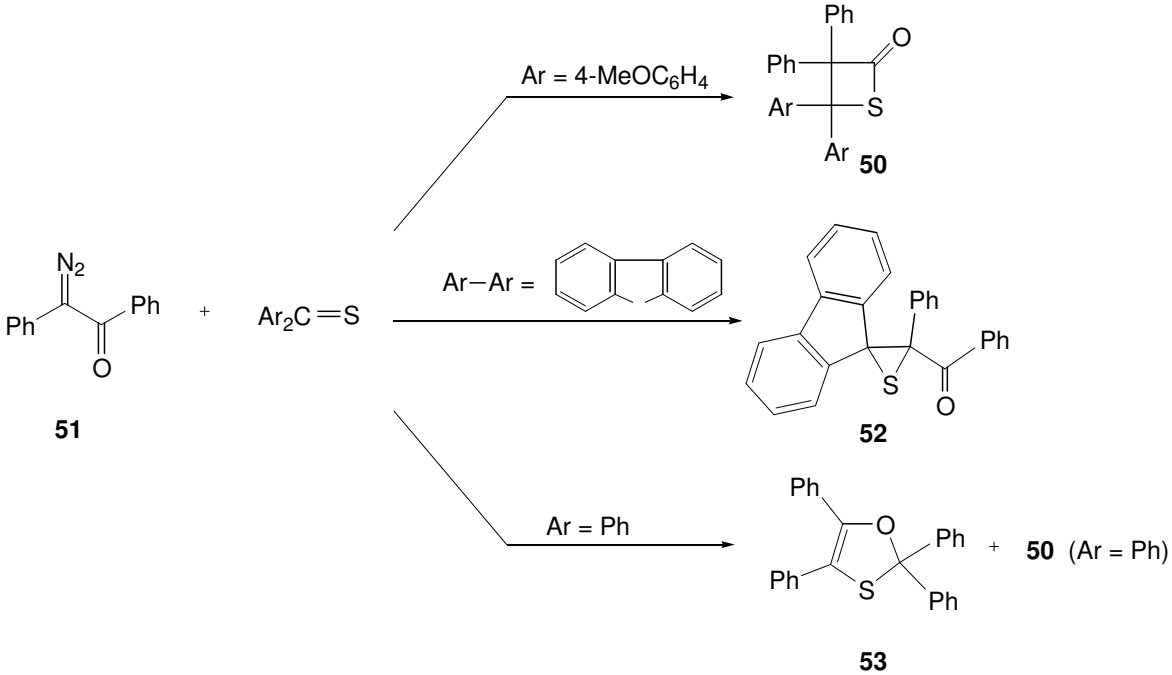


49 **50**

Scheme 10

In the case of the 4,4′-(dimethylamino)thiobenzophenone (**1d**), the corresponding tetraarylethene was obtained as the only product.[71] Its formation was explained by the extrusion of COS from the initially formed thietan-2-one.

An analogous reaction of **1a** with methyl vinyl ketene was reported to give the corresponding 3-methyl-4,4-diphenyl-3-vinylthietan-2-one in 90% yield.[73]



51 **50** **52** **53**

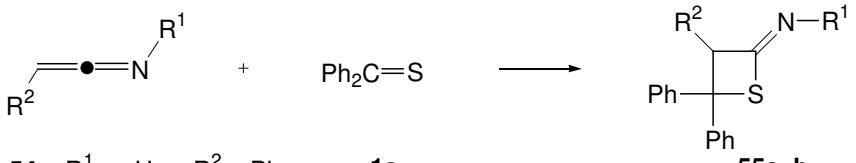
Scheme 11

The formation of **50** (Ar = 4-$MeOC_6H_4$) was also observed in the reaction of 'azibenzil' (2-diazo-1,2-diphenylethanone, **51**) with **1c** in boiling benzene.[74] Under the reaction conditions, diphenylketene is formed

in situ via Wolff-rearrangement of the α-ketocarbene generated from the diazo compound. Under the same conditions, the more reactive thiofluorenone (**2**) reacted with the diazoketone to give the thiirane **52** (Scheme 11; see also Scheme 7). Thiobenzophenone (**1a**) and **51** gave thietanone **50** (Ar = Ph) as a minor product along with the 1,3-oxathiole **53** as the main product.

The reaction of thiobenzophenone (**1a**) with differently substituted ketenimines leading to thietan-2-imines are also known. Using *N*-cyclohexyl-*C*-phenylketenimine (**54a**), the conversion was complete after 17 h at 45 ºC in CCl_4 to give **55** in 85% yield[75] (Scheme 12).

Similarly, *N*-tolyl-*C*-vinylketenimine (**54b**) and **1a** yielded **55b** as the major product, which, without isolation, was converted into 3,3-diphenyl-2-vinylacrylthioamide by heating to 50 ºC in CCl_4.[76] In addition to **55b**, a 1,3-benzothiazine derivative was formed *via* a competitive hetero-*Diels-Alder* reaction followed by aromatization. In general, the presence of two substituents at C(2) of the ketenimine drives the reaction with **1a** completely towards formation of the [2+4] cycloadducts.

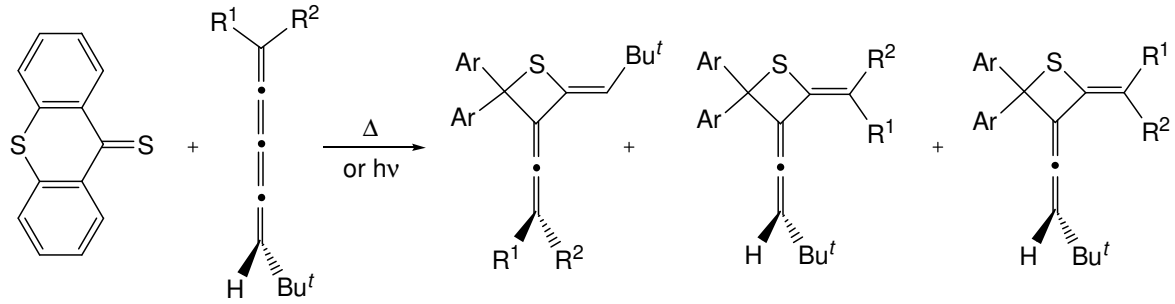


54a R^1 = cHex, R^2 = Ph **1a** **55a**, **b**
b R^1 = 4-MeC_6H_4, R^2 = CH_2=CH

Scheme 12

Furthermore, it has been shown that thiobenzophenone (**1a**) and 9*H*-xanthene-9-thione (**3a**) undergo thermal [2+2] cycloadditions with differently substituted allenes of type H_2C=C=CHX (X = aryl, RO, RS, Me_2N) to give mixtures of two isomeric 2-methylidenethietanes together with one of two isomers of 3-methylidene-2-benzothiopyrans[77] (Scheme 15).

In the case of more extended cumulenes, *i.e.* the pentatetraenes **56**, the thermal as well as the photochemical reaction with 9*H*-thioxanthene-9-thione (**3b**) afforded mixtures of three isomeric thietanes **57** presented in Scheme 13. All additions occur chemoselectively at the central C,C-double bonds with different ratio for the thermal and photochemical process.[78] The total yield of isolated products **57** is higher then 60%.

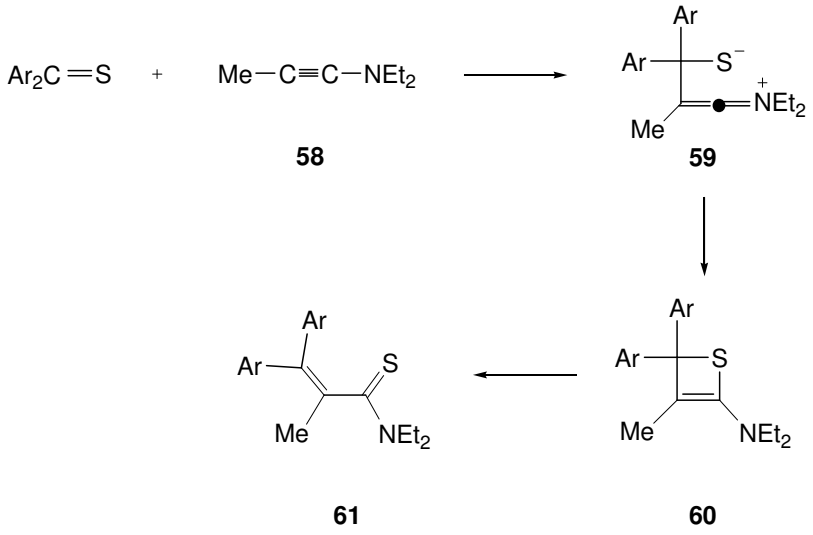


3b **56** **57a** **57b** **57c**

Scheme 13

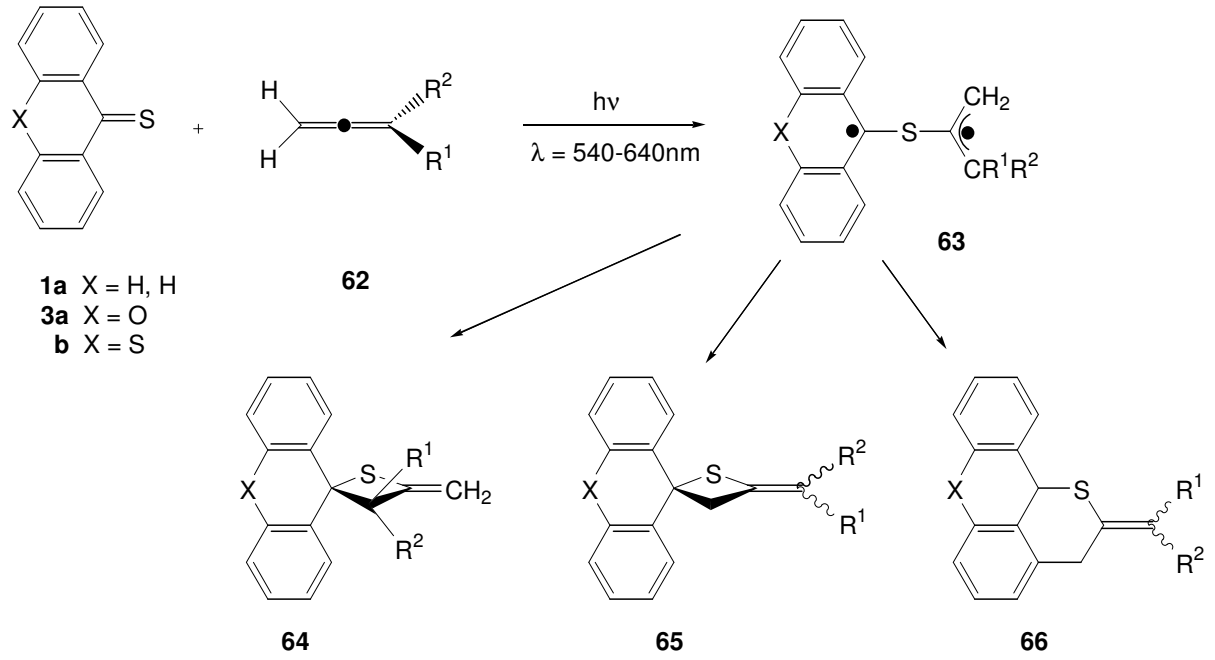
The electron-rich alkyne 1-(diethylamino)propyne (**58**) adds to thiobenzophenone (**1a**) and 9*H*-xanthene-9-thione (**3a**) at room temperature to yield acrylthioamides **61**, which are formed by electrocyclic

ring opening of the thietes **60**, the initial [2+2] cycloadducts[79] (Scheme 14). The first intermediate postulated for this reaction is the zwitterion **59** formed by the carbophilic addition of **58** onto the thiocarbonyl group.



Scheme 14

Numerous papers report on the photochemical [2+2] cycloaddition of aromatic thioketones with cumulenes and electron-poor as well as electron-rich alkenes. In addition to the thermal reactions with diphenylketene (**49**) presented in Scheme 10, the photochemical cycloaddition with 9*H*-xanthene-9-thione (**3a**) at -60 ºC in CH_2Cl_2 leads regioselectively to the corresponding spirocyclic thietan-2-one **50** in quantitative yield.[80]

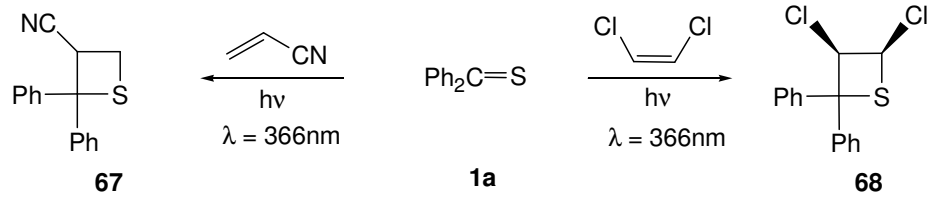


Scheme 15

In addition to thermal reactions of aromatic thioketones with allenes **62**, these systems were also studied under photochemical conditions.[81] In order to avoid the formation of undesired side products, the irradiations were carried out at low temperature (*e.g.* -80 ºC in CH_2Cl_2). In analogy to the thermal reactions,

two isomeric thietanes **64** and **65** are the main products (Scheme 15). Depending on the nature of the aromatic thioketone and allene used, occasionally, the formation of 2-benzothiopyran **66** was observed. The comparable results of the photochemical and thermal reactions prompted the authors to postulate the same diradical intermediate **63** for both types of reactions.

The photochemically mediated formation of thietanes by [2+2] cycloaddition of aromatic thioketones and alkenes has been studied extensively. Some reviews summarize the results, which have been published until 1984.[82-84] Numerous examples of regioselective photocycloadditions with electron-deficient alkenes are known. A typical example with **1a** and acrylonitrile carried out in cyclohexane is shown in Scheme 16.

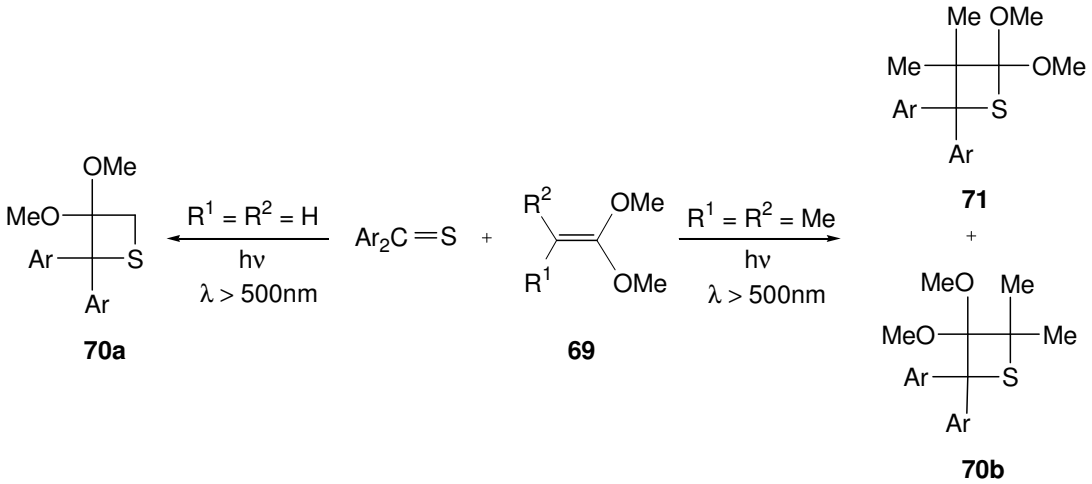


67 **1a** **68**

Scheme 16

In order to avoid the dimerization of **1a**, the alkene was used in excess. The formation of thietanes occurs also stereoselectively as evidenced by the reaction with (*Z*)- and (*E*)-1,2-dichloroethane, respectively.[82] When **1a** was irradiated in excess crotononitrile (*E*) and isocrotononitrile (*Z*), respectively, 2:1-mixtures of the regioisomeric 3-cyano- and 2-cyanothietanes were obtained with high conservation of the stereochemical properties of the respective alkene.

Analogous photocycloadditions of aromatic thioketones with electron-rich alkenes such as vinylethers,[85,86] ketene acetals,[87] and alkyl substituted alkenes[82,85] are well known. In general, they were carried out in diluted benzene solutions under irradiation with visible light (λ = 589 nm). A competitive reaction at higher concentration is the formation of 1,4-dithianes. Whereas in the case of vinylethers and diarylthioketones the regioselective formation of 3-alkoxy-2,2-diarylthietanes was observed, the regioselectivity in the reactions with ketene acetals **69** depends on the substitution pattern.[87] Thus, the reaction with less substituted **69** ($R^1 = R^2 = H$) gave the regioisomer **70a** exclusively (Scheme 17).



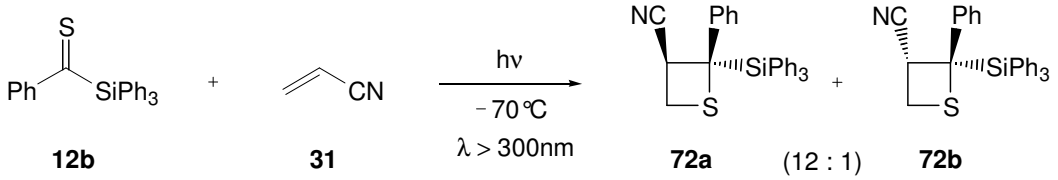
70a **69** **71** **70b**

Scheme 17

On the other hand, the disubstituted ketene acetal **69** ($R^1 = R^2 = Me$) afforded a 1:1-mixture of **70b** and **71** in the case of 4,4′-dimethoxythiobenzophenone (**1c**), but only the product of type **71** was formed with 9*H*-xanthene-9-thione (**3a**). With phenylketene acetal **69** ($R^1 = Ph$, $R^2 = H$), thiethanes of type **71** were obtained by using **1c** as well as **3a**.

Conjugated dienes are also able to undergo photochemical [2+2] cycloaddition with aromatic thioketones.[83,86,88] In many of these systems, the formation of 3-vinylthietanes competes with the conversion leading to the six-membered isomers, *i.e.* dihydrothiopyrans. The exclusive formation of the [2+2] cycloadduct is reported for the irradiation (λ = 366 nm) of **1a** and 1,3-cyclooctadiene.

In a more recent report, [2+2] photocycloadditions of the silyl thioketone **12b**, a synthetic equivalent of thiobenzaldehyde, with electron-deficient and electron-rich alkenes are described.[89] In analogy to **1a**, the reactions of **12b** in acrylonitrile and methyl acrylate, respectively, at -70 ºC furnished the expected thietanes as *cis*/*trans* mixtures (Scheme 18).

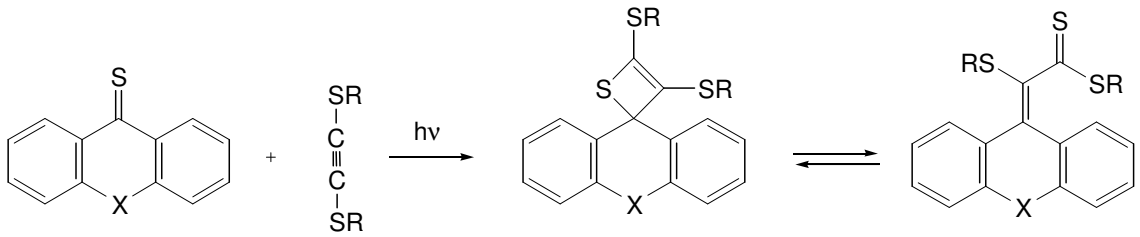


12b **31** **72a** **72b**

Scheme 18

The reaction of **12b** with (*E*)-and (*Z*)-1,2-dichloroethene yielded *trans*- and *cis*-3,4-dichloro-2-phenyl-2-(triphenylsilyl)thietane, respectively, in a highly stereoselective manner. In contrast to the reaction presented in Scheme 17, vinyl ethers combine with **12b** to yield four stereoisomeric thietanes in rather poor yield. It is worth mentioning that the silylated thietane **72a** on treatment with fluoride in DMSO/water or THF/water solutions led to a *cis*/*trans* mixture of 3-cyano-2-phenylthietane.[89]

The attempts to prepare thietes by the analogous photochemical [2+2] cycloaddition of aromatic thioketones with 1,2-bis(alkylsulfanyl)acetylenes led to acyclic products, which were identified as α,β-unsaturated-α-alkylsulfanyl dithioesters of type **74**[79] (Scheme 19). In the case of the products obtained in the reactions of **3a** and **3b** with acetylenes bearing bulky substituents (RS = Bu^{t}S), an equilibrium of the thiete **73** and **74** was observed.[90] The irradiation of **3a** and diphenylacetylene was reported to give an adduct in 91% yield, the structure of which was elucidated as 3,4-diphenylthiete of type **73**.[91]



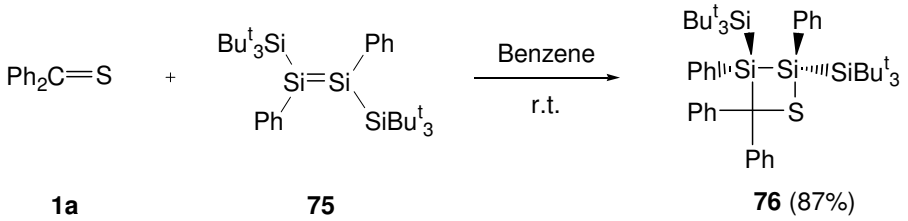
3a X = O
b X = S

73 **74**

Scheme 19

In many of these reactions, benzothiopyrans are formed as minor products, and in the case of monosubtituted acetylenes, they are formed exclusively.[92]

A very special case of a thermal [2+2] cycloaddition of thiobenzophenone (**1a**) with the sterically congested disilene **75** was recently reported. The structure of the 1,2,3-thiadisiletane **76** was established by X-ray crystallography[93] (Scheme 20).

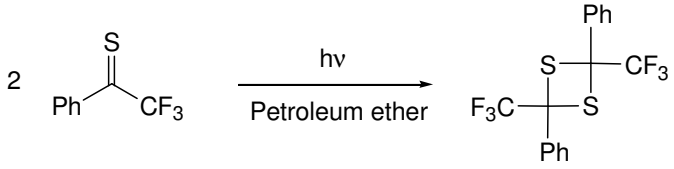


1a **75** **76** (87%)

Scheme 20

Dimerizations of thiofluorenone (**2**) and thiobenzophenone (**1a**) leading to 1,3-dithietanes were reported.[94] However, in both cases the proposed structures were shown to be wrong. In the case of **2**, the dimer is the product of a hetero-*Diels-Alder* reaction followed by aromatization,[24] and the postulated dimer of **1a** was shown to be dibenzhydryldisulfane.[67]

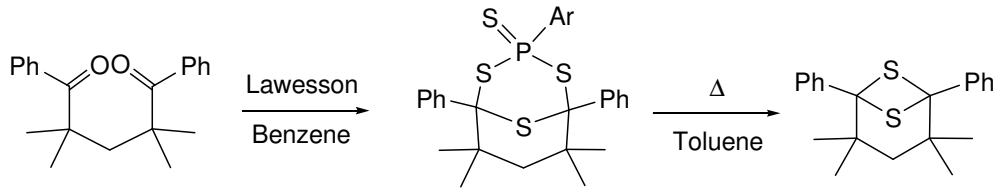
Only recently, some inter- and intramolecular processes which open an access to 1,3-dithietanes *via* formal [2+2] cycloadditions were reported. A spontaneous dimerization of 1,2-diphenyl-2-thioxoethanones at room temperature results in 2,4-dibenzoyl-2,4-diphenyl-1,3-dithietane.[95] The photochemical dimerization of trifluorothioacetophenone (**77**) yields the head-to-tail dimer **78**[96] (Scheme 21).



77 **78**

Scheme 21

Thionation of some 1,5-diketones of type **79** with B_2S_3 in toluene or with *Lawesson's* reagent in benzene leads to bicyclic 1,3-dithietanes **80** *via* a formal intramolecular [2+2] cycloaddition of the intermediate thioketones[69,97] (Scheme 22).



79 **81** **80**

Scheme 22

In the case of **79** and *Lawesson's* reagent, the phosphaheterocycle **81** was obtained as the initially formed product, which upon heating in toluene was converted into **80** quantitatively.

5. Conclusions

Numerous reports show that relatively easily available aromatic thioketones are very valuable building blocks for the preparation of thiiranes *via* [2+3] cycloaddition with alkyl- and aryl-substituted diazomethanes

and subsequent elimination of nitrogen or *via* reaction with carbenes. Combined with the desulfurization to yield ethene derivatives, this is an attractive and preparatively useful method for C,C-double bond formation similar to the '*Eschenmoser* sulfide contraction'. Aromatic thioketones undergo easily thermal [2+2] cycloadditions with cumulenes and can be combined photochemically with both electron-rich and electron-deficient ethenes to form four-membered thiaheterocycles.

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BIOTRANSFORMATIONS IN THE SYNTHESIS OF 2-PYRROLIDINONES AND 2-PYRROLINONES

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Dedicated to the memory of the long time friend Prof. Marino Novi

Abstract. *Biotransformations in the synthesis of enantiomerically enriched γ-lactams are described. In particular, the biological chemical methods for the obtainment of aza paraconic acids, i.e. 5-oxo-3-pyrrolidinecarboxylic acids, and the hydroxy substituted 2-pyrrolidinones and 2-pyrrolinones are examined. Examples of chemoenzymatic synthesis of bioactive γ-lactams and their derivatives are also described.*

Contents

1. Introduction

The γ-lactam ring (2-pyrrolidinone) characterizes the structure of many natural and synthetic compounds, possessing wide-ranging biological and pharmacological activities.[1]

A few examples of important bioactive γ-lactams are given in Figure 1. Lactacystine **1** is a microbial product, isolated from a *Streptomyces* strain. It is easily converted into the β-lactone Omuralide **2**. Both compounds were found to deactivate irreversibly the 20S proteasome, a large polymolecular protein complex, responsible for the degradation of ubiquitin-labeled proteins.[1c] The many synthetic approaches to these compounds,[2] having four contiguous stereocentres, have been reviewed by E. J. Corey.[1c]

Further examples are represented by pilolactam **3**,[3] recently patented by Garst and coworkers,[4] which is important as a drug of muscarinic activity and (*R*)-(–)-Rolipram **4**, a potent and selective PDE4 inhibitor and an HIV-1 replication inhibitor *in vitro*, synthesized by several research groups[5] and currently produced by

Schering AG.

(±)-Nebracetam **5** (X = NH_2), (±)-WEB-1868 **6** (X = OH), and *R*-(+)-Fasoracetam (NS-105) **7** belong to the class of cognitive enhancers.[6]

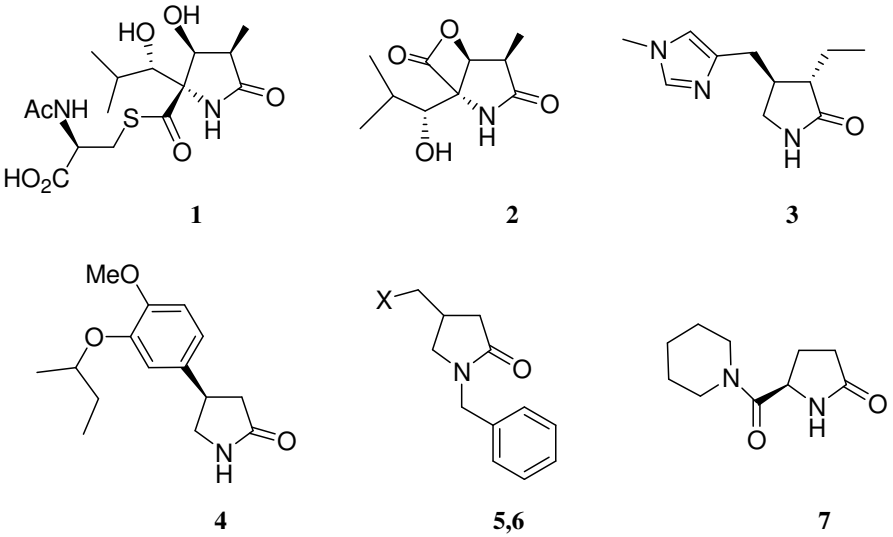


Figure 1

γ-Lactams have also been proved to be effective intermediates in the synthesis of pyrrolidines[7] and γ-aminobutyric acid (GABA) analogs.[8]

The demand for chiral, non racemic compounds from the pharmaceutical, agrochemical and food industry is continuously increasing not only because of the higher specificity exhibited by a pure enantiomer in its activity, but also because of the health and environmental risks often associated with the use of racemic mixtures, in which the inactive enantiomer may present dangerous side effects.[9]

The development of asymmetric synthetic methodologies is therefore a challenge for many a research group and it is strongly encouraged by the industry.

Among the possible strategies aimed at the production of enantiomerically pure compounds, biotransformations have become a conventional methodology used in academic and industrial research laboratories as an alternative to pure chemical methods, due to their chemo-, regio-, and enantioselectivity.[10] The mild conditions, under which they operate, and their safe and easy decomposition in the environment after their use, make the biotransformations an environmentally friendly and a highly successful stategy for the synthesis of enantiomerically pure chiral compounds. The biocatalysts used in these processes can be intact microorganisms, plant and animal cells, or purified enzymes isolated from them and have found widespread use in industry.[11]

The efforts in this field have increased in the last decades, in which new techniques, such as immobilization,[10,12] genetic manipulation[13] and combinatorial approaches[14] have been developed.

The preparation of chiral synthons is the field of organic synthesis where enzymes have shown the greatest potentiality, commonly by kinetic resolution of racemic mixtures, but also by enantioselective transformation of prochiral and meso compounds. The most usually encountered biotransformations are hydrolysis, esterification and transesterification reactions, and reductions of carbonyl compounds.[10,15,16]

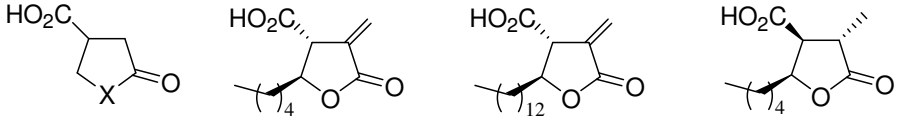
Aim of the present work is to offer a survey on the more recent examples of optically pure, polyfunctionalized γ-lactams, whose syntheses have been achieved by chemoenzymatic methods. In the

majority of the cases described, a chiral racemic γ-lactam bearing a carboxylic or alcoholic function is chemically synthesized and used as a substrate for a kinetic resolution, followed in some cases by further chemical transformations. In other examples, when the γ-lactam does not possess a functional group which can be accepted and transformed by an enzyme, the asymmetric synthesis of the targeted 2-pyrrolidinone is achieved through a key intermediate, obtained in an optically pure form by a biotransformative step.

2. 4-Carboxy-2-pyrrolidinones

Among the variety of substances containing the lactam ring mojety, β-carboxy-γ-lactam **8** (Figure 2) has received recent attention as it is the aza analog of paraconic acid **9**.[1b] This latter compound is the parent member of a small class of natural, biologically active, trisubstituted β-carboxy-γ-lactones,[17] differing in the substituent at the α carbon atom, which is usually either a methyl or a methylene group, while the γ carbon atom bears a linear alkyl chain, functionalysed in some cases.

Examples are (–)-methylenolactocin **10**,[18] an antitumor and antibiotic agent, protolichesterinic acid **11**,[19] an antitumor, antibacterial and growth regulating compound, and (–)-phaseolinic acid **12**,[20] a metabolite of a fungus, *Macrophomina phaseolina*.



X = NH: **8**
X = O: **9**

10 **11** **12**

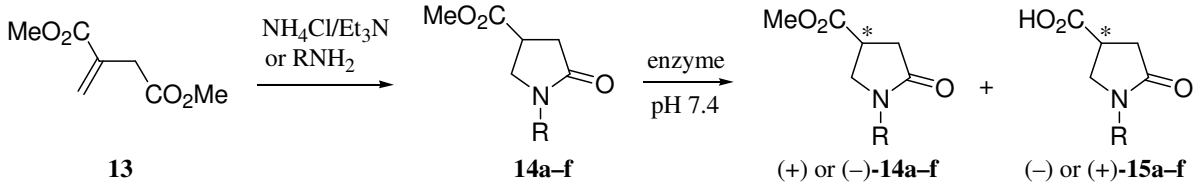
Figure 2

The γ-lactams, structurally related to this class of γ-lactones, are compounds of interest due their potential biological activities associated with a lower toxicity of the lactam ring, when compared to that of the lactone ring.[21]

The first chemoenzymatic synthesis of some β-carboxy-γ-lactam derivatives, based on enzymatic hydrolysis of the methoxycarbonyl group of the corresponding racemic methyl esters, was published in 2001.[1b]

The substrates chosen were methyl 5-oxo-3-pyrrolidinecarboxylate **14a** and a series of its derivatives **14b**–**f**, having the nitrogen substituted with different alkyl groups. These compounds were synthesized in high yields by Michael addition of the appropriate primary amine (NH_4Cl/Et_3N in the case of **14a**) to itaconic acid dimethyl ester **13** (Scheme 1).

Commercial hydrolases such as Pig Liver Acetone Powder (PLAP), Porcine Pancreatic Lipase (PPL), and α-Chymotrypsine (α-Ct) were checked, but the enzyme of election for the resolution of the γ-lactams was found to be α-Ct. In fact, this enzyme was found active in the majority of the cases examined (**14c**,**e**,**f**), showing a different degree of enantioselectivity depending on the substituent at the nitrogen atom. The enantiopreference of the enzyme was always for the *S*-enantiomer of **14c**,**e**,**f**. As a consequence, the hydrolyses gave the corresponding (*S*)-carboxylic acids **15c**,**e**,**f**. The only exception was **14a** which was transformed into racemic **15a**. The other enzymes also proved efficient with **14a**,**b**,**d**, however with low enantioselectivities.



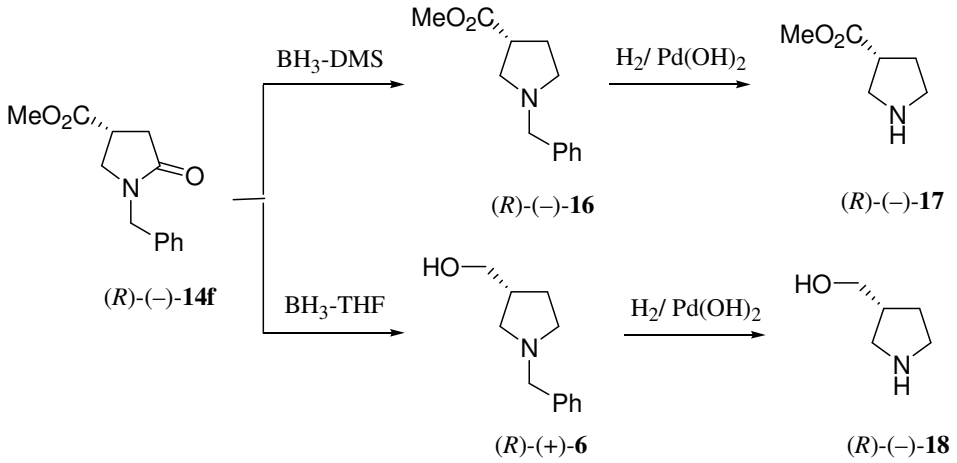
13 **14a–f** (+) or (–)-**14a–f** (–) or (+)-**15a–f**

a: R = H; **b**: R = Et; **c**: R = *i*-Pr; **d**: R = *n*-Bu; **e**: R = $(CH_2)_2OH$; **f**: R = Bn

Scheme 1

It is worthwhile underlining the excellent result obtained in the hydrolysis of 1-benzyl pyrrolidinone **14f** with α-Ct.[1b] According to the very high enantiomeric ratio[22] exhibited by the enzyme (E>200), the unreacted ester (*R*)-(–)-**14f** was isolated with >99% e.e. and good yield at 54% conversion, while the acid (*S*)-(+)-**15f** was obtained with >99% e.e. and 28% yield at 29% conversion.

Interestingly, the optically pure (*R*)-(–)-**14f** and (*S*)-(+)-**14f**, this latter derived from the carboxylic acid by esterification with diazomethane, could be easily transformed into the enantiomers of methyl β-proline **17**[1b,23] (Scheme 2). This latter compound is a non proteinogenic imino acid, having high affinity towards the GABA receptor and the strichnine sensitive glycine receptor. The transformation occurred by reduction of the carbonyl group with BH_3-DMS, followed by hydrogenolytic debenzylation of the resulting *N*-protected pyrrolidine **16**. By using BH_3-THF, the reduction proceeded also on the carboxylic function to give the corresponding γ-aminoalcohol **6**, a cognitive activator,[6] from which the optically active pyrrolidine **18** could be obtained by hydrogenolysis.



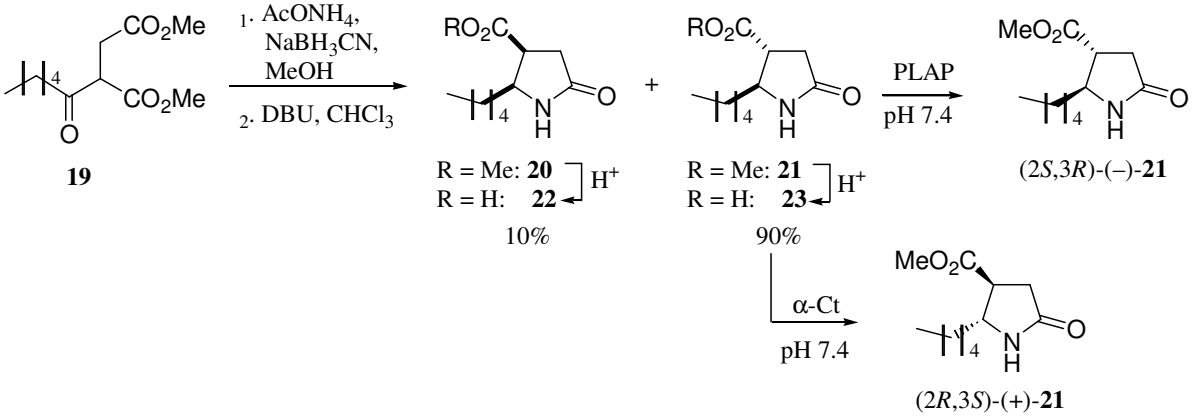
(*R*)-(–)-**14f** (*R*)-(–)-**16** (*R*)-(–)-**17** (*R*)-(+)-**6** (*R*)-(–)-**18**

Scheme 2

The study of aza paraconic acids was subsequently extended[24] to the chemoenzymatic preparation of *cis*-5-oxo-2-pentyl-3-pyrrolidinecarboxylic acid **22** and its *trans* isomer **23** (Scheme 3), which can be considered as the precursors of the aza analogs of phaseolinic acid and methylenolactocin respectively. A 1:1 diastereomeric mixure of their racemic methyl esters *cis* (±)-**20** and *trans* (±)-**21** was synthesized by reductive amination[25] of dimethyl hexanoylbutanedioate **19** with ammonium acetate and sodium cyanoborohydride, followed by cyclization under heating. The *trans* isomer could be isolated in a higher yield, after equilibration of the mixture, in the presence of equimolar DBU, and chromatographic separation.

The enantiomers (2*R*,3*S*)-(+)-**21** and (2*S*,3*R*)-(–)-**21** were obtained with 99% e.e. (18% yield) and 98% e.e. (20% yield), respectively, in the enantiocomplementary hydrolyses mediated by α-chymotrypsin and Pig

Liver Acetone Powder respectively. The corresponding carboxylic acids were isolated at low conversion values with moderate enantiomeric excesses.



Scheme 3

The *cis* isomer **20**, direct precursor of the aza analog of phaseolinic acid, was hydrolysed by α-Ct, however without enantioselectivity, and no other enzyme was found to be active or enantioselective towards its hydrolysis.

The enantioselectivity and enantiopreference shown by α-Ct in the hydrolysis of **14c**,**e**,**f** as well as of **21** were fully rationalized by means of molecular mechanics/dynamic simulations.[26,27]

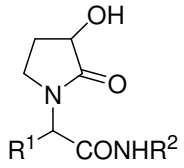
3. Hydroxylated 2-pyrrolidinones

Hydroxylated five membered nitrogen heterocycles are widespread in nature and components of many bioactive compounds.[28]

Among them, γ-lactams bearing a hydroxy group at one of the ring positions have attracted the attention of many a researcher, because they often constitute the core of more complex compounds of biological relevance.

3.1. 3-Hydroxy-2-pyrrolidinones

The 3-hydroxy-2-pyrrolidinone nucleus is present in compounds of the type **24** (Figure 2), which are active in the treatment of brain insufficiencies and as cognition activators,[29] and are characterized by a very low toxicity.



24

R^1, R^2 = H, alkyl

Figure 2

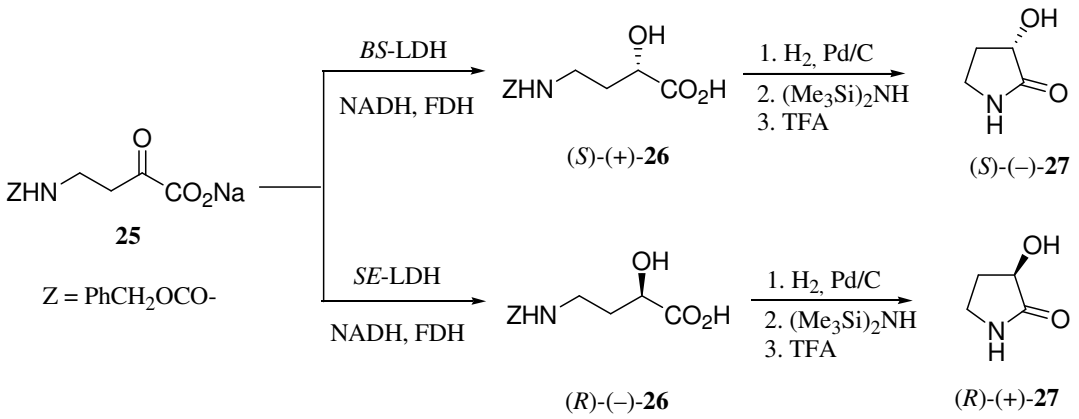
The absolute configuration of C-3 in this synthon has a strong influence on the biological properties of the molecule containing it. Therefore enantioselective strategies for the synthesis of α-hydroxy-γ-lactams derivatives have been explored using chemical[30] as well as enzymatic methodologies.[31]

In a process directed to the preparation of (3*R*,4*R*)- and (3*S*,4*S*)-3-hydroxy-4-hydroxy-methylpyrrolidine, *Candida antarctica lipase* was used for the enzyme-catalyzed enantioselective hydrolysis of the parent ester derivative.[31a] Such amino-cyclitols are useful synthons toward the preparation of inhibitors of purine nucleoside phosphorylases and as potential use as therapeutic agents in the treatment of cancer.

Among the chemoenzymatic strategies, the one reported by Wills[31b] employed a Lactate dehydrogenase (LHD) mediated reduction of a suitable α-ketoacid to produce an optically pure pyrrolidinone precursor.

In particular, the starting sodium salt of 4-benzyloxycarbonylamino-2-oxobutanoate **25**, prepared by a literature method,[32] was reduced within 40 h to the corresponding α-hydroxy acid (*S*)-(+)-**26** (99% e.e and 91% yield) using LDH from *Bacillus stearothermophilus* (*BS*-LDH) (Scheme 4). In order to prepare the enantiomeric (*R*)-(–)-**26**, LDH from *Staphilococcus epidermidis* (*SE*-LDH) was employed. In this latter case the reduction took seven days to be complete, giving the targeted product with 99% e.e. and in 95% yield. In both cases an *in situ* recycling procedure of NADH using the formate-formate dehydrogenase (FDH) protocol[33] was adopted.

Deprotection of the amino group by hydrogenolysis, followed by cyclization under literature conditions[34] completed the synthesis of the targeted 3-hydroxy-2-pyrrolidinone (*S*)-(–)- and (*R*)-(+)-**27**.



Scheme 4

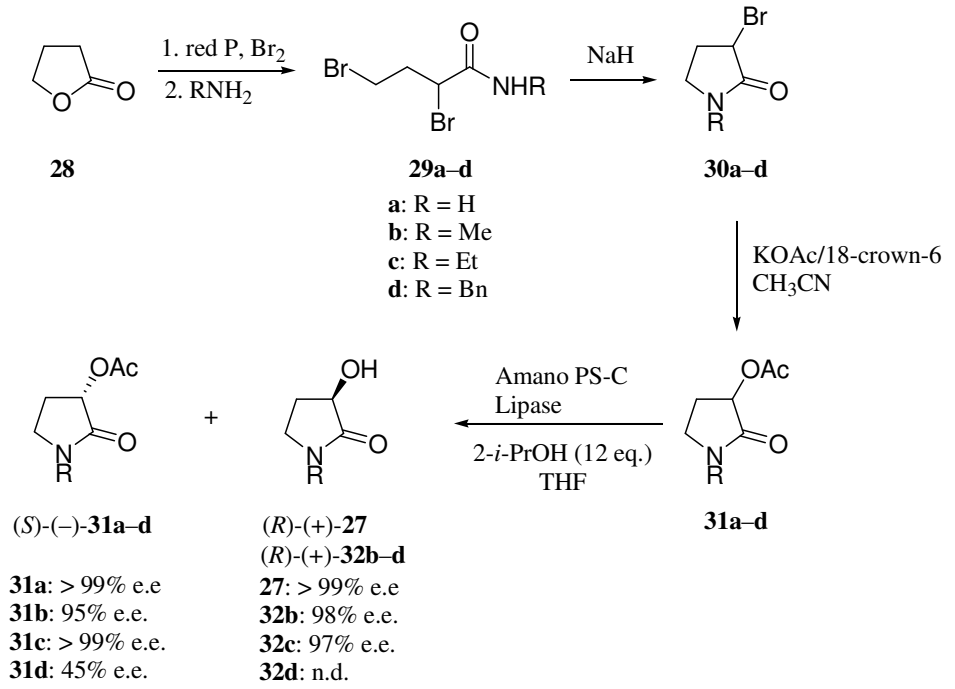
The use of lactate dehydrogenase, which was later extended by the authors to the synthesis of enantiomerically pure 3-hydroxypiperidin-2-one,[35] turned out to be of advantage with respect to the previously reported[35,36] baker's yeast reduction of ethyl 4-benzyloxycarbonylamino-2-oxobutanoate, which gave the corresponding (*S*)-(+)-2-hydroxy ester in 49% e.e. and 88% e.e..

The need for the expensive cofactor NADH and for long reaction times, however, represented a major drawback for this method.

An easier strategy starting from more common and inexpensive materials which makes use of a conventional lipase-catalysed resolution in the enantiodifferentiating step, was recently proposed by Kamal and coworkers[37] for the synthesis of both enantiomers of 3-hydroxy-2-pyrrolidinone (*R*)-(+)- and (*S*)-(–)-**27** and a series of its 1-substituted derivatives (R = Me, Et, Bn).

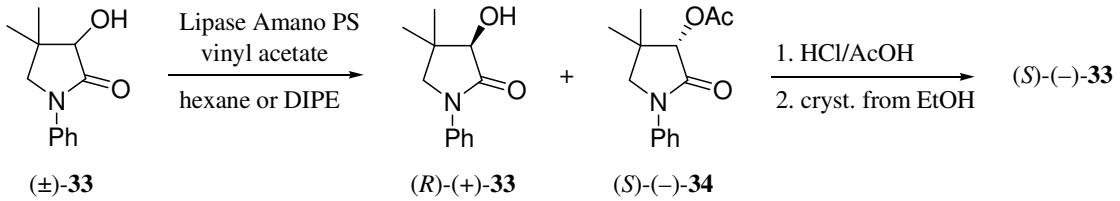
The synthesis involves the cleavage of γ-butyrolactone **28** by red phosphorus and Br_2, followed by treatment with ammonia or a primary amine to yield the corresponding 2,4-dibromo substituted butyric acid amide **29** (Scheme 5). After treatment of the amide **29** with sodium hydride, which afforded the γ-lactams **30**,

the subsequent nucleophilic substitution of the α-bromine atom with the acetoxy group, in the presence of 18-crown-6, gave the racemic 3-acetoxy-γ-lactams **31**. These compounds were resolved by enzymatic alcoholysis with *i*-PrOH, mediated by immobilized Amano PS-C lipase (Lipase from Pseudomonas Cepacia immobilized on chemically modified ceramic). The corresponding alcoholic lactams (*R*)-(+)-**27** and (*R*)-(+)-**32b–d** were obtained with simultaneous recovering of the unreacted (*S*)-(–)-acetates **31a–d** (Scheme 5). The highest enantioselectivities were found for R = H, Me, Et, whose resolutions were characterized by E > 200. On the contrary, lower enantioselectivity was observed for the *N*-benzyl derivative. Starting from δ-valerolactone, the same approach lead to optically pure 3-hydroxy-2-piperidones (e.e. > 99%).



Scheme 5

A similar approach had already been used by Camps and coworkers in 1995[38] for the synthesis in a multigram scale of the pantolactone-type chiral auxiliary (*R*)-(+)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone **33**. The corresponding racemic (±)-**33**, prepared in high yield by reacting pantolactone with aniline,[39] was resolved by enzymatic transesterification with vinyl acetate (Scheme 6).



Scheme 6

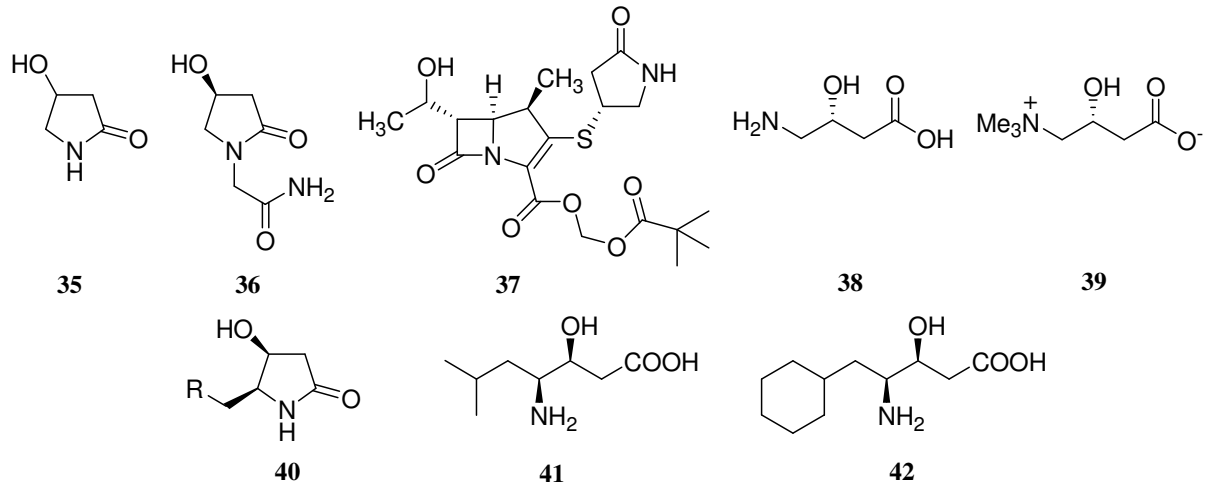
After a screening of several lipases and reaction conditions, Amano PS Lipase was chosen as the most effective biocatalyst. When the reaction was carried out with vinyl acetate in excess in diisopropyl ether as the solvent, the alcohol (*R*)-(+)-**33** was recovered after 72 h with 99% e.e. and in 92% yield, while the acetylated product (*S*)-(–)-**34** was isolated with 92% e.e. In *n*-hexane, after 64 h, the acetate derivative

(*S*)-(–)-**34** was obtained with a slightly better enantiopurity (95% e.e.) but in lower yield. Acidic hydrolysis of (*S*)-(–)-**34** and subsequent crystallization from ethanol allowed the isolation of the alcohol (*S*)-(–)-**33** with 99% e.e..

3.2. 4-Hydroxy-2-pyrrolidinones

The optically active 4-hydroxy-2-pyrrolidinone ring system **35** is also a nucleus of interest, in particular as an intermediate in the synthesis of useful pharmaceuticals.[40] The homochiral (*S*)-(–)-**35**, which is a component of *Amanita Muscaria*,[41] is used for the syntheses of the nootropic agent oxiracetam **36**[42] and the antibiotic CS-834 **37**[43] (Figure 3). The opposite enantiomer (*R*)-(+)-**35** is an intermediate to (*R*)-Rolipram **4**.[5b,c] β-Hydroxy-γ-lactams are also key precursors of important β-hydroxy-γ-aminoacids, such as the anticonvulsant drug (*R*)-γ-amino-β-hydroxybutyric acid (GABOB)[44,45] **38** and (*R*)-carnitine (vitamin B_T) **39**,[45] an antihyperlipoproteinemic agent playing an important role in the human metabolism and transport of long-chain fatty acids.

Moreover, *cis* 5-alkyl-4-hydroxy-2-pyrrolidinones of the type **40** are cyclic precursors of statines. These latters constitute a group of *syn* β-hydroxy-γ-aminoacids, such as (3*S*,4*S*) statine **41**[46] and its congener (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACHPA) **42**,[47] which have found wide applications in the design and synthesis of peptidomimetics exhibiting potent activity as inhibitors of proteases.



R = *i*-Pr, Cyclohexyl

Figure 3

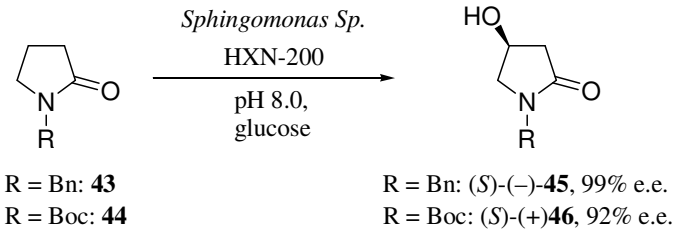
The biological relevance of hydroxylated derivatives of GABA justifies the efforts devoted to the synthesis of these compounds and/or of their cyclic 4-hydroxy-2-pyrrolidinone derivatives **35** as pure enantiomers.

Among the methods available[48] for the synthesis of these latters, biohydroxylation of *N*-substituted 2-pyrrolidinones has been considered as a possible methodology.

Maurey and Srairy[49,34] employed the fungus *Beauveria Sulfurescens* (ATCC 7159) for the hydroxylation of various *N*-substituted 2-pyrrolidinones. However, the regio- and stereoselectivity of this transformations proved to be a problem. In fact, only the *N*-benzoyl derivative was transformed at the C-4 carbon atom exclusively, while hydroxylation of other related compounds (1-phenylacetyl, 1-benzoyl-5-

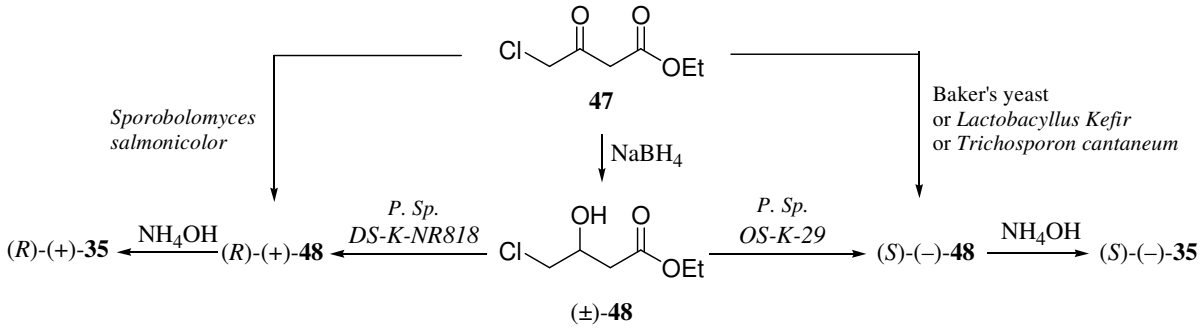
methyl, 1-benzyl) gave complex mixtures of 3-, 4-, and 5-hydroxylated regioisomers. Furthermore, in all cases the enantioselectivity was very poor, the e.e.'s ranging between 12 and 35%.

On the contrary, a successful hydroxylation of *N*-benzyl- and *N-tert*-butoxycarbonyl-2-pyrrolidinone **43** and **44**, respectively, was reported by Li.[50] The reaction, mediated by *Sphingomonas sp.* HXN-200, occurred in both a regio- and enantioselective manner to give the sole 4-hydroxy derivatives (*S*)-(–)-**45**, having 99% e.e. (46% yield), and (*S*)-(+)-**46**, with 92% e.e. (68% yield), respectively.



Scheme 7

A different biotransformative approach to 4-hydroxy-2-pyrrolidinones consists in the microbially or enzymatically mediated preparation of an optically active open-chain precursor to be transformed into the desired γ-lactam in a cyclization step. In this context, the most explored intermediate has been the optically active ethyl ester of 4-chloro-3-hydroxybutyric acid **47**, as it can be easily aminated with ammonia at the γ-carbon to give the targeted pyrrolidinone **35**,[42b] (Scheme 8).



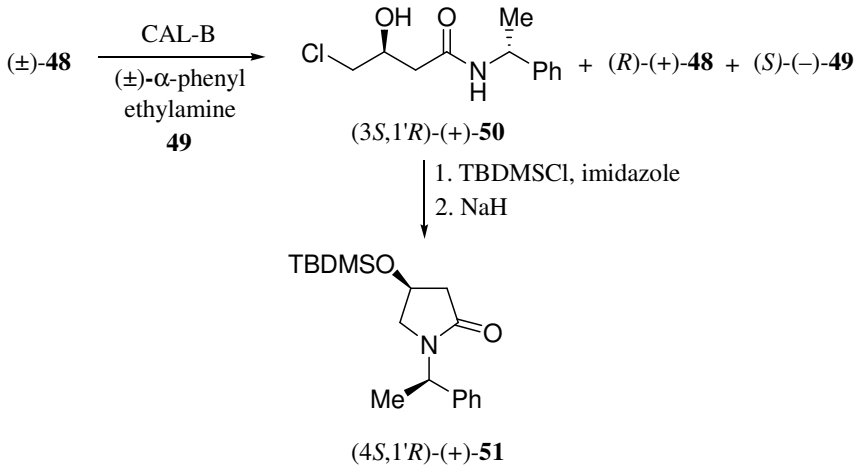
Scheme 8

Baker's yeast reduction of ethyl 4-chloro-3-oxobutanoate **47** has been reported by Santaniello[41b] and Sih[45b] to occur with modest enantioselectivity to give ethyl (*S*)-(–)-4-chloro-3-hydroxybutanoate **48**. Higher enantioselectivities were reported for other microbial asymmetric reductions of the same ketoester. *Lactobacyllus Kefir*[51] was reported to reduce **47** to (*S*)-(–)-**48** with 99% e.e.. Shimizu[52] and coworkers found that *Sporobolomyces salmonicolor* and *Trichosporon cantaneum* transformed **47** into (*R*)-(+)-**48** and (*S*)-(–)-**48** respectively.

More recently, Suzuky[53] developed a microbial resolution of racemic **48** by stereoselective dechlorination. *Pseudomonas sp* OS-K-29, a microorganism isolated from soil, degradated the *R* enantiomer of the hydroxy ester allowing the recovery of the residual (*S*)-(–)-4-chloro-3-hydroxybutanoate **48** with 98.5% e.e. and in 33% yield. On the contrary, *Pseudomonas sp.* DS-K-NR818, which is a mutant of *Pseudomonas sp*. OS-K-29, gave the opposite enantiomer (*R*)-(+)-**48** with excellent optical purity (98.4% e.e.) in 40% yield. In both cases dechlorinated compounds were formed as the reaction by-products.

The use of a conventional Lipase for the obtainment of homochiral ethyl 4-chloro-3-hydroxybutanoate **48** was reported by Gotor in 1999,[54] who described a "doubly enantioselective aminolysis" of (±)-**48**.

Due to its well-known ability to catalyse efficiently simple kinetic resolution of racemic hydroxyesters by aminolysis, as well as that of racemic amines by acylation reactions, *Candida Antarctica* B (CAL B, Novozym SP 435) was chosen by the authors as the biocatalyst for the reaction between (±)-**48** and racemic α-phenylethylamine **49**. As the enzyme recognized both chiral reagents enantioselectively, the formation of an optically active diastereomeric amide **50**, and the resolution of the amine and the acyl donor were achieved in the same step (Scheme 9).



Scheme 9

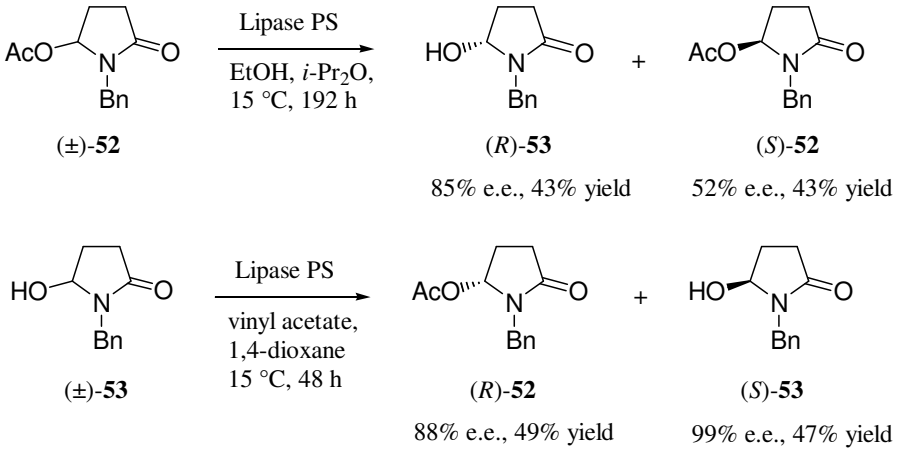
The racemic reagents were reacted in 1,4-dioxane over 4Å MS, in the presence of CAL B. The diastereoselective aminolysis of the hydroxy ester led to the amide (3*S*,1'*R*)-(+)-**50** (99:1 d.e. *vs*. (3*R*,1'*R*)-(–)-**50**, the other two possible diastereomers being absent in the reaction mixture) and in enantiomerically pure form (> 99% e.e.), at a conversion value around 50%. The resolved amine (*S*)-(–)-**49** and the hydroxy ester (*R*)-(+)-**48** were recovered, at the same conversion value, with high e.e.'s (93% and 92% e.e. respectively). A slightly lower enantioselectivity and activity was exhibited by the same enzyme by using chiral amines bearing different α-substituents (2-furyl, *n*-pentyl). The transformation of (+)-**50** into the corresponding γ-lactam (+)-**51** was promoted by NaH, after protection of the OH group.

3.3. 5-Hydroxy-2-pyrrolidinones

Among the hydroxylated γ-lactams, chiral 5-hydroxy-2-pyrrolidinone derivatives are valuable building blocks for the asymmetric synthesis of natural products.[55]

To our knowledge, little is reported in the literature on chemoenzymatic preparations of this nucleus and its derivatives. The group of Takabe described[56] the enzymatic kinetic resolution of (±)-5-acetoxy-1-benzyl-2-pyrrolidinone **52** mediated by Lipase PS (*Pseudomonas Cepacia*), which catalysed the transesterification of the substrate in EtOH/*i*-Pr_2O, furnishing (*R*)-1-benzyl-5-hydroxy-2-pyrrolidinone **53** in 85% e.e. and 43% yield, after 192 h stirring (Scheme 10). The recovered unreacted acetate (*S*)-**52** had 53% e.e. (E = 24).

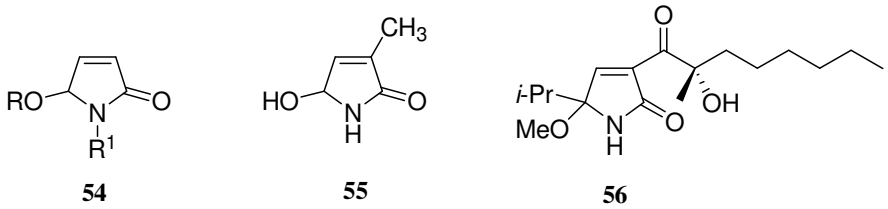
A better enantiomeric ratio (E = 42) was found for the reverse reaction. In fact, acetylation of racemic 1-benzyl-5-hydroxy-2-pyrrolidinone **53** with vinyl acetate occurred in 1,4-dioxane to give after 48 h (*R*)-**52** with 88% e.e., and the residual unreacted hydroxy derivative (*S*)-**53** with 99% e.e..



Scheme 10

4. 5-Hydroxy-2-pyrrolinones

Optically active substituted 3-pyrrolin-2-ones (2(5*H*)-pyrrolinones)[55] **54** are ubiquitous structural subunits found in a variety of natural products, such as alkaloids, nucleosides, antineoplastic agents or immunosupressant.[57] In particular, the 5-hydroxy-2-pyrrolinone mojety is found in Jatropham **55**,[58] an antitumor alkaloid isolated in 1973[59] from *Jatropha Macrorhiza*, and in the platelet aggregation inhibitor PI-091 **56**[60] (Figure 4).



54 **55** **56**

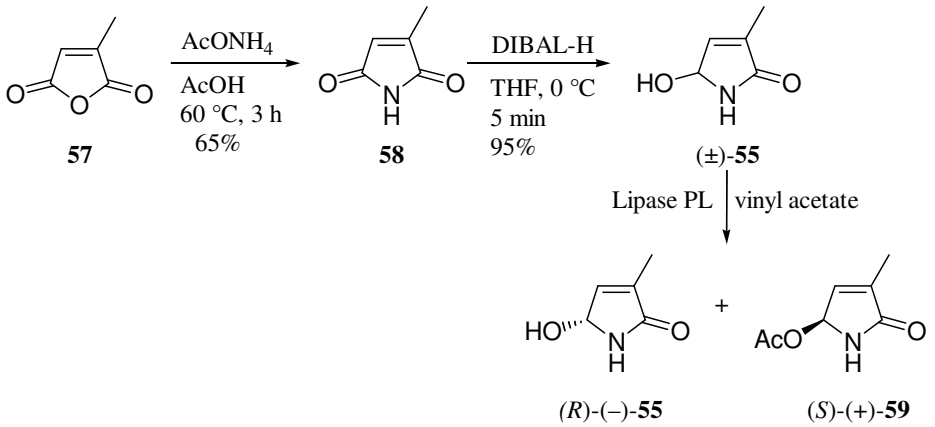
R = H, alkyl, acyl
R^1 = alkyl, aryl, acyl

Figure 4

The only asymmetric synthesis of natural Jatropham (*R*)-(–)-**55**, published in 1999,[61] was achieved by a chemoenzymatic method. The authors describe a three step process, starting from the inexpensive citraconic anhydride **57**, which was first converted into citraconic imide **58** by a known literature procedure[62] (Scheme 11). Reduction of **58** with DIBAL-H was a key step for the achievement of the targeted product in good yield, as it occurred in a completely regioselective way to give (±)-Jatropham **55** in 95% yield.

Subsequently, (±)-Jatropham **55** was kinetically resolved by transesterification with vinyl acetate in the presence of Lipase PL. The reaction proceeded smoothly at 25 °C to give (*R*)-(–)-**55** in 35% yield and 98% e.e., while the corresponding acetate (*S*)-(+)-**59**, was produced in a 53% yield and 50% e.e.

Due to their multifunctional nature, pyrrolinone-containing derivatives are versatile building blocks for the preparation of more complex structures. They take part in stereoselective conjugated additions of amines and thiols,[63] cuprates[64] and stabilized anions,[65] Diels-Alder cycloadditions,[66] allylic substitution,[67] as well as transformations into *N*-acyliminium ions.[64] Enantiopure 5-substituted 2-pyrrolinones have been used in the total synthesis of alkaloids[68] and unnatural amino acids[69] such as statine and its analogs.



Scheme 11

This explains the efforts many researchers have devoted to find a convenient preparation of this important heterocyclic synthon.

A classical method for the synthesis of enantiopure (*R*)-1-acetyl-5-isopropoxy-2-pyrrolinone starting from a derivatives of easy available (*S*)-malic acid, was disclosed by Hiemska.[66] This procedure however requires many steps, leading to the targeted compound in 40% yield.

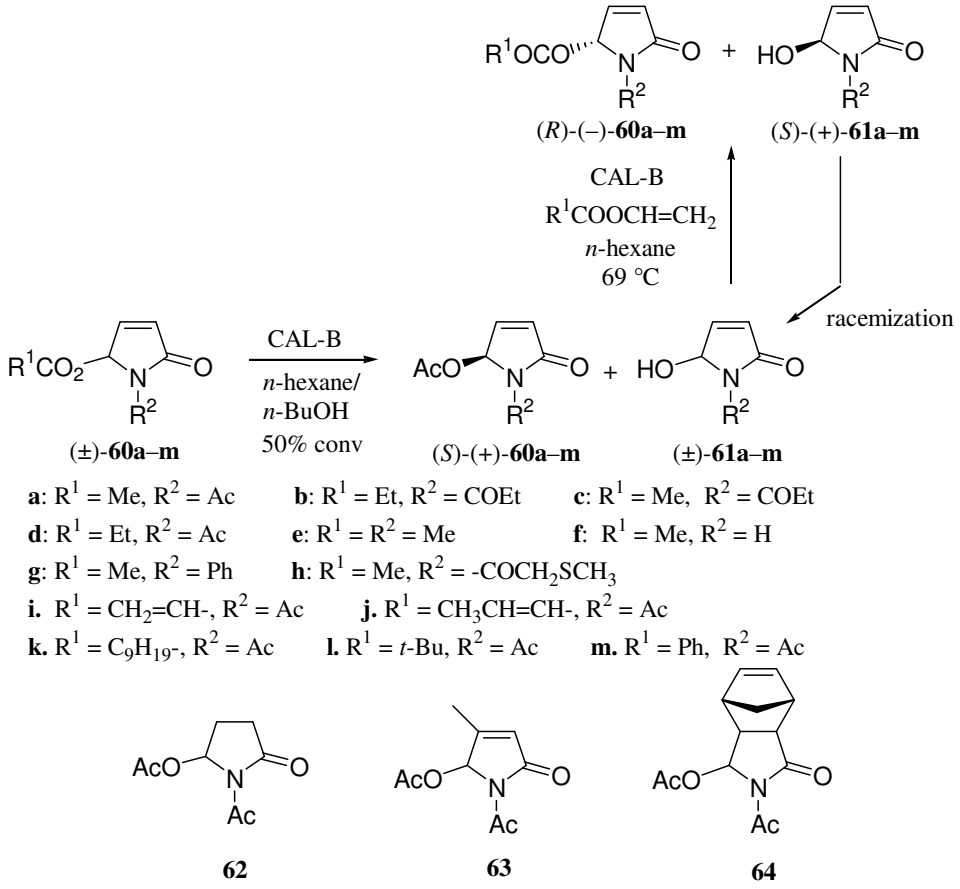
A very elegant and convenient enzymatic route to larger amounts of similar building blocks was developed by Feringa and Cuiper.[70] In their strategy, racemic 1-acetyl-5-acetyloxy-3-pyrrolinone **60a** (Scheme 12) was first treated with *Candida Antarctica Lipase* (CAL-B) immobilized on Hyflo Super Cell, for kinetic resolution. In a 3:1 mixture of *n*-hexane and *n*-BuOH at room temperature, enzymatic transesterification occurred, which converted the substrate to an extent of 50%, after which the reaction did not proceed any further. At this conversion value, the unreacted (*S*)-(+)-**60a** was isolated with >99% e.e. and 50% yield.

Surprinsingly, the reaction product **61a**, also formed in 50% yield, was isolated as a racemate because it underwent racemization *in situ* during the transesterification. This observation suggested the authors to couple the kinetic resolution to the reverse reaction with the same enzyme, namely the enantioselective CAL-B mediated esterification of the alcohol with vinyl acetate. Carrying out this latter reaction at 69 °C, the rate of racemization was enhanced, thus allowing the conversion to be taken up to 100%, affording the enantiomerically pure (*R*)-(–)-**60a** with > 99% e.e and in quantitative yield (Scheme 12, upper part). This elegant enzymatic methodology is an example of a second-order asymmetric transformation, giving access to both enantiomers of the product **60a**, by the use of a single enzyme, simply switching the technique from a transesterification to an esterification.

The high stereoselectivity observed, both in the transesterification (kinetic resolution) and in the esterification (asymmetric transformation) strictly depend on the nature of the substituents at the ring, as shown in a subsequent publication by the same research group.[71] In this work a systematic study of the CAL-B mediated transformations of a variety of 5-acyloxy and 5-hydroxy-3-pyrrolinones, differing in the ring substitution pattern, was presented (Scheme 12).

Compared to the case of **60a**,[70] it was shown that in the transesterification of other 5-acyloxy-3-pyrrolinones **60b**–**m**, **62**, **63**, and **64**, variations in the alkyl or acyl substituents at nitrogen, as well as in the acyl substituents at C-5, were tolerated by the enzyme without significant changes in the enantioselectivity and activity. Only the the *N*-unsubstituted substrate **60f** was transformed to a racemate, while the presence of

a methyl group at C-4, such as in substrate **63**, made the reaction much slower, and no activity at all was detected in the presence of bulkier substituents, such as in the case of **64**.



Scheme 12

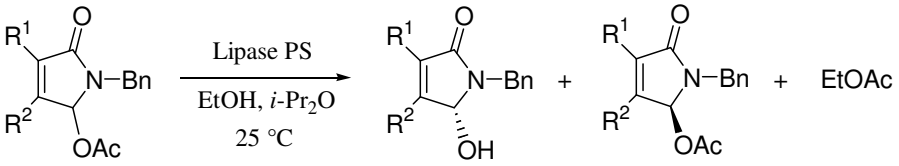
A general enantiopreference of the enzyme for the *R* enantiomer (or the laevorotatory compound when the absolute configuration could not be assigned) was observed. In the reverse process, *i.e.* the esterification with vinyl esters of a series of 5-hydroxy-3-pyrrolinones **61b–m** differing in the substituent at nitrogen (Scheme 12, upper part), the best result was found for the the reaction of the *N*-acylated substrates (R^2 = Ac, COEt) with vinyl acetate (R^1 = Me) or vinyl propionate (R^1 = Et), which gave the corresponding products (*R*)-(–)-**60a–h** with >99% e.e., at 90% conversion of the reaction. Moreover, the use of different vinyl esters, (R^1 = CH_2=CH-, CH_3CH=CH-, C_9H_{19}-, *t*-Bu, Ph) gave access to a variety of other acyloxy derivatives (*R*)-(–)-**60i–m**, in most cases with good enantioselectivity.

In general, those 5-acyloxy-3-pyrrolinones which were converted with high enantioselectivities in the transesterification, could be obtained with high e.e. in the asymmetric esterification. Similarly, those pyrrolinones transformed in the transesterification with low enantioselectivity were converted to the corresponding acyloxy derivatives having low e.e.'s in the related esterification process.

A description of a fast and universal method, based on circular dichroism technique, for the determination of the absolute configuration of 3-pyrrolinone derivatives was described by the same authors in a subsequent publication.[72]

The kinetic enzymatic resolution of a series of α,β-unsaturated-γ-lactams derived from citraconic and maleic imide has been the object of the already mentioned publication of Takabe.[56] The Lipase PS

transesterification of the *N*-benzyl-5-acetoxy-3-pyrrolinone **65a** and its 3- and 4-methyl derivatives **65b** and **65c** respectively, was described to occur in EtOH/*i*-Pr_2O at 25 °C. The reaction was enantioselective only in the cases of **65a** and **65c** (Scheme 13), which were transformed into the corresponding alcohols (*R*)-**66a**,**c** (99% e.e.) with the residual acetates (*S*)-**65a**,**c** having 90% and 43% e.e. respectively. The isomer **65b** was found unreactive under the same conditions.



(±)-**65a–c**

a: $R^1 = R^2 = H$
b: $R^1 = H$, $R^2 = Me$
c: $R^1 = Me$, $R^2 = H$

(*R*)-**66a–c**

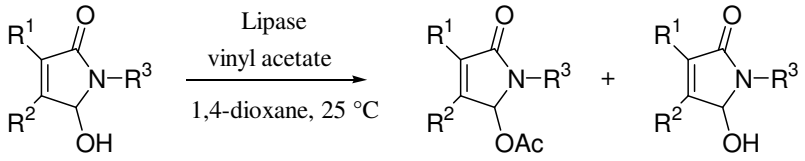
a: >99%e.e.
c: >99%e.e.

(*S*)-**65a–c**

a: >90% e.e.
c: 43% e.e.

Scheme 13

The low activity exhibited in these enzymatic transformations (reaction times 72-480 h) prompted the authors to examine the reverse reaction, namely the Lipase mediated acetylation of the 5-hydroxy unsaturated lactams **66a–g** with vinyl acetate to give the corresponding 5-acetoxy derivatives **65a–g** (Scheme 14). For the best results 1,4-dioxane was employed as the solvent, with a tenfold excess of vinyl acetate and a 1:1 ratio (w:w) between the substrate and the enzyme at 25 °C. Lipase PS, PL, and Novozym 435 showed the highest activity and selectivity.



(±)-**66**

(+) or (–)-**65**

(+) or (–)-**66**

a: $R^1 = R^2 = H$, $R^3 = Bn$
b: $R^1 = H$, $R^2 = Me$, $R^3 = Bn$
c: $R^1 = Me$, $R^2 = H$, $R^3 = Bn$
d: $R^1 = R^2 = H$, $R^3 = allyl$
e: $R^1 = Me$, $R^2 = H$, $R^3 = allyl$
f: $R^1 = R^2 = H$, $R^3 = H$
g: $R^1 = Me$, $R^2 = H$, $R^3 = H$

Scheme 14

An interesting point underlined by the authors was the observed dependance of the enzyme activity and enantioselectivity on the presence of a substituent at the nitrogen atom. In fact Lipase PS and Novozym 435 catalyzed the acetylation of the *R*-enantiomer of the nitrogen substituted γ-lactams **66a–e**, leading to the corresponding acetates **65a–e** in *R* configuration.

On the other side, Lipase PS was found to be unactive towards *N*-unprotected γ-lactams **66f**,**g** while Lipase PL and Novozym 435 exhibited an opposite enantioselectivity compared with the previous cases, resulting in the formation of the *S*-acetates **64c**,**g**. The enantiomeric excesses for all compounds are shown in Table 1.

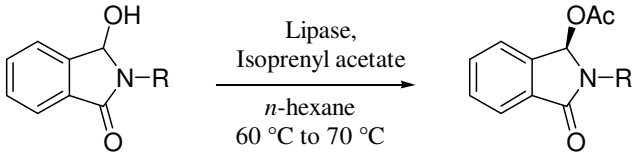
The isoindolin-1-one (2,3-dihydro-1*H*-isoindol-1-one) nucleus is part of many natural substances and compounds possessing a variety of pharmacological properties,[73] as well as a building block in the synthesis of pyrrolizidinone alkaloids[74] and other bioactive compounds, particularly 3-substituted isoindolin-1-ones.[75]

An example of lipase catalyzed dynamic kinetic resolution of 2-acyl-3-hydroxy-2,3-dihydroisoindolin-1-ones was reported by Kaga and coll.[76]

Table 1.

Substrate	Lipase	Product, e.e (%)	Unreacted Substrate, e.e. (%)
66a	Lipase PS	(*R*)-**65a**, >99	(*S*)-**66a**, >99
66a	Novozym 435	(*R*)-**65a**, >99	(*S*)-**66a**, >99
66b	Lipase PS	(*R*)-**65b**, 98	(*S*)-**66b**, 38
66c	Novozym 435	(*R*)-**65c**, >99	(*S*)-**66c**, >99
66d	Lipase PS	(*R*)-**65d**, 96	(*S*)-**66d**, 70
66d	Novozym 435	(*R*)-**65d**, 81	(*R*)-**66d**, 93
66e	Novozym 435	(*R*)-**65e**, 79	(*S*)-**66e**, 81
66f	Lipase PL	(*S*)-**65f**, 75	(*S*)-**66f**, >99
66f	Novozym 435	(*S*)-**65f**, 75	(*S*)-**66f**, 99
66g	Lipase PL	(*S*)-**65g**, 50	(*R*)-**66g**, 98

Enzymic acetylation of (±)-**67**, differing in the acyl group at nitrogen, was carried out with isoprenyl acetate in *n*-hexane at high temperature (60–70 °C) (Scheme 15). Under these conditions, racemization of the substrate occurred *in situ,* allowing its quantitative conversion to the corresponding acetates (*R*)-(–)-**68**. In the screening of the Lipases, the best results were obtained with Lipase PS *(Pseudomonas Cepacia*), AK (*Pseudomonas Fluorescens*) and QL (*Alcaligenes Species*), this latter enzyme showing the higher activity (reaction time, 1 day). All the enzymes tested showed the same enantiopreference towards the (*R*)-enantiomers, whose acetylated products **68** were isolated with enantiomeric excesses exceeding 99% in most cases.



(±)-**67a–f**

a: R = MeCO
b: R = EtCO
c: R = *n*-PrCO
d: R = *i*-PrCO
e: R = *t*-BuCO
f: R = PhCO

(*R*)-(–)-**68a–f**

a: 63% e.e.
b–f: > 99% e.e.

Scheme 15

5. Enantioselective synthesis of γ-lactams by enzymatic hydrolysis of the lactam ring

Enzymatic hydrolysis of the γ-lactam function is not a facile process due to the necessity for not readily accessible enzymes.

A research group of the University of Exeter (UK), working in connection with Enzymatix Ltd., Cambridge, studied the resolution of the bicyclic lactam 2-azabicyclo[2.2.1]hept-5-en-3-one **69a**[77-79] by the use of lactamase-type enzymes.

The azanorbornenone compound **69a** and its derivatives **69b**,**c** are important intermediates in the manufacture of a series of chemotherapeutic agents, named carbocyclic nucleosides, in which the (deoxy)ribofuranose oxygen of the parent nucleoside is substituted for a methylene group.

Examples are (–)-Carbovir **70**,[80] (–)-Abacavir **71**,[81] carbocyclic 2'-deoxy-5-[(*E*)-2-bromovinyl]uridine **72** (c-BvdU),[82] and carbocyclic 2'-deoxy-2'-fluoroguanosine **73**[83] (Figure 6), which have been extensively studied for their activity against viral infections as HIV, HBV and herpes.

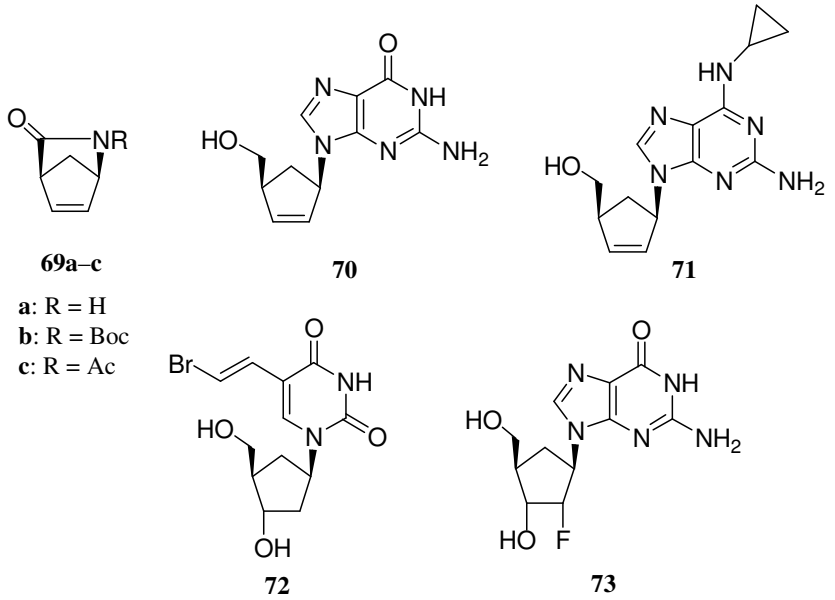
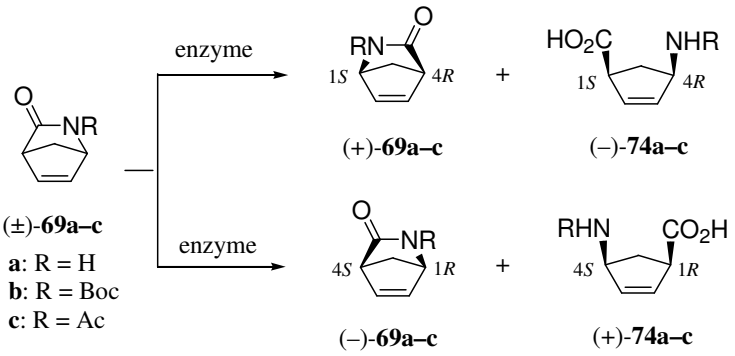


Figure 6

Both enantiomers of 2-azabicyclo[2.2.1]hept-5-en-3-one **69a** have been obtained using whole cells biocatalysis for the resolution of the racemic starting substrate.[77] An enantiocomplementary γ-lactamase activity was shown by microbial *Rhodococcus equi* NCIB 40213 (referred to as ENZA-1) and *Pseudomonas solanacearum* NCIB 40249 (ENZA-20). Incubation of the cells, at 25 °C and pH 7, with a 6 g/l concentration of the biocatalyst and 50 g/l concentration of the substrate, resulted in the formation within 3h of (1*S*,4*R*)-(+)-**69a** from the fermentation with ENZA-1, whereas the fermentation with ENZA-20 gave the opposite enantiomer (1*R*,4*S*)-(–)-**69a** (Scheme 16).



Scheme 16

They both were produced in a 45% yield and 98% e.e.. The products of the reaction were the optically pure amino acids (1*S*,4*R*)-(–)-**74a** and (1*R*,4*S*)-(+)-**74a** respectively, which are precursors of the GABA agonist *cis*-3-aminocyclopentanecarboxylic acid.[84] Both the microbial strains could be used for the rapid resolution of the bicyclic racemic γ-lactam **69a** at a concentration up to 100 g/l.

Compound (–)-**74a** was then converted by a multistep procedure into the anti-HIV agent (–)-carbovir **70**.[80]

As an extension of this work, other microorganisms with γ-lactamase activity were selected from sewage and soil samples.[79] One was identified as a *Pseudomonas fluorescens* strain (ENZA-22), and it showed the same enantiopreference as ENZA-20, cleaving the (1*S*,4*R*)-(+)-enantiomer of the bicyclic substrate to give the residual lactam (1*R*,4*S*)-(–)-**69a** and the aminoacid (1*R*,4*S*)-(+)-**74a**, each with 93% e.e. (Scheme 16).

Another microorganism was identified as an *Aureobacterium species* (ENZA-25), which exhibited an opposite enantiospecificity, giving (+)-**69a** with 97% e.e., and the aminoacid (–)-**74a** with 91% e.e. From the latter strain a particularly thermostable (up to 70 °C) γ-lactamase was isolated and immobilized onto a glutaraldehyde polymeric support. This supported enzyme resolved the same substrate in a totally enantiospecific manner and it could be reused without loss of activity.

Although very efficient, the procedure here described is of limited applicability due to the use of non-commercially available biocatalysts.

Mahmoudian[85] *et al.* developed a facile procedure based on the enantioselective hydrolysis of the amide lactam bond of *N*-acyl-2-aza-bicyclo[2.2.1]hept-5-en-3-one **69b**,**c** (**b**: R = Boc; **c**: R = Ac) by the use of commercially available enzymes (Scheme 16).

The presence of the acyl group at nitrogen in compounds **69b**,**c** resulted in the activation of the ring, allowing conventional hydrolases, inactive towards unprotected **69a**, to be used for the hydrolysis. Up to 16 enzymes among esterases, lipases, proteases of microbial and mammalian origin were screened, and the reaction conditions were found which prevented the chemical hydrolysis of the substrates to occur. The best results were obtained using Savinase (Subtilisin, EC 3.4.21.62), a serine-type protease. This enzyme hydrolysed in 50% THF/phosphate buffer solution the (+)-enantiomers of **69b**,**c** to the corresponding amino acids **74b**,**c**, which were not isolated, leaving the residual γ-lactams (–)-**69b**,**c** with >99% e.e., possessing the correct (1*R*,4*S*) absolute configuration for the synthesis of (–)-carbovir, (–)-abacavir and the other carbocyclic nucleases (Figure 6).

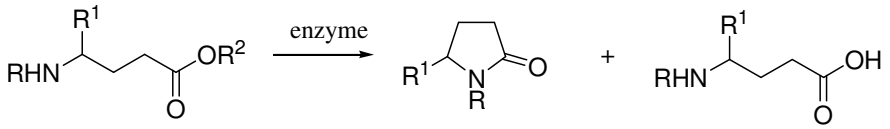
More recently, the cloning, sequencing, characterization of a thermophilic γ-lactamase from *Sulfolobus solfataricus* MT4 and its potential use in biotransformation reactions, were studied.[86] This enzyme was found to selectively cleave the (+)-enantiomer of **69a** at 85 °C. Its thermostability and substrate specificity makes this natural catalyst a good candidate for its use in industrial biotransformations aimed at the syntheses of carbocyclic nucleosides.

6. Enantioselective synthesis of γ-lactams by ring closure of γ-amino esters

In connection with their studies on the enzyme catalysed synthesis of γ- and δ-lactones, Gutman[87] and coworkers exploited the possibility of forming four to seven membered ring lactams by enzymatic cyclization of the appropriate ω-amino esters in organic solvent. Thus PPL was found to catalyse the ring closure of variously substituted γ-amino esters of the type **75** (Scheme 17) to the corresponding γ-lactams.

The reactions were performed preferentially on hindered isopropyl esters in dry *tert*-amyl alcohol, which were shown to be the best conditions for avoiding the undesired uncatalysed cyclization. Depending on the substituents on the substrate, the reaction took 2–6 days to reach 30-45% conversion.

Starting from the chiral racemic substrates **75a**,**c** no enantioselection was observed. A very low e.e. (23%) was found for the lactamic product **76c** by replacing PPL with Subtilisin.



75a-e **76a-e** **77a-e**

a: R = H, $R^1 = CO_2Et$, R^2 = Et
b: R = R^1 = H, R^2 = *i*-Pr
c: R = H, R^1 = Me, R^2 = *i*-Pr
d: R = Me, R^1 = H, R^3 = *i*-Pr
e: R = H, R^1 = Ph, R^2 =Et

Scheme 17

In contrast, Pig Liver Esterase proved[88] capable to catalyse the enantioselective ring closure of racemic ethyl 4-phenyl-4-aminobutanoate **75e**, to give (*S*)-5-phenyl-2-pyrrolidone **76e** with 90% e.e. together with the hydrolysis product (*R*)-4-phenyl-4-aminobutanoic acid **77e**.

7. γ-Lactams precursors of homo-β-proline and Baclofen

As already mentioned, γ-lactams are important also as intermediates to pyrrolidines and GABA (γ-aminobutyric acid) analogs.

The former are usually obtained by borane reduction of the carbonyl group, the latter either *via* acidic hydrolysis (6N HCl, heating) or by basic (LiOH) hydrolysis of the *N*-Boc protected pyrrolidinones.[89]

GABA is the major inhibitory neurotransmitter in the mammalian Central Nervous System.[90] The disfunctioning of the central GABA system is responsible for epilepsy, Huntington's and Parkinson's diseases,[91] and other psychiatric disorders such as autism, anxiety and pain.[92]

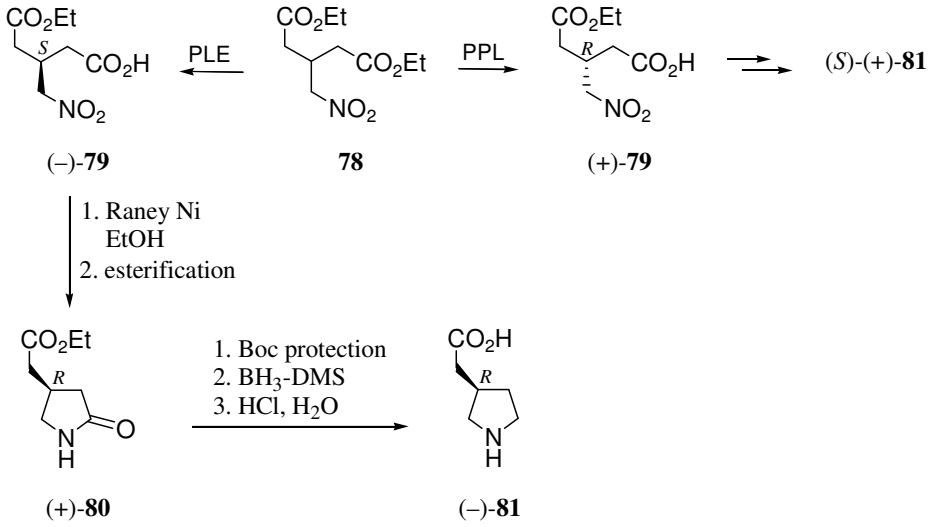
Many unnatural γ-amino acids have been designed for their promising therapeutic use in the treatment of these diseases. Among them, the cyclic GABA analogs (*S*)-(–)- and (*R*)-(+)-homo-β-proline are known to act as potent inhibitors of the neuronal and glial uptake mechanism of GABA.[93]

A short and simple chemoenzymatic synthesis of ethyl (*S*)-(–)- and (*R*)-(+)-homo-β-proline **81** was recently achieved[94] through the intermediacy of the corresponding enantiomerically pure ethyl (*S*)-(–)- and (*R*)-(+)-2-oxo-4-pyrrolidineacetate **80** (Scheme 18).

The enzymatic desymmetrization of the prochiral nitrodiester diethyl 3-(nitromethyl)pentanedioate **78**, by two enantiocomplementary enzymes, constitutes the asymmetric key step of the synthesis. In particular, PLE hydrolysed the pro-*S* ester group of **78**, giving the monoester (*S*)-(–)-**79** with 99% e.e. and 82% yield, in 2 h. Porcine Pancreatic Lipase showed an opposite enantiopreference, transforming the substrate **78** into the monoester (*R*)-(+)-**79** (98% e.e. and 79% yield), in 72 h.

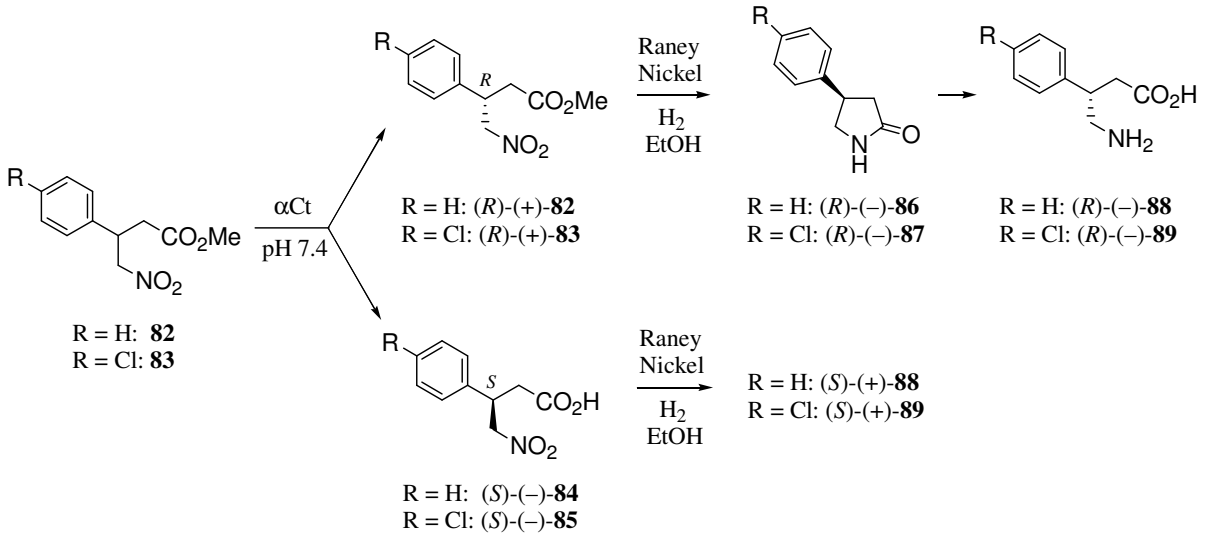
The conversion of (*R*)-(+)- and (*S*)-(–)-**79** into the corresponding lactamic precursors (*S*)- (–)- and (*R*)-(+)-**80** of the target GABA analogs (Scheme 18) was carried out by hydrogenation of the nitro group over

Raney Nickel, followed by spontaneous cyclization. *N*-Boc protection followed by reduction with BH_3-DMS in THF, removal of the *tert*-butoxycarbonyl group and final acidic hydrolysis of the ester function led the the target molecules (*R*)-(–)- and (*S*)-(+)-homo-β-proline **81**, in approximately 50% overall yield starting from **78**.



Scheme 18

The syntheses of two optically active β-aryl-substituted-γ-lactams (*R*)-(–)-**87**[95] and (*R*)-(–)-**89** (Scheme 19), precursors of the GABA analogs 4-amino-3-phenylbutyric acid[96] (β-phenyl GABA) (*R*)-(–)-**88** and 4-amino-3-(4-chlorophenyl)butyric acid (Baclofen)[97] (*R*)-(–)-**89** respectively were also based on the enzymatic kinetic resolution of the easy available racemic γ-nitroester precursors **82** and **83**. The former GABA derivative is a mood elevator and tranquillizer,[98] while *R*-Baclofen is widely used in the treatment of spasticy.[99] Compound (*R*)-(–)-**87** is an important lipophilic pro-drug related to GABA, showing itself muscle relaxant activity.[100]



Scheme 19

The presence of an aromatic substituent on the substrates, fitting the hydrophobic binding site of the enzyme, proved to be crucial for the enantiopreference of α-chymotrypsin. In fact hydrolyses of (±)-**82** and

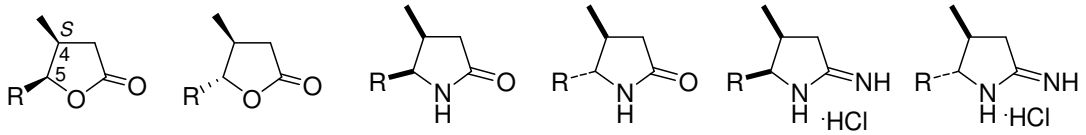
(±)-**83** proceeded enantioselectively. In the former case (E = 50) the hydrolysis product (*S*)-(–)-**84** was obtained with 95% e.e. at 23% conversion value, while the unreacted γ-nitroester (*R*)-(+)-**82** was recovered in optically pure form (99.9% e.e) at 70% conversion value. In the hydrolysis of (±)-**83**, owing to the high enantiomeric ratio (E = 120), the reaction did not proceed beyond 53% conversion, and both the acid (*S*)-(–)-**85** and the ester (*R*)-(+)-**83** could be obtained in optically pure forms, with 96% and 99.9% e. e. respectively (Scheme 19).

The optically pure γ-nitroesters were transformed into the corresponding 4-substituted γ-lactams (*R*)-(–)-**86** and (*R*)-(–)-**87**, by reduction of the nitro group under hydrogen atmospheric pressure, in the presence of Raney Nickel as the catalyst.

8. Aza analogs of Quercus Lactones

Cis- and *trans*-5-*n*-butyl-4-methyl-2-pyrrolidinone **94** and **95** and *cis*- and *trans*-4-methyl-5-*n*-pentyl-2-pyrrolidinone **96** and **97** are the nitrogen analogs of the so-called "Quercus lactones",[101] which are natural flavours isolated from the wood of oak barrels, where wine and aged alcoholic beverages, such as whisky, brandy and cognac were kept for maturing. In particular, *cis*-(–)-**90** and *trans*-(+)-**91** (R = C_4H_9) are called whisky lactones, while *cis*-(–)-**92** and *trans*-(+)-**93** (R = C_5H_{11}) are called cognac lactones (Figure 7). The importance of the diastereoisomeric 4,5-disubstituted pyrrolidones **94–97** derives from the fact that they are the direct precursors of the relevant 2-iminopyrrolidine derivatives **98–101** (Figure 7).

Some of them are known to be potent and selective inhibitors of the human inducible isoforms of nitric oxide synthase both *in vitro* and *in vivo*, and therefore potentially useful in the treatment of many diseases correlated with a harmful NO overproduction.[102] Interestingly, the biological activity exhibited by 4-methyl-5-*n*-pentyl-2-iminopyrrolidines **100** and **101** was found to be strongly affected by their sterochemical features. Among the possible stereoisomers of the 5-*n*-pentyl derivative, *cis*-(+)-**100**, derived from the corresponding γ-lactam *cis*-(+)-**96**, proved the most active and selective.



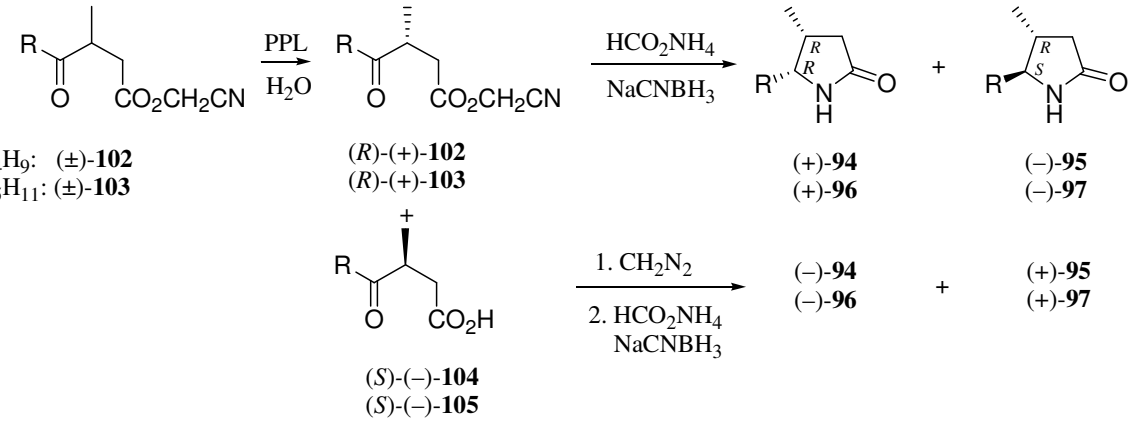
R = C_4H_9: (–)-**90**	(+)-**91**	**94**	**95**	**98**	**99**
R = C_5H_{11}: (–)-**92**	(+)-**93**	**96**	**97**	**100**	**101**

Figure 7

The enantioselective synthesis of all steroisomers of **94–97**[103] was based on the kinetic resolution with PPL of racemic cyanomethyl β-methyl-γ-ketoesters **102** and **103** (Scheme 20). These activated esters were resolved by the Lipase in water at pH 7.2 (E value > 100) more efficiently then the corresponding ethyl esters. At low conversion values, the γ-ketoacids (*S*)-(–)-**104** and (*S*)-(–)-**105** were isolated with 96% e.e. and 97% e.e. and in 20% and 25% yield respectively, while at higher conversion (around 50%), the unreacted esters (*R*)-(+)-**102** and (*R*)-(+)-**103** having e.e.'s > 99% were recovered.

Reductive amination of (*R*)-(+)-**102** and (*R*)-(+)-**103** (>99% e.e.) with $HCOONH_4$ and sodium cyanoborohydride proceeded to give *cis*-(+)-**94** and *trans*-(–)-**95** (R = C_4H_9), and *cis*-(+)-**96**, and *trans*-(–)-**97** (R = C_5H_{11}), each of them obtained with 93% e.e., after chromatographic separation of the corresponding

diasteroisomeric mixtures. The opposite enantiomers of these compounds were prepared by the same procedure from (*S*)-(–)-**104** and (*S*)-(–)-**105**, after esterification of the carboxylic group with diazomethane.



Scheme 20

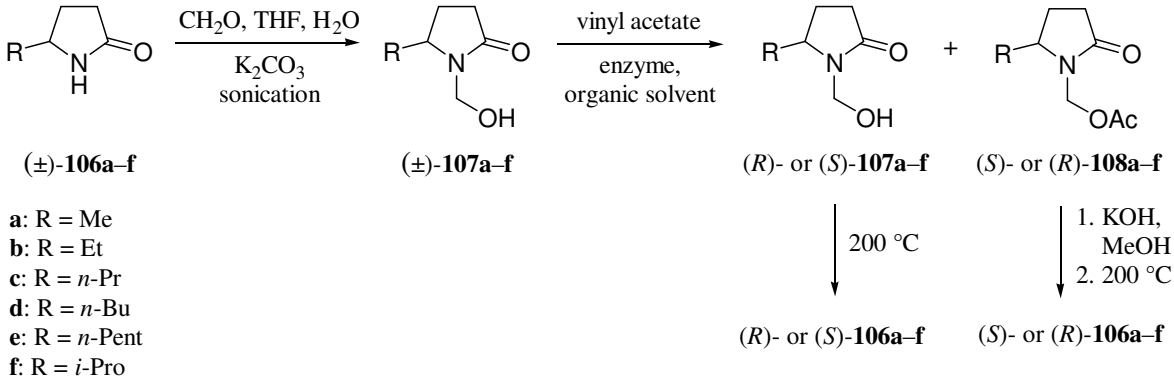
9. Enzymatic resolution of N-hydroxymethyl γ-butyrolactams

The functionalization of the lactamic nitrogen by the hydroxymethylene group was first reported by Rousseau[104] as an expedient to allow the enzymatic kinetic resolution of a series of 5-alkyl substituted 2-pyrrolidinones. The CH_2OH function was chosen as it can be quantitatively introduced by common reagents (HCHO, K_2CO_3, H_2O, sonication) and it can be removed easily under basic conditions (NH_4OH, MeOH, heating) after the enzymic transformation.

In the work published by Rousseau the substrates **106a–f**, after being transformed into **107a–f** were subjected to enzymic transesterification with vinyl acetate in organic solvent (Scheme 21).

PL-HSC (Lipase from Pseudomonas Cepacia immobilized on Hyflo Super Cel®) gave the most significant results. In particular the lactam (±)-**107a** was transformed with the highest enantioselectivity (E = 97) in *n*-pentane. Under these conditions, the resulting acetate (*S*)-**108a** was isolated at 44% conversion with 94% e.e., while the unreacted alcohol (*R*)-**107a** had 75% e.e..

For the other 5-alkyl-substituted derivatives **107b–f**, excellent results were obtained when TBME (*tert*-butyl methyl ether) was used as the solvent. The alcoholic compounds (*R*)-**107b–e** and (*S*)-**107f** were isolated at 50% conversion with e.e. up to 98%, while the corresponding acetates **108b–f** with opposite configuration exhibited e.e.'s in the range 86-93%.

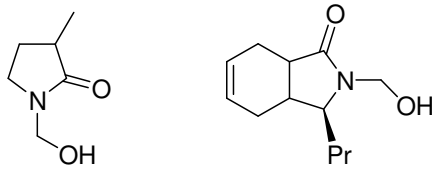


Scheme 21

The enzymic resolutions were followed by removal of the nitrogen protecting group, giving access to the corresponding optically active 5-alkyl-2-pyrrolidinones **106a–f**.

The proximity of the reacting OH group to the chiral centre seemed to be crucial for the stereoselectivity of the enzyme. In fact 1-hydroxymethyl-3-methyl-2-pyrrolidinone **109** (Figure 8) was transformed under the same conditions with very low enantioselectivity.

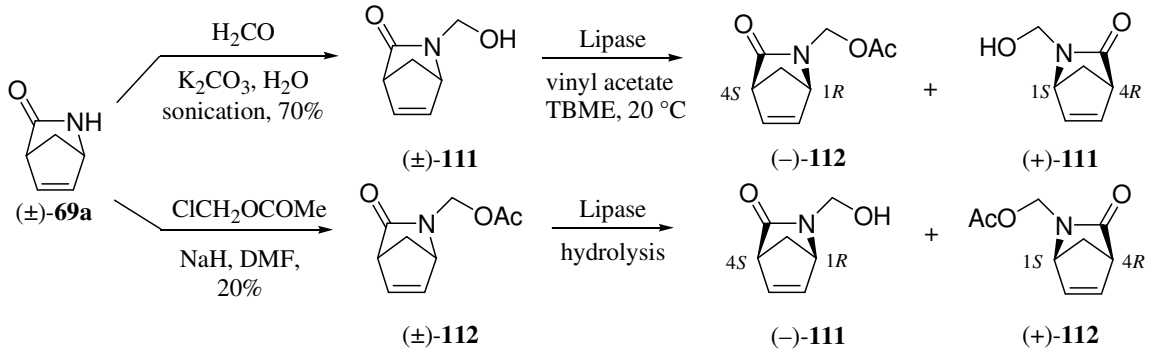
The methodology described is not limited to monocyclic γ-lactams. The bicyclic compound **110** (Figure 8) bearing three asymmetric centres, was resolved under the same conditions as above to give the remaining alcohol derivative with 90% e.e. and the corresponding acetate product with 80% e.e. at 47% conversion (E = 48).



109 **110**

Figure 8

Later Hongo[105] and coworkers extended this method to the resolution of the racemic carbonucleoside precursor 2-aza-bicyclo[2.2.1]hept-5-en-3-one **69a**, by resolution of the corresponding *N*-hydroxymethyl derivative **111** under enzymatic transesterification conditions and by resolution of the *N*-acetoxymethyl derivative **112** under enzymatic hydrolytic conditions (Scheme 22).



Scheme 22

Transesterification with vinyl acetate in TBME was attempted with different Lipases, but the highest degree of enantioselectivity and the best activity was shown by Lipase PS. By stopping the reaction at approximately 50% conversion, the acetate (–)-**112** was isolated with 94% and 38% yield (93% e.e. and 43% yield using imm-PS on diatomite), with recovering of (+)-**111** with 89% e.e. (98% with imm-PS on diatomite) and good yield (40% and 48% respectively).

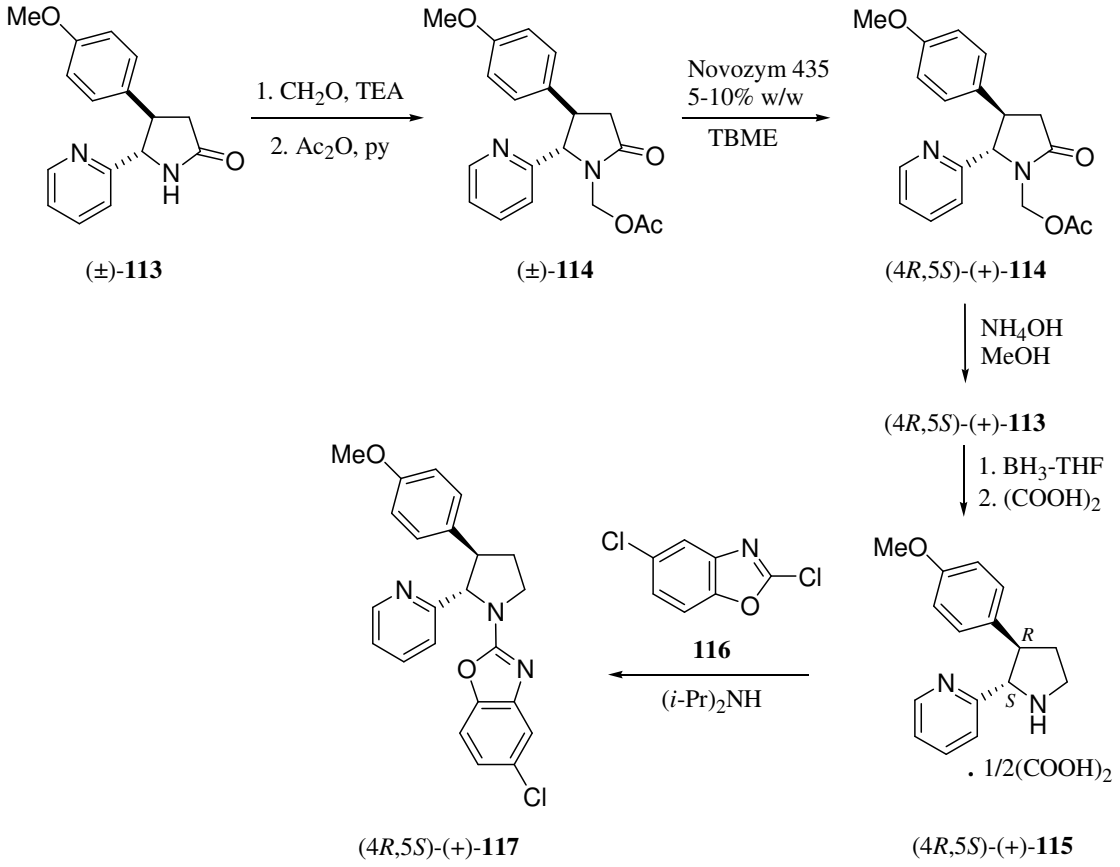
In the reverse reaction (Scheme 22), the alcohol (–)-**111** (41% yield, 95% e.e.) was obtained as the Lipase PS-mediated hydrolysis of (±)-**112**, with recovery of (+)-**112** with 41% yield and 96% e.e..

The chiral alcohol (–)-**111** and the corresponding acetate (–)-**112**, having the requested (1*R*,4*S*) absolute configuration, were transformed into (–)-**74a**, precursor of (–)-carbovir.

A practical synthesis of the optical pure Leukotriene B4 inhibitor BIRZ-227 **117**, a candidate for treatment of inflammatory disorders such as asthma, arthritis, inflammatory bowel diseases and psoriasis,

was reported in 1998 by Yee.[106] The intermediate of the synthesis was the *trans*-4,5-disubstituted pyrrolidinone (±)-**113** which was prepared as a racemic modification in a large scale (9.1 kg, 52% yield).

Hydroxymethylation of (±)-**113** (37% CH_2O, TEA, THF), followed by acetylation (Ac_2O, Py) gave 1-acetyloxy-2-pyrrolidinone (±)-**114**. This was used as a substrate for hydrolysis which was performed on a microscale in the presence of immobilized Novozyme 435 (50% = 2M *i*-Pr_2O-H_2O, rt), to give (4*R*,5*S*)-(+)-**114** with 97% e.e. and 32% yield, after chromatographic purification. Transformation of this latter compound into the pyrrolidine derivative (4*R*,5*S*)-(+)-**115** was accomplished by removal of the nitrogen protecting group and reduction of the carbonyl group. Subsequent reaction of (4*R*,5*S*)-(+)-**115** with 2,5-dichlorobenzoxazole **116** gave the targeted compound (4*R*,5*S*)-(+)-**117** (Scheme 23).



(±)-**113** (±)-**114** (4*R*,5*S*)-(+)-**114**

(4*R*,5*S*)-(+)-**113**

(4*R*,5*S*)-(+)-**117** (4*R*,5*S*)-(+)-**115**

Scheme 23

Optimized experimental conditions, involving non-chromatographic separation of the products, were found for the accomplishment of the process on multikilogram scale.

Resolutions of γ-lactams *via* their *N*-hydroxymethylderivatives were successfully applied also to β-lactam derivatives.[107]

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RING EXPANSION AND RING OPENING OF AZETIDINES

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Abstract. *The reactivity of azetidines, which is mostly a result of the ring strain of this four-membered heterocycle, is reviewed. The first part focuses on ring expansions into 5-, 6- and 7-membered aza-heterocyles while nucleophilic opening of activated azetidines (e.g., azetidinium ions) is discussed in the second part. This survey of the literature (up to July 2005) puts emphasis on the highly chemo- and regioselective mechanistic pathways that can be achieved with these underrated heterocycles.*

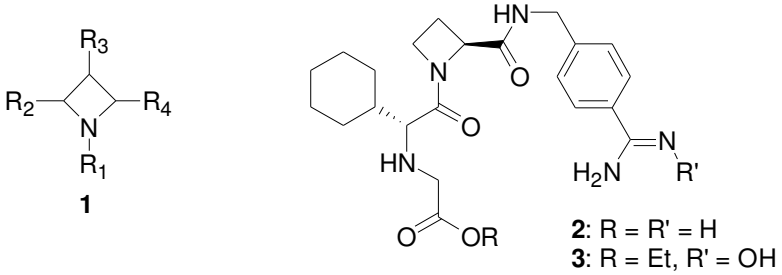
Contents

1. Introduction

Azetidines **1**, *i.e.* saturated four-membered nitrogen heterocycles belong to a little studied class of heterocycles. In the organic chemist's mind, these compounds often suffer from a preconceived unfavorable reputation as regards their difficult preparation, mainly associated with the ring strain present in this four-

membered ring, and their uncontrollable reactivity, also associated with this strain. As a matter of fact, the literature concerning the preparation[1] and the reactivity of this heterocycle is not abundant, especially when compared to the impressive number of publications dedicated to their lower or higher homologues, aziridines, pyrrolidines and piperidines.[2] Nonetheless, the interest in this heterocycle is growing, especially within pharmaceutical companies since their original structure, together with their scarce description in the chemical literature make them attractive patent targets. Well-known examples of biologically active azetidines are AstraZeneca's thrombin inhibitors Melagatran®**2** and Exanta®**3**[3] which incorporates an azetidine-2-carboxylic acid framework: the discovery of these new drugs has considerably boosted the disclosure of patents for the production of this amino acid in enantiomerically pure form.[4]

This review will focus on the reactivity of the azetidine ring associated with its strain,[5] first surveying the literature dealing with ring expansion reactions of this heterocycle, which lead to 5-, 6-, or 7-membered nitrogen heterocycles and, in the second part, covering ring opening reactions, which give acyclic amines. No doubt this "exotic" heterocycle, for which efficient syntheses under enantiomerically pure form have been recently reported[6] will play a growing part as a key intermediate for the preparation of nitrogen containing compounds in the near future.



Scheme 1

2. Ring expansion of azetidinic compounds

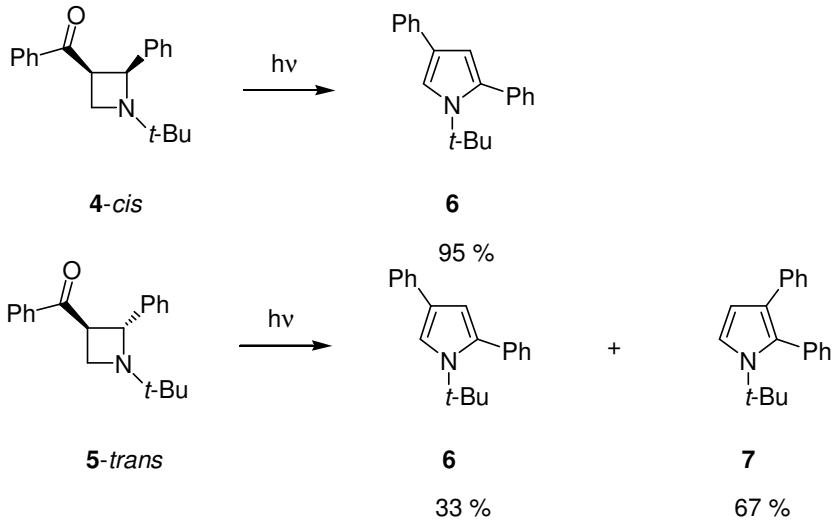
The ring strain of azetidines mostly accounts for their reactivity. Therefore, in order to release this strain, ring expansions are favoured processes from a thermodynamic and kinetic viewpoint. Depending either on the mechanism involved or the nature of the substituent of the ring, rearrangements can lead to five, six or even seven-membered rings. The reactions presented in this section will be classified according to the nature of the ring formed, trying to demonstrate that this strain release can be controlled, therefore leading to very selective reactions.

2.1. Four-membered to five-membered ring expansions

2.1.1. Expansions to pyrroles, pyrrolidinones and pyrrolidines

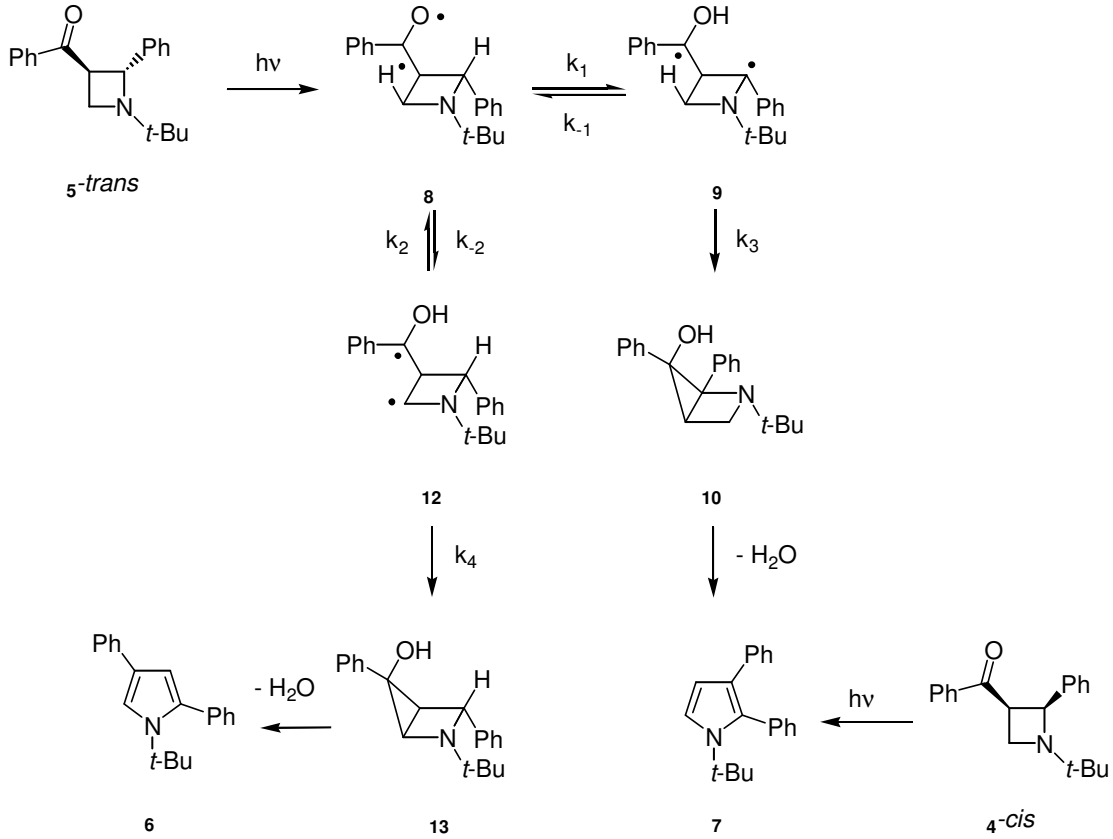
The study of these ring expansions has been somewhat hampered by the avaibility of functionnalized azetidines and has only begun quite recently. To the best of our knowledge, Padwa reported the first example of such a process in the early 1970's:[7] the irradiation under UV light of *N-tert*-butyl-2-phenyl-3-benzoylazetidine **4**-*cis* and **5**-*trans* respectively led to pyrrole **6** or to its mixture with regioisomeric pyrrole **7** (Scheme 2).

The striking difference of reactivity between these two diastereoisomers, giving, with high yield, a unique compound in the case of **4**, and two regioisomeric pyrroles in the case of **5** led the authors to investigate the mechanism of this reaction in detail.[8]



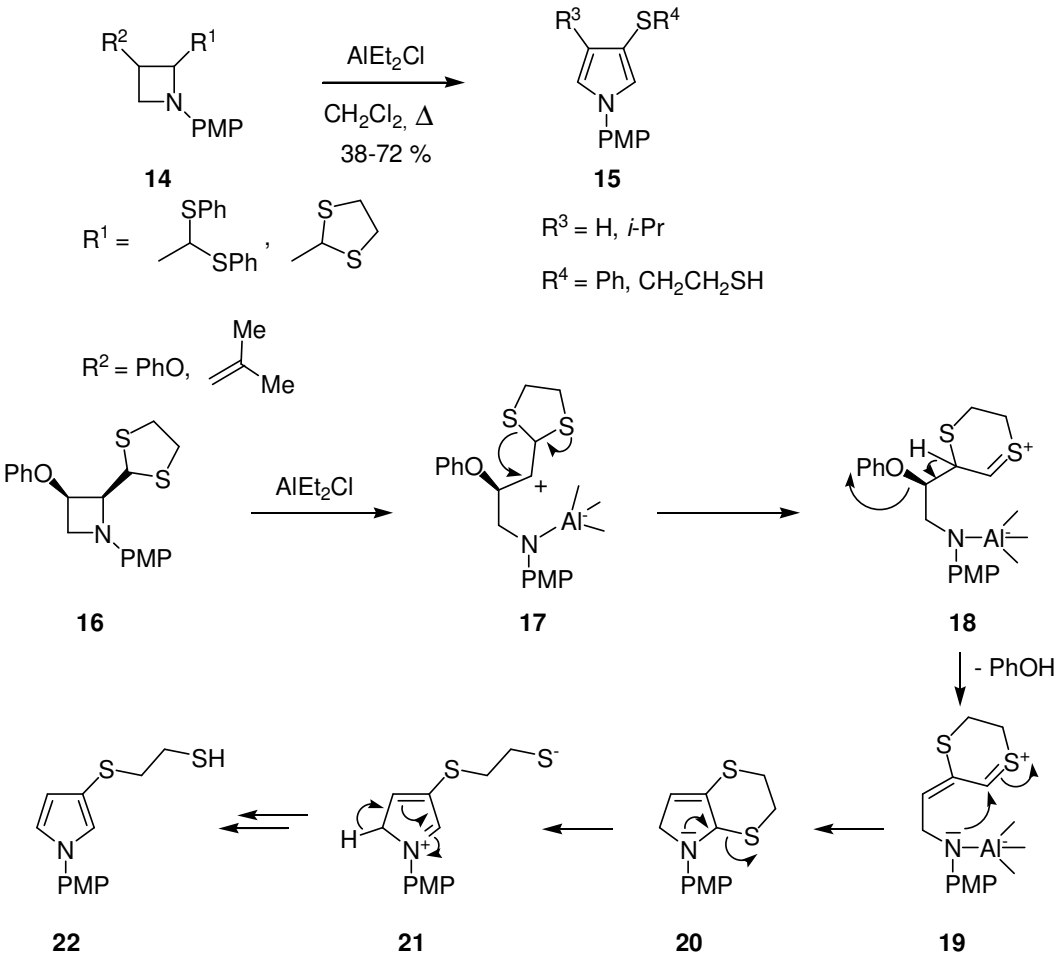
Scheme 2

Through kinetic studies and measurement of isotopic effects, they postulated as key step a 1,4-transfer of a hydrogen radical from an endocyclic carbon to the oxygen *via* the diradical intermediate **8**, followed by C-C bond formation, and aromatization by loss of water (Scheme 3). This mechanism not only explains the formation of **7** from **5** as the major product, since the abstraction of a benzylic hydrogen to give **9** occurs faster than the abstraction of hydrogen radical at the methylene position to give **12**, ($k_{1app} > k_{2app}$) but also explains the fact that the *cis* isomer **4** gives only one pyrrole since only one 1,4-hydrogen transfer is possible with this stereoisomer.



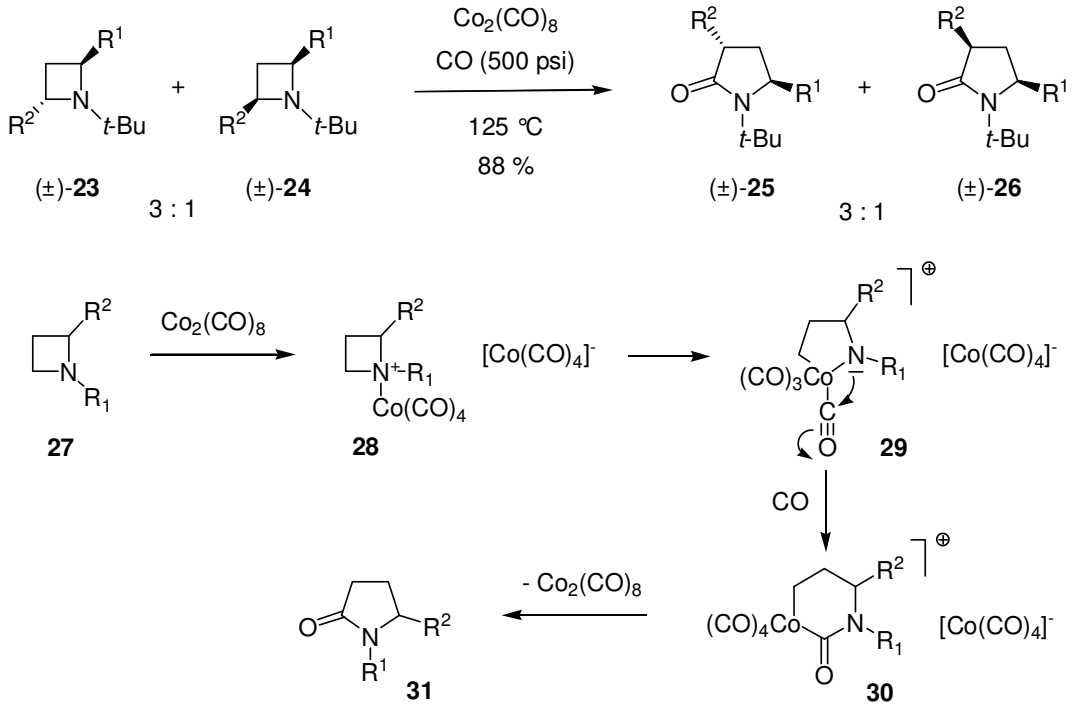
Scheme 3

Pyrroles have been also obtained more recently by Alcaide[9] upon treatment of 2-thioacetalazetidines **14** with $AlEt_2Cl$. However, the presence of a phenoxy or an isopropylidene substituent at C-3 of the azetidine ring is crucial for the rearrangement to take place, which somewhat narrows the scope of this reaction. The need for the latter substituent can be explained by the mechanism proposed by the authors which is summarized in Scheme 4, starting from phenoxy substituted azetidine **16**. Elimination of phenol within intermediate **18** allows for aromatization to occur stepwise after initial cleavage of the N-C_2 bond. If the substrate does not bear a phenoxy or isopropylidene substituent, the reaction goes through another path to give pyrrolidines (*vide infra*).



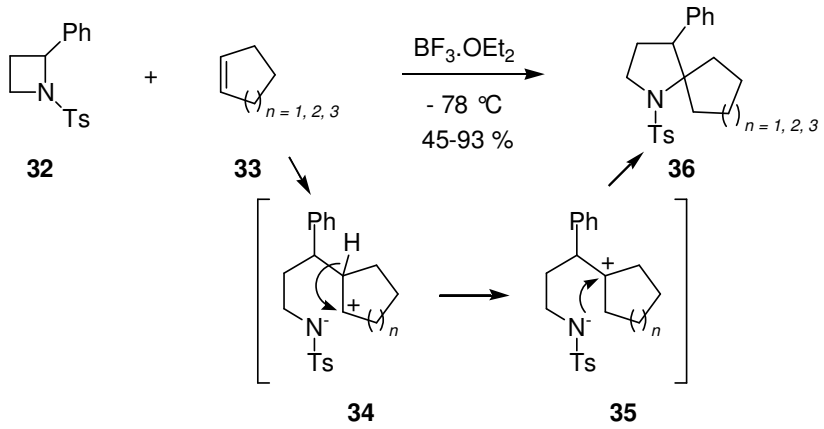
Scheme 4

Ring expansion of azetidines into pyrrolidin-2-ones can efficiently be done through cobalt-catalyzed carbonylation. This reaction, reported by Alper,[10] involves a stereospecific process since a mixture of 2,4-*cis* and 2,4-*trans* azetidines **23** and **24** produces an identical isomeric ratio of pyrrolidinones upon carbonylation. Moreover, the reaction is highly regioselective: after formation of ionic complex **27**, cobalt inserts within the less substituted C-N bond, probably to minimize the steric strain into metallacycle **29**. Carbon monoxide insertion into the Co-N bond leads to **30** and then to **31**, with catalyst regeneration (Scheme 5). It should be noted that this reaction was later applied to the ring expansion of aziridines into azetidin-2-ones (β-lactams).[11]



Scheme 5

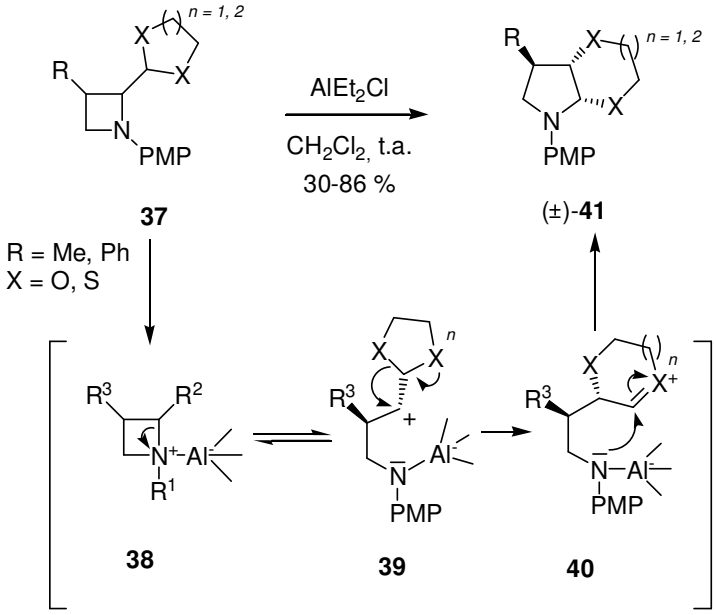
The ring expansion of azetidines into pyrrolidines has been further investigated. Mann[12] reported that *N*-tosyl-2-phenyl azetidine **32** reacts with cyclic alkenes in the presence of $BF_3{\cdot}OEt_2$ to give spiropyrrolidines. This reaction involves the cleavage of the azetidine ring which acts as a 1,4-dipole to give intermediate **34**. After a 1,2-hydride shift, ring closure gives the pyrrolidine **36** (Scheme 6). The nature of the alkene is of importance in this reaction since other substitution patterns lead to different pathways (*vide infra*).



Scheme 6

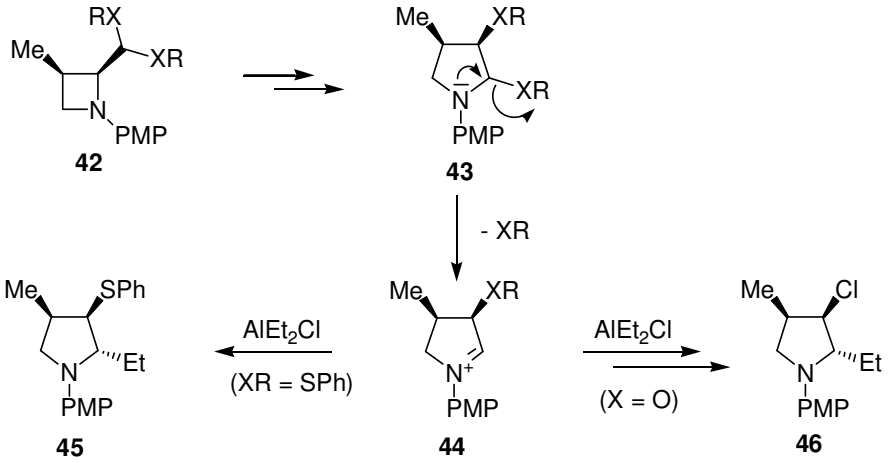
Alcaide[9] studied the ring expansion of functionalized azetidines in the presence of $AlEt_2Cl$ as we discussed earlier. The same group also reported that azetidines bearing an acetal or a thioacetal at C-2, and a methyl (or phenyl) group at C-3 rearrange stereoselectively into bicyclic pyrrolidines **41** when treated with the Lewis acid. This reaction is diastereoconvergent since both 2,3-*cis* or *trans* starting azetidines give the

same product. The mecanism proposed by the authors involves ring cleavage under the action of the Lewis acid, followed by rearrangement of the zwitterionic intermediate **39** to stereoselectively give **40**. Final ring closure gives the pyrrolidine **41**, in which the 2,3-*cis* relative stereochemistry is a result of an anomeric effect (Scheme 7).



Scheme 7

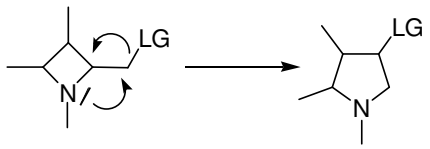
Under these conditions the behaviour of acyclic acetals and thioacetals is somewhat different: after production of a similar intermediate pyrrolidine **43** as described above, the Lewis acid promotes the formation of an iminium ion **44** which undergoes *trans*-selective addition of the ethyl group, delivered by the organometallic. In the case of an acetal (X = O), further substitution proceeds at the 3-position of the pyrrolidine, to give 3-chloro pyrrolidine **46** (Scheme 8).



Scheme 8

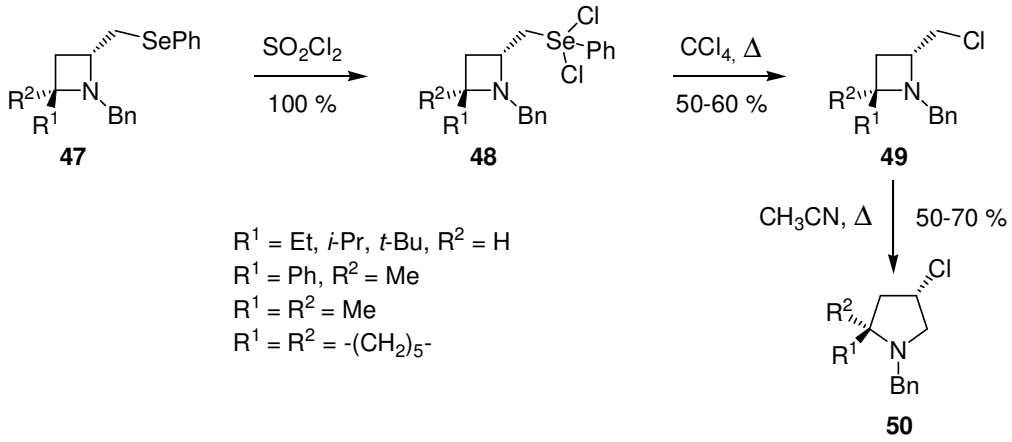
Pyrrolidines can also be obtained from azetidines through a thermal rearrangement. If the azetidine bears at the 2-position a suitable moiety able to act both as a leaving group (LG) and as a nucleophile, then

ring expansion can occur through an intramolecular reaction illustrated in Scheme 9. First examples of this rearrangement, previously known starting with homologous pyrrolidines,[13] and widely used for the synthesis of piperidines of biological relevance,[14] were recently reported by Outurquin[15] and ourselves.[16]



Scheme 9

Outurquin reported that 2-phenylselanylmethylazetidines **47**, when treated with sulfuryl chloride, give 2-chloromethylazetidines, through dichloroselenuranes **48**. Upon heating in acetonitrile, these primary chlorides rearrange into 3-chloropyrrolidine in a stereospecific way (Scheme 10).

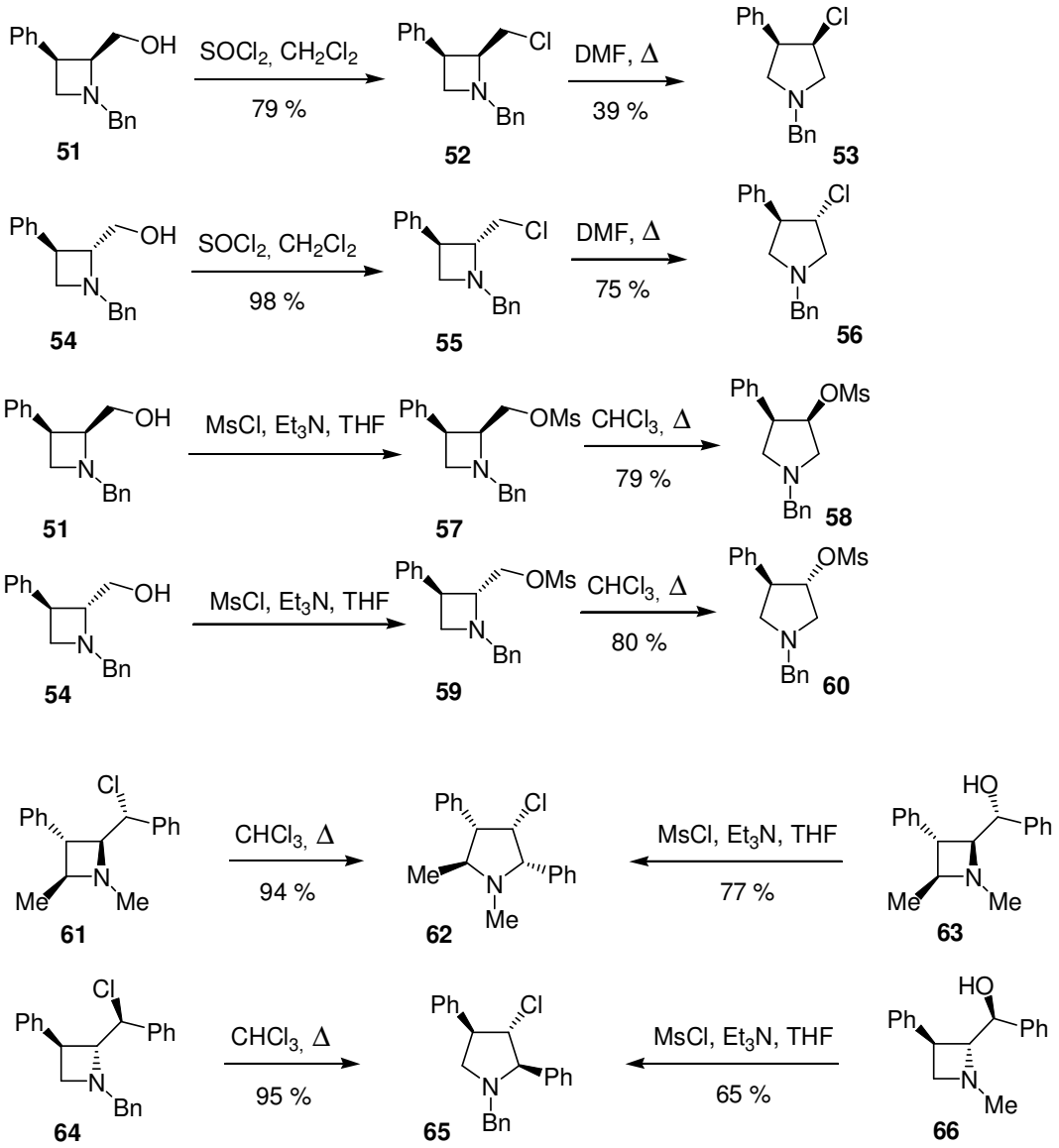


Scheme 10

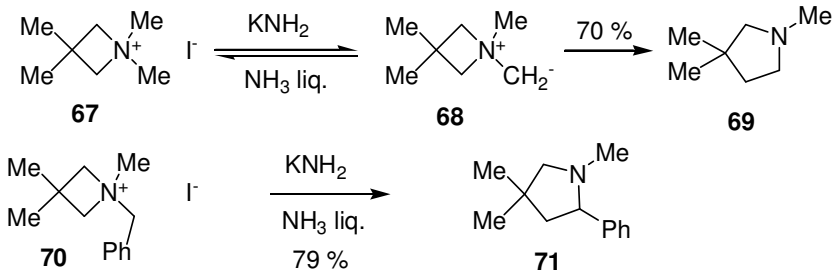
In our group, having devised a method for the stereocontrolled preparation of α-hydroxylated azetidines, we studied the behaviour of a set of primary, secondary and tertiary azetidinic alcohols involved in this ring expansion after activation of the hydroxyl group as a leaving group (chloride or mesylate). This reaction was found to occur stereospecifically and was general when primary and secondary alcohols were involved, as shown in Scheme 11, but failed to produce any rearranged product in the case of tertiary alcohols.

Pyrrolidines can also be produced from azetidines using the Stevens rearrangement of azetidinium ylides. Initial studies in this area where made in the early 1970's by Wills and Anderson[17] who demonstrated that treatment of 1,1,3,3-tetramethylazetidinium iodide **67** with potassium amide led to a unique compound **69** in good yield, resulting from the Stevens rearrangement of intermediate ylide **68**. Similarly, the *N*-benzyl azetidinium salt **70** gave 2-phenyl pyrrolidine **71** exclusively (Scheme 12).

Measurements of primary and secondary kinetic isotopic effects involving various deuterated azetidinic substrates unambiguously showed that the mechanism of this rearrangement follows the now commonly admitted one, *i.e.*, (*i*) formation of the ylide, which is the rate determining step, then (*ii*) concerted rearrangement of the ylide involving a diradical intermediate stabilized within a solvent cage.[18]



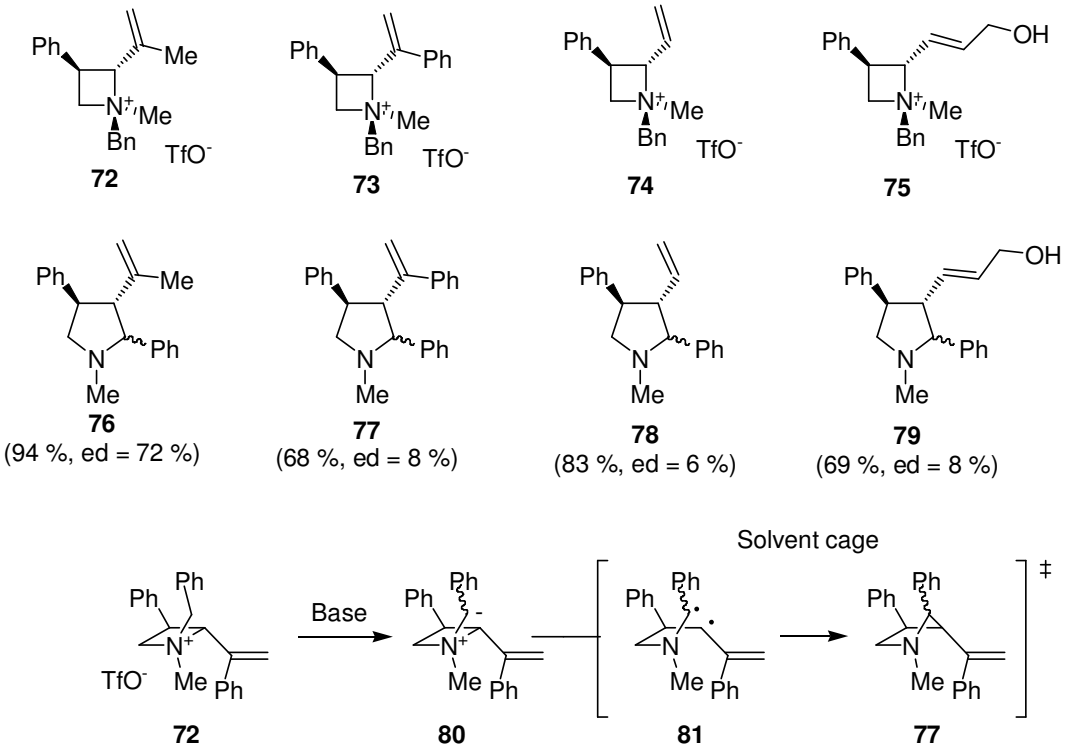
Scheme 11



Scheme 12

We recently contributed to the knowledge of this reaction, demonstrating its regio and diastereoselectivity.[19] For this, a set of 2-alkenyl azetidines **72**-**76** was prepared stereoselectively from the corresponding 2-cyano azetidines. Treatment of these azetidinium salts with LiHMDS in THF led to the selective deprotonation of the benzylic ammonium and the produced ylides undergo a Stevens rearrangement in a regio- (exclusive N-C_2 cleavage) and stereoselective (conservation of the configuration of the migrating

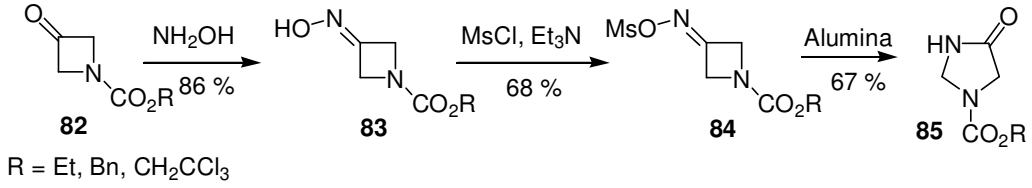
carbon) manner. The pyrrolidines **75**-**79** were produced as mixture of isomers at C-2, probably resulting from a non-selective abstraction of the diastereotopic benzylic protons in the initial ammonium salt (respectively **72**-**76**) (Scheme 13). The mechanism of this reaction is depicted in the same Scheme.



Scheme 13

2.1.2. Expansions to imidazolidinones

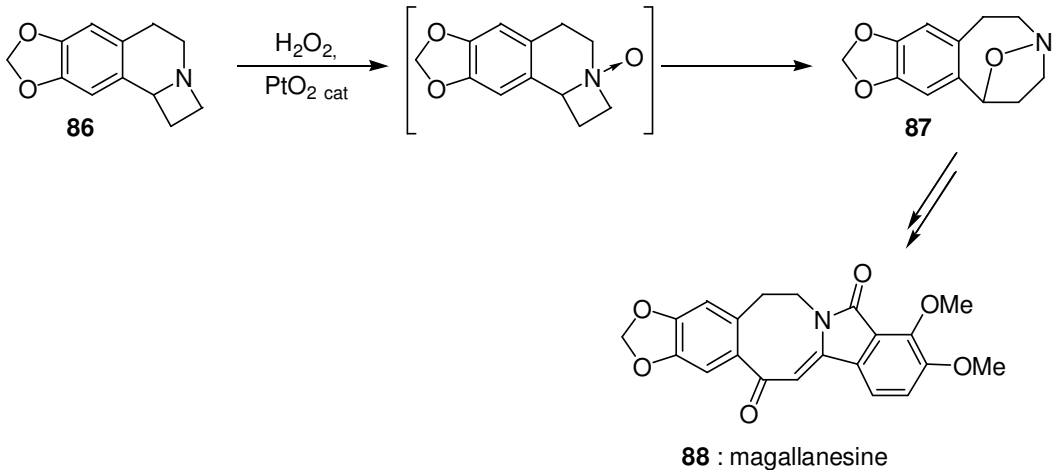
The chemistry of azetidin-3-ones has been reviewed recently.[20] These compounds can be enlarged into 4-imidalozidinones using the Beckmann rearrangement under mild conditions.[21] Thus, treatment of oxime derivative **84** on alumina affords 4-imidazolidinone **85** in fair yield. This is, to our knowledge the only example of ring enlargement of azetidinic derivatives into polyheteroatomic five-membered rings (Scheme 14).



Scheme 14

2.1.3. Expansions to isoxazolidines

An especially elegant use of ring rearrangement of azetidines has been reported *en route* to Magallanesine: the unstable azetidine N-oxide obtained by oxidation of **86**, undergoes a Meisenheimer rearrangement yielding isoxazolidine **87**, a precursor to the eight membered ring of Magallanesine **88** (Scheme 15).[22]

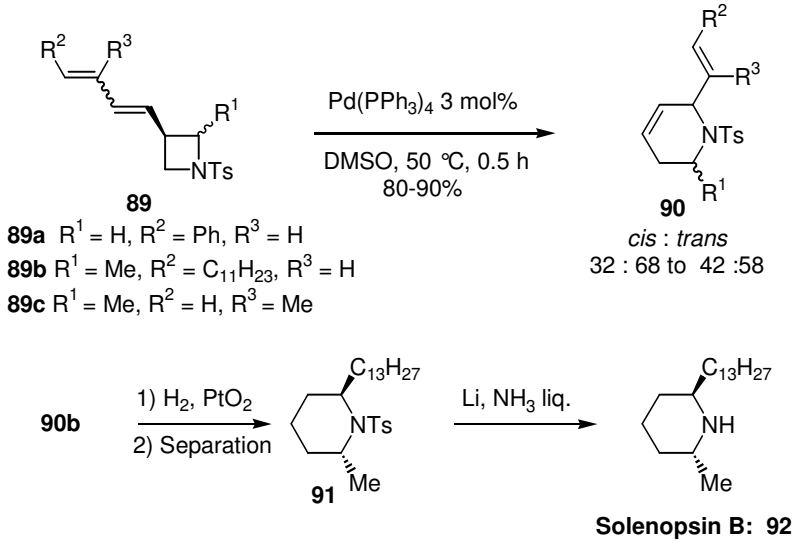


Scheme 15

2.2. Four-membered to six-membered ring expansions

2.2.1. Expansion to piperidines

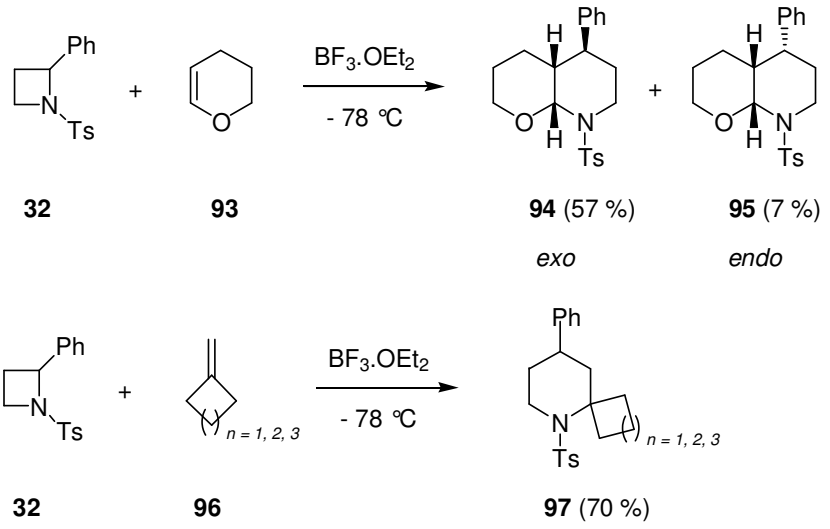
To the best of our knowledge, two examples of such ring enlargements have been described so far in the literature. The first example relies on the use of *N*-tosyl-2-alkadienyl azetidines **89**.[23] When treated with Pd catalyst, these substrates undergo ring opening with formation of a π-allyl intermediate. Ring closure finally affords a piperidine ring in high yield but with low 2,6-diastereoselectivity. It should be noted that this kind of process was found to occur also with aziridines,[23] giving the corresponding pyrrolidines with higher 2,5-diastereoselectivity. This reaction was used for the synthesis of a natural piperidine Solenopsin B **92** produced by the red ant *Solenopsis saevissima*, in its racemic form (Scheme 16).



Scheme 16

Another ring expansion to piperidines was reported by Mann.[12] As commented upon in section **2.1.1.** (extension to pyrrolidines), pyrrolidines could be obtained by reaction of *N*-tosyl-2-phenyl azetidine **32** with cycloalkenes. However, **32** undergoes a formal [4+2] cycloaddition when reacted with dihydropyrane **93** or exomethylene cycloalkanes **96**, to respectively give diastereoisomeric piperidines **94** and **95** or

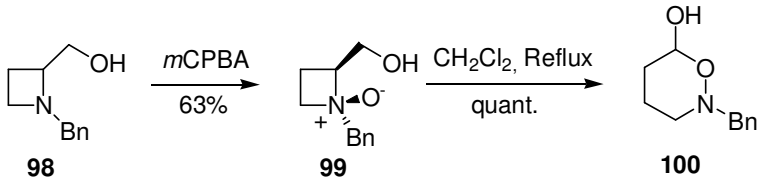
spiropiperidines **97**. Note that the 2,3-*cis* diastereoselectivity in **94** and **95** is explained by the authors on the basis of an anomeric effect that stabilises these diastereoisomers. Similar reactions had been previously carried out successfully with *N*-tosyl-2-phenyl aziridines.[24]



Scheme 17

2.2.2. Expansion to 1,2-oxazin

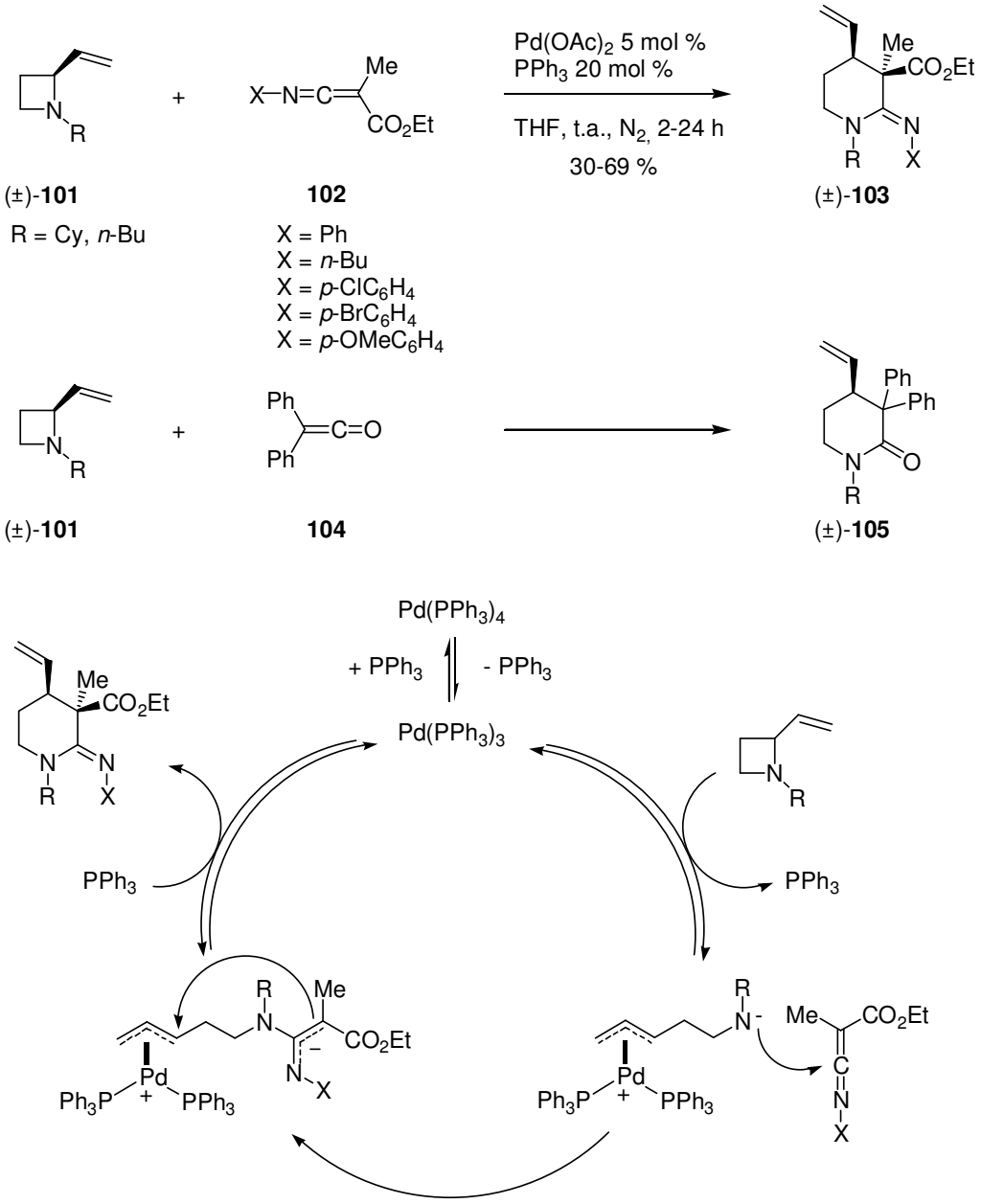
A single example of the ring expansion of an azetidine derivative into a 1,2-oxazin has been reported by O'Neil.[25] This reaction takes place with an azetidine *N*-oxide **99**, prepared by *m*CPBA oxidation of the corresponding amine **98**. This crystalline azetidine, upon attempted recrystallization in boiling DCM underwent quantitative transformation into 6-hydroxy oxazin **100**, whose structure was confirmed by X-ray radiocrystallography. Formation of this compound, as suggested by the authors, results either from a Cope-type elimination, followed by tautomerism of the enol into aldehyde and lactol formation or from a direct [1,2] rearrangement (Scheme 18).



Scheme 18

2.2.3. Expansion into piperidine-2-ones or 2-iminopiperidines

Alper[26] recently reported the ring expansion of 2-alkenylazetidines into 2-iminopiperidine **103** or piperidin-2-one **105**, when reacted with heterocumulenes such as respectively **102** or **104** in the presence of a Pd(II) catalyst. This reaction is favoured when the heterocumulene is electron poor, and the alkyl group on the nitrogen of the azetidine is not too bulky. Regio- as well as stereo- selectivities of this reaction are excellent and particularly striking is the total diastereoselectivity observed during the formation of **103**: only the isomer showing a *cis* relationship between the ester and vinyl moieties is produced. The catalytic cycle of this interesting reaction, previously reported in the case of 2-vinyl aziridines[27] is shown in Scheme 19.



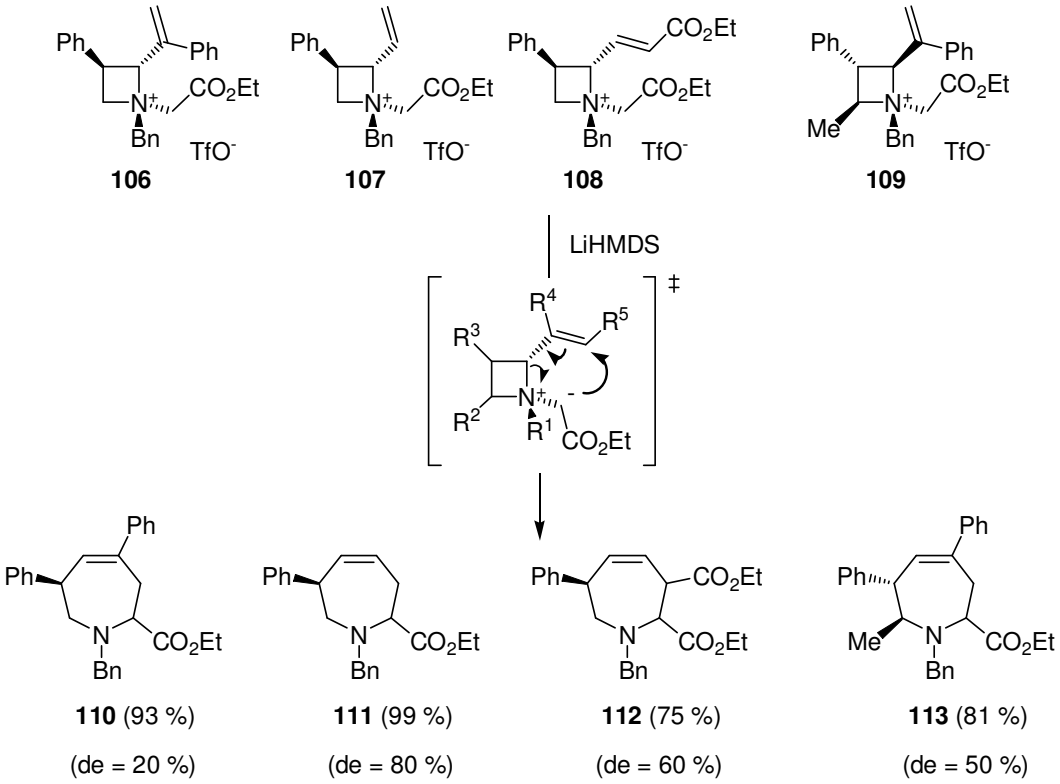
Scheme 19

2.3. Four-membered to seven-membered ring expansions

2.3.1. Expansion into azepanes

Azepanes can be produced in good yield from 2-alkenyl azetidinium salts.[28] When azetidinium salts **106**-**109** are reacted with LiHMDS in THF, a [2,3] sigmatropic rearrangement involving the ylide produced by a chemoselective deprotonation α to the ester moiety gives respectively azepanes **110**-**113**. It is interesting to note that no trace of pyrrolidines resulting from a Stevens rearrangement can be detected in these reactions (compare with the ring expansion in Scheme 13). The relative configuration of the ylide with respect to the adjacent alkenyl moiety has a dramatic effect on the outcome of the reaction: with a *cis*-relationship such as in ylides derived from **106**-**109**, azepanes are formed. However, when those two groups possess a *trans*-relationship such as in the ylides derived from **75**-**78** (Scheme 13), then exclusive formation of pyrrolidines is observed through a Stevens rearrangement. This difference in reactivity exemplifies the influence of the

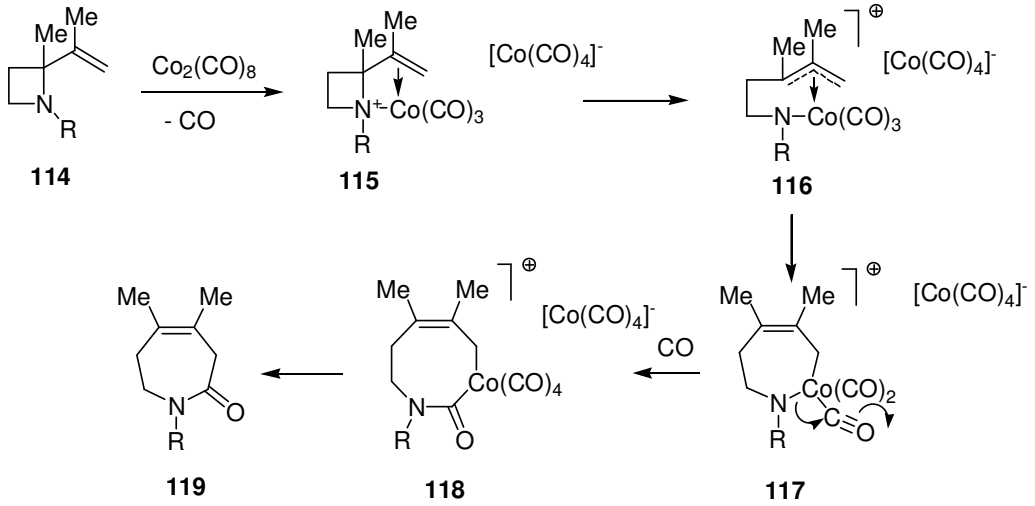
relative stereochemistry of azetidinic substrates on these mechanistic pathway and clearly illustrates that high chemoselectivity can be reached with these compounds (Scheme 20).



Scheme 20

2.3.2. Expansion to azepane-2-ones

As mentioned before, pyrrolidin-2-ones can be produced by cobalt-catalyzed carbonylation of azetidines (Scheme 5). However, when the latter possess an insaturation at C-2, azepan-2-ones **119** are produced using this cobalt-catalyzed carbonylation, as reported by Alper.[10] The mechanism suggested by the authors, depicted in Scheme 21, involves the formation of a cationic π-complex **116**.



Scheme 21

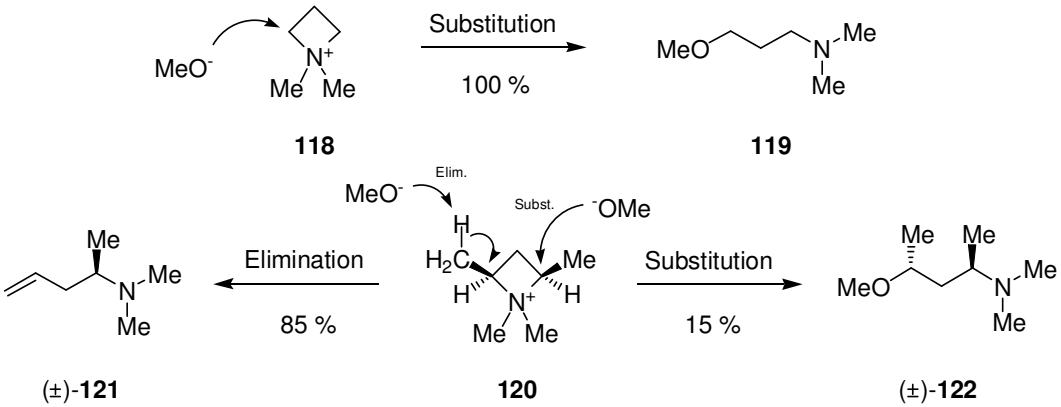
Ring-closure under carbon monoxide pressure then gives the eight-membered metallacycle **118** that undergoes a reductive elimination to give the azepan-2-one (Scheme 21). The dramatic change in reactivity induced by the presence of the additional alkene substituent clearly demonstrates that a simple change in the nature of a group on the azetidine ring can totally change the reactivity of this heterocycle since no pyrrolidin-2-ones were obtained starting with these 2-alkenylazetidines (see Scheme 5).

Besides the rearrangement of the azetidine skeleton to larger ring systems, another part of their reactivity relies on the nucleophilic ring opening of these azetidines, which will be presented in the following section. Reactions in this section will be classified according to the nature of the nucleophile.

3. Nucleophilic ring opening of azetidinic compounds

3.1. Introduction

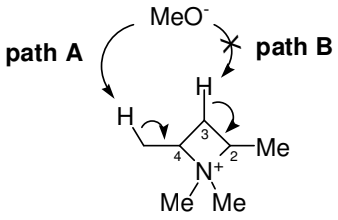
The nucleophilic ring opening of three-membered heterocycles is a basic tool in organic synthesis and such reactions have been recently reviewed for aziridines,[29] highlighting their high synthetic potential. However, the nucleophilic opening of their higher homologues, azetidines, remains largely unexplored. A major reason for this probably lies in the lower ring strain in azetidines compared to aziridines. As a consequence, and this will be the focus of the next section, the nucleophilic ring opening of an azetidine only occurs upon strong activation of the amine moiety by the mean of a Lewis or Bröndsted acid or, even better, after quaternization. However, when activated as azetidinium salts, they possess a unique and quite astonishing reactivity towards nucleophiles as first demonstrated by Illuminati in the early 1980's.[30] In fact, detailed kinetic studies showed that azetidinium salts such as **118** or **120** open much more rapidly than the equivalent pyrrolidinium or piperidinium salts (25 to 1000 times faster) when reacted with sodium methoxide. As a consequence, substitution occurs exclusively within unsubstituted azetidinium **118** and **120** gives a mixture resulting from a substitution (leading to **122**) but also from an elimination (to give **121**) while no trace of substitution product derived from disubstituted homologous salts related to **120** can be observed (Scheme 22).



Scheme 22

This detailed study emphasizes the detrimental effect of α substitution of the azetidinium ring with respect to nucleophilic opening, since ring opening of azetidinium salt **120** occurs 200 times slower compared to the unsubstituted analogue **118**. Also noteworthy is the total absence of elimination resulting from endocyclic process (path B in Scheme 23) which diminishes the chance of formation of by-products

when using these strained compounds as electrophiles. In this case, Hoffman elimination is probably prohibited by the high activation energy of this process since the proton to be eliminated and the ammonium leaving group cannot adopt a *trans* coplanar relationship due to the nature of the azetidine ring. This work summarises perfectly the main characteristics of the reactivity of these salts towards nucleophiles. However, still probably due to the lack of general methods for the preparation of azetidines, only few applications have emerged so far in synthesis.



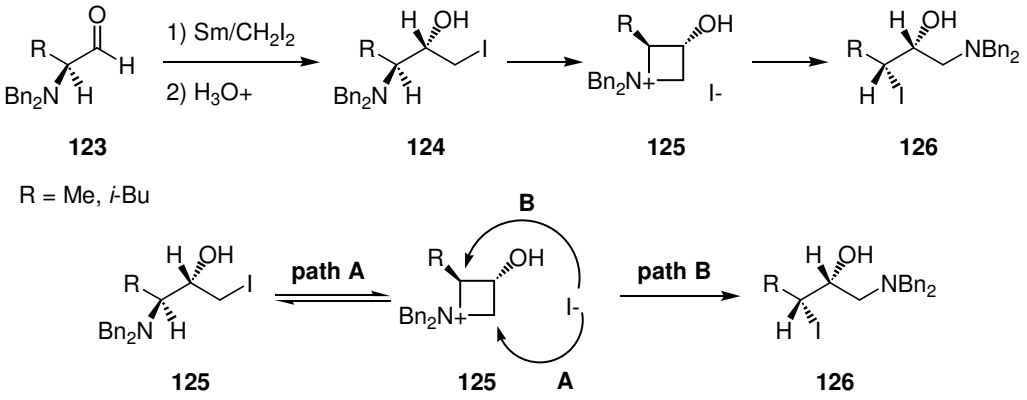
Scheme 23

3.2. Ring opening with heteroatomic nucleophiles

Heteroatomic nucleophiles are the most common class of nucleophiles used for the ring opening of activated azetidines, especially halides, oxygen, nitrogen or sulfur nucleophiles which will be discussed in this order in the following paragraphs.

3.2.1. Opening with halide nucleophiles

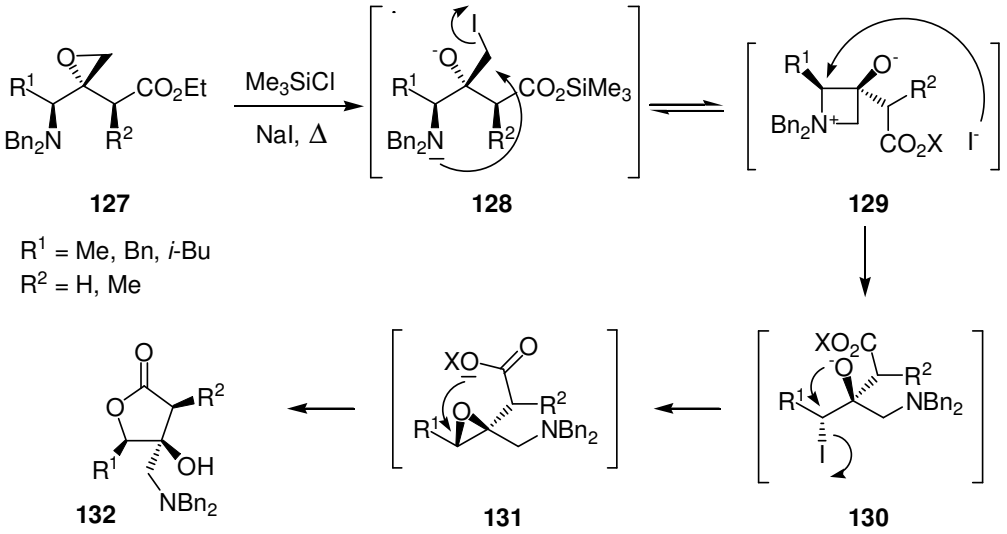
In the course of his study of iodomethylation of α-aminoaldehydes with diiodomethane induced by samarium diiodide, Concellón[31] noticed that azetidinium iodides **125**, produced from primary iodides **124** by intramolecular alkylation, were not stable and spontaneously gave iodohydrin **126** through a nucleophilic opening of the azetidinium salt by the iodide anion, the later attacking the unsubstituted position (path A, Scheme 24). This regioselectivity is in fact the result of a thermodynamic control of the reaction, since the produced secondary iodide is much less reactive towards intramolecular alkylation and does not go back to the azetidinium salt. Therefore, iodide anion is sufficiently nucleophilic to react with azetidiniums and the absence of epimerisation in this process precludes the intervention of a S_N1 mechanism.



Scheme 24

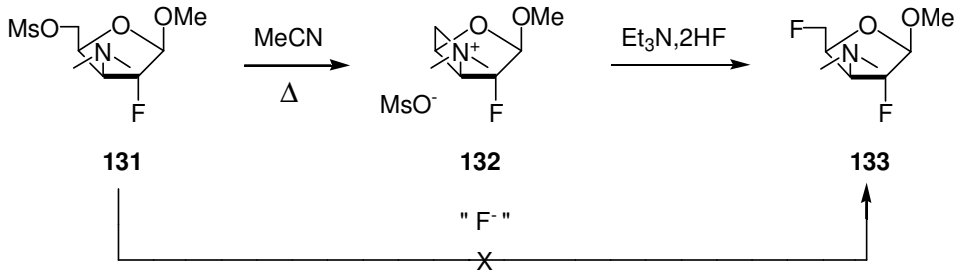
Concellón used this new rearrangement to devise a synthesis[32] of β-hydroxy-γ-butyrolactones **132**. In this process, transesterification of ester **127** in the presence of TMSCl and sodium iodide and concomitant

opening of the epoxide by the iodide anion gives **128** that evolves stepwise to butyrolactone **132** as depicted in Scheme 25.



Scheme 25

Such nucleophilic opening of azetidinium salts was used by Giudicelli *et al.*[33] to prepare fluorinated derivative **133**. Thus, intramolecular alkylation of mesylate **131** gave azetidinium salt **132**, which reacted with 2HF·Et_3N complex, to give **133**, resulting from a nucleophilic opening of the salt at the least hindered position (Scheme 26). Note that direct substitution of the starting mesylate **131** by fluoride anion proved ineffective.

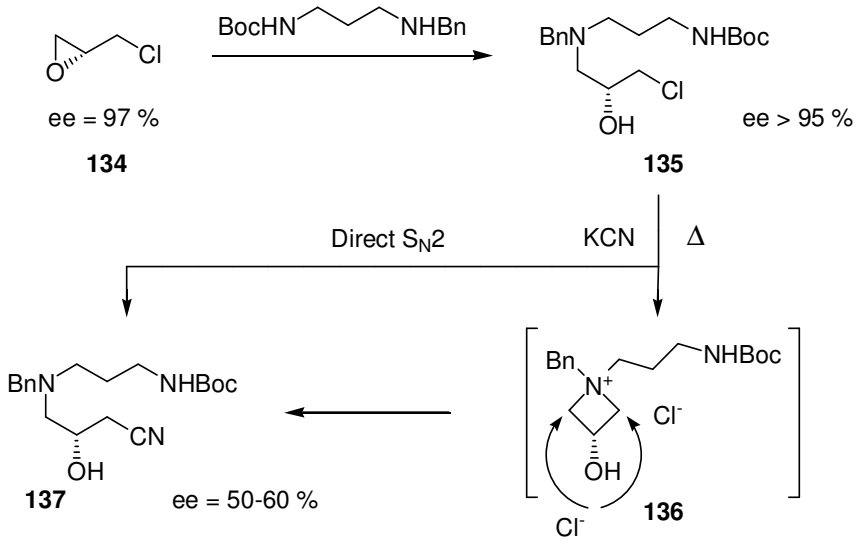


Scheme 26

If the previous example was found to be beneficial in terms of synthetic efficiency, such nucleophilic opening by halides can result in unpleasant surprises and therefore have to be taken into account. In the course of his synthesis of 3-hydroxyspermidin,[34] Overman and coworkers tried to carry out the nucleophilic substitution of primary chloride in **135** by cyanide anion. To their surprise, they found that the obtained cyanide **137** had partially racemized in the process, which could be explained by the competitive formation of an achiral azetidinium salt intermediate **136**, which is then opened by the chloride (or cyanide) anion (Scheme 27).

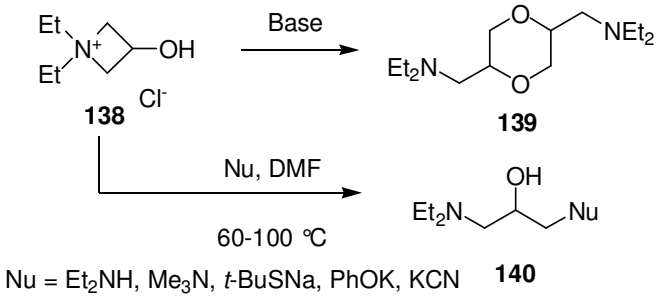
3.2.3. Opening with oxygen nucleophiles

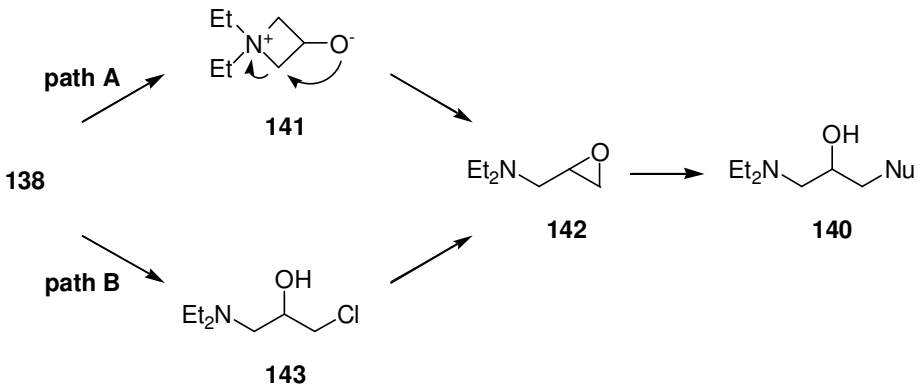
The earliest studies on the nucleophilic opening of azetidinium salts mainly involved alcohols or alkoxides as nucleophiles and Gaertner[35] and Leonard[36] both pioneered this area. Gaertner studied the mechanism of dimerisation of 3-hydroxyazetidinium **138** into 1,4-dioxane **139**.



Scheme 27

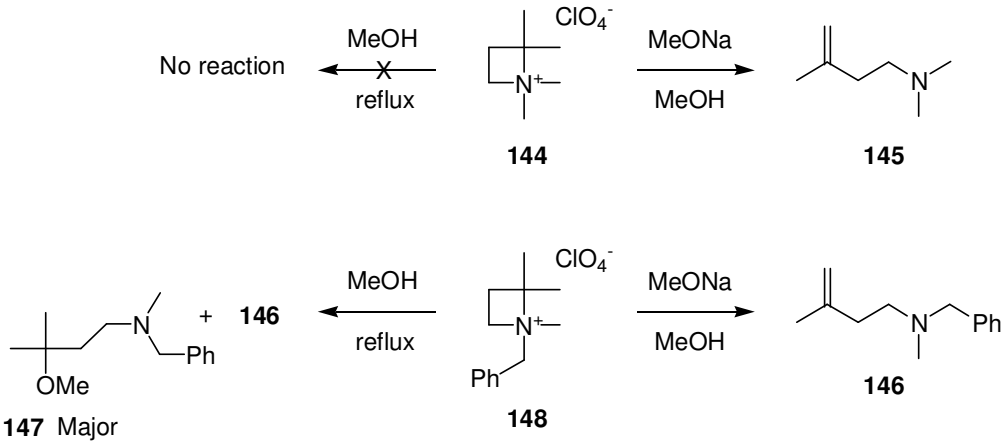
Moreover, he observed that a range of nucleophiles reacted with this salt, to give in good yields the corresponding acyclic amine **140**. Although a direct intermolecular substitution could account for the formation of **140** (and **139**) alternative mechanisms can also be envisioned. The first one involves an intramolecular ring opening to give epoxide **142** which is further opened by the nucleophile (path A in Scheme 28). The second possible mechanism involves a nucleophilic opening by chloride anion yielding to chlorohydrin **143** which next cyclizes to epoxide **142** (path B in Scheme 28). Trifluoromethanesulfonate salts having the same behavior as chloride salt **138**, path B could be discarded; path A however remains a possible mechanism.





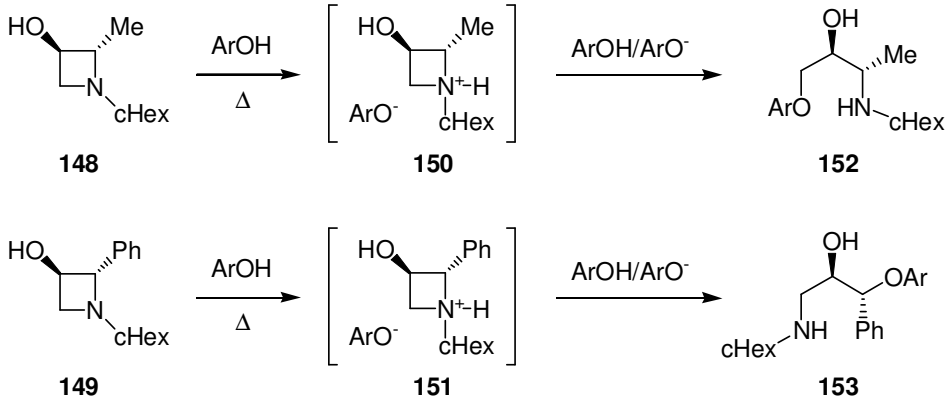
Scheme 28

Gaertner also studied the reactivity of α-disubstituted azetidinium salts **144** and **148** in the presence of methanol or sodium methoxide (Scheme 29). Although **144** was stable in refluxing methanol and underwent exclusive Hofmann elimination yielding **145** in the presence of sodium methoxide, the behavior of *N*-benzylated ammonium salt **148** was different: it reacted smoothly, presumably through a S_N1 process, to regioselectively give **147** together with some elimination product **146**. This example again shows that slight variations of substituents can profoundly affect the resulting mechanistic paths with these substrates.



Scheme 29

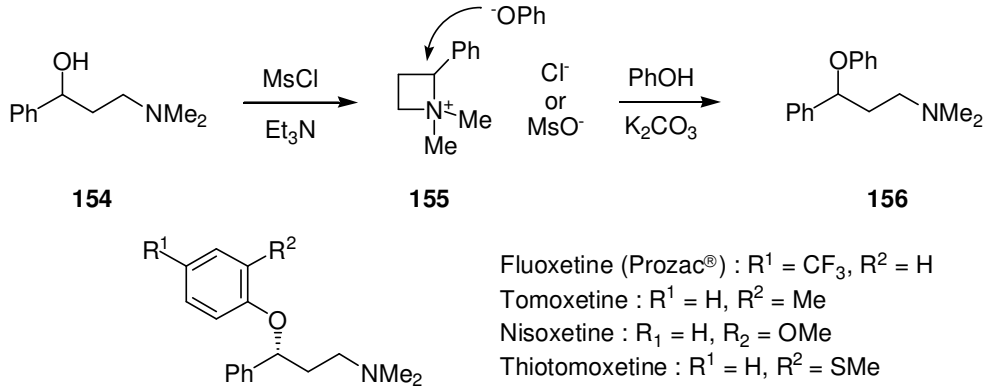
These first examples of nucleophilic opening of azetidinium salts were not very promising in terms of synthetic efficiency: the strong influence of the presence of alpha substituents and the competitive Hofmann elimination of these substitutents together with the lack of efficient synthetic methodologies for the preparation of these heterocycles meant that their use as electrophiles did not draw much attention for some years. However, several reports began to unveil their usefulness in the 1990's. Higgins reported[37] the ring opening of 2-methyl or 2-phenyl aztidin-3-ol **148** or **149** by phenol: while **148** is regioselectively opened at the less substituted carbon, **149** is opened at the benzylic position, with clean inversion of configuration. These reactions were thought to occur on the protonated intermediates **150** and **151** (Scheme 30).



Scheme 30

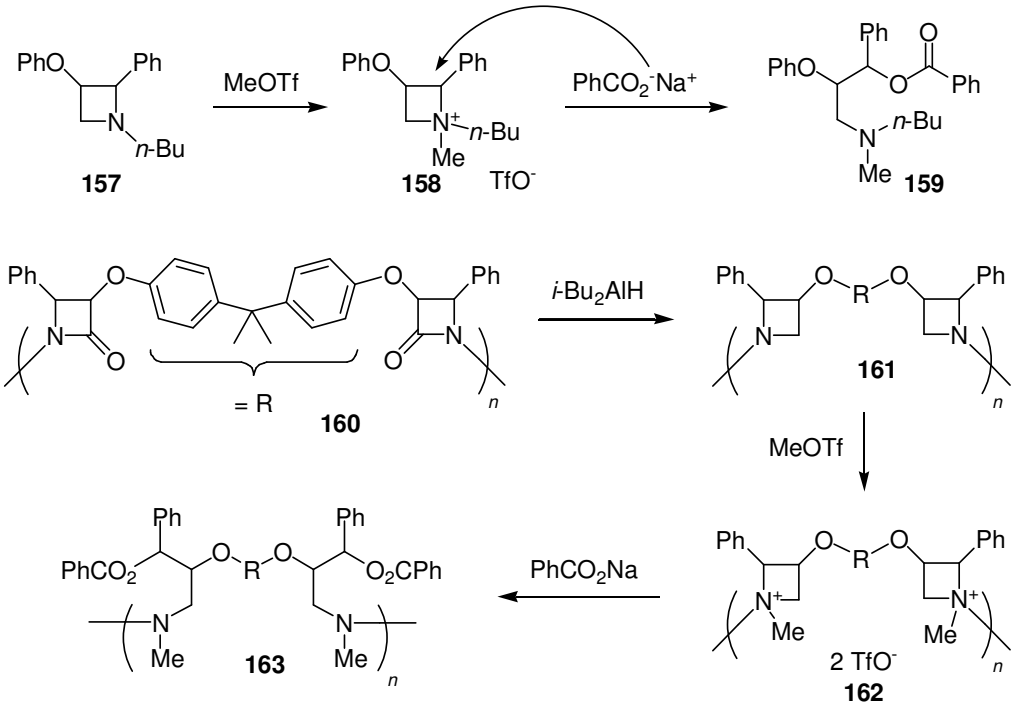
More recently, O'Brien reported[38] a rapid access to 3-aryloxy-3-aryl propanamines, such as Prozac®, which are known to be selective inhibitors of serotonin and noradrenaline uptake. Thus, mesylation of γ-

amino alcohol **154** gave azetidinium salt **155** which was regioselectively opened by potassium phenoxide (Scheme 31).



Scheme 31

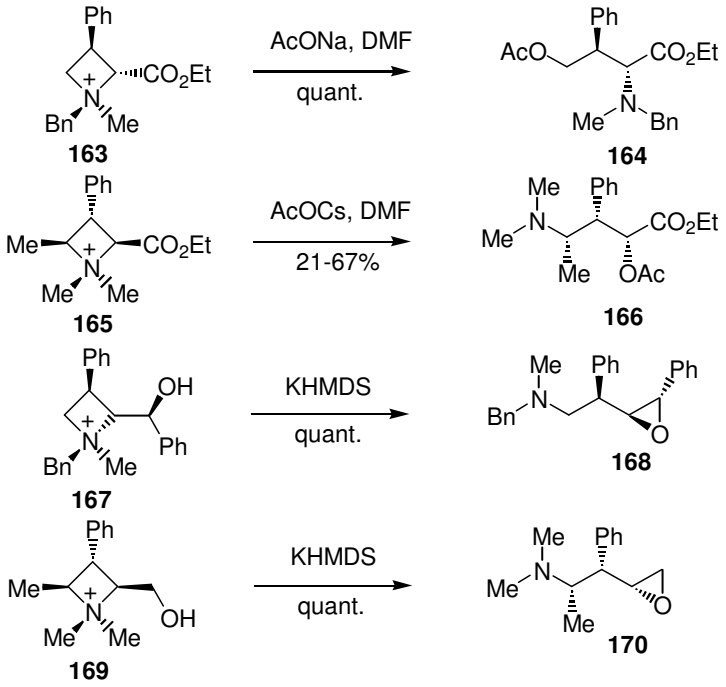
Carboxylates were also reported to regioselectively open azetidinium salts. Recently, Sudo and coworkers, aiming at developing a synthesis of new polyaminated polymers, studied the electrophilic behaviour of azetidinium salt **158** when reacted with sodium benzoate.[39] They reported a highly regioselective opening at the benzylic position, and applied this to the preparation of polymer **163**, starting from polymeric azetidin-2-one **160** and using a three step sequence: DIBALH reduction, reaction with methyl trifluoromethanesulfonate, and, finally, reaction with sodium benzoate (Scheme 32).



Scheme 32

We recently showed that high regioselectivity can be obtained in these ring opening reactions, thus enhancing considerably their synthetic usefulness.[40] Scheme 33 summarizes some representative examples of

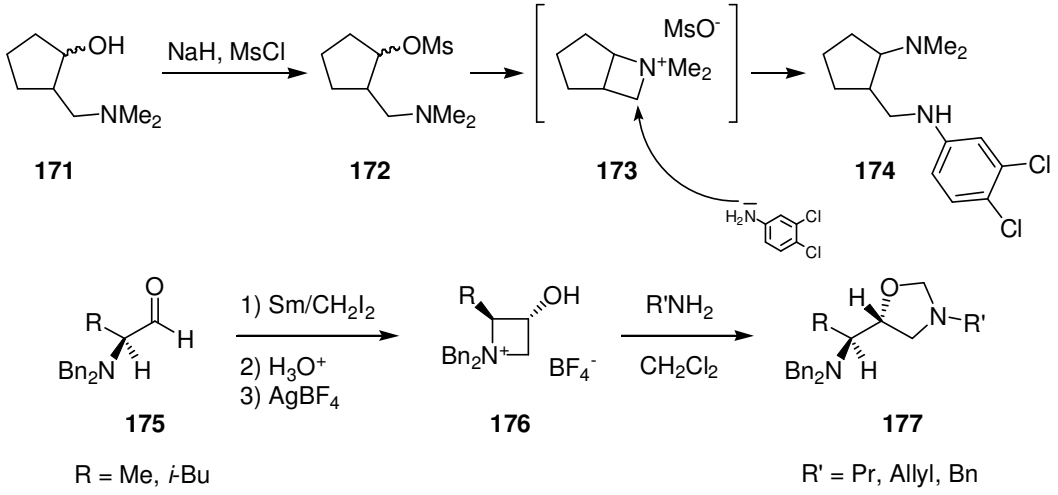
functionalized azetidinium substrates that we have used in this ring opening, when reacted with acetate or alcoholate salts. Thus, azetidinium salt **163** opens regioselectively at the unsubstituted position to give **164**, but disubstituted azetidinium **165** showed reversed regioselectivity: the cesium acetate reacted exclusively at the C-2 carbon, bearing the ester moiety, and with a total diastereoselectivity. Intramolecular ring opening also occured with alcoholates from **167** and **168**, to afford the corresponding epoxides **169** and **170**.



Scheme 33

3.2.3. Opening with nitrogen nucleophiles

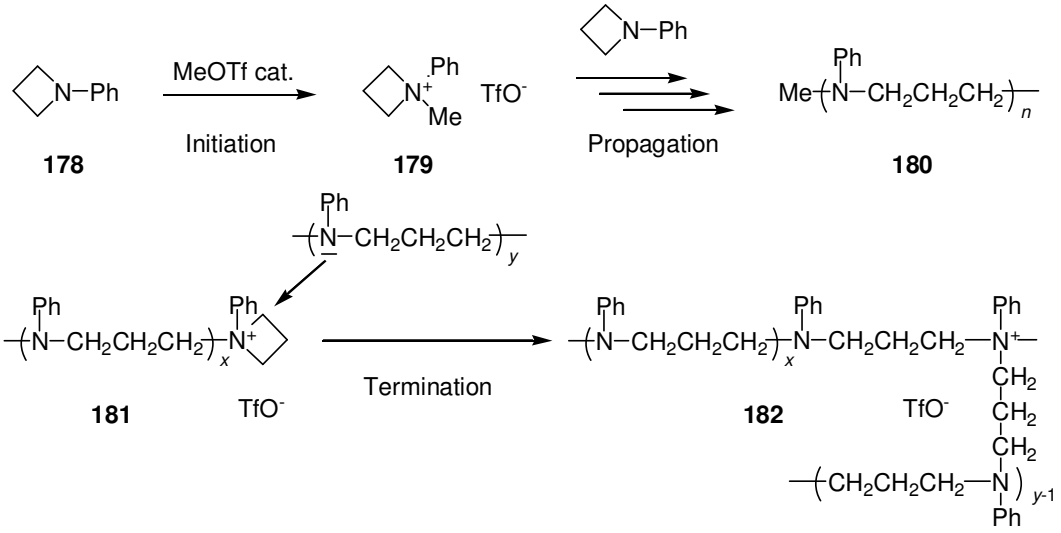
Nitrogen nucleophiles have also been reported to react with azetidinium compounds. In 1971, Bernstein[41] reported that a steroidal, α,α'-disubstituted azetidinium salt reacted with ethanolamine to regioselectively give the corresponding opened product, together with some Hofmann elimination by-product. Later, Szmuszkovicz[42] reported the preparation of diamine **174** *via* a regioselective opening of azetidinium salt **173** by 3,4-dichloroaniline at the less hindered position.



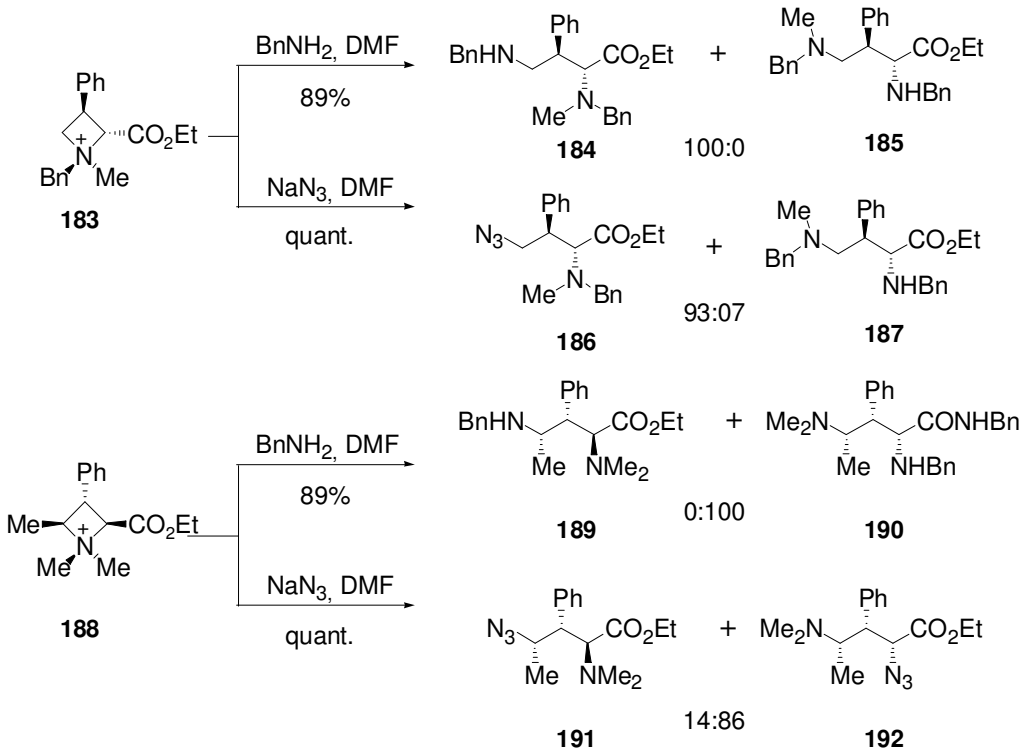
Scheme 34

More recently, Concellón showed that tetrafluoroborate azetidinium salts **176** react with amines in DCM to give oxazolidines **177**.[31] These compounds result from a regioselective ring opening on the less substituted carbon, followed by reaction of both the hydroxyl and amine groups with DCM (Scheme 34).

Ring-opening of azetidinium salts by amines can be used as a powerful tool for the cationic polymerization of *N*-phenyl azetidine **178** as depicted in Scheme 33. This polymerization was recently reported by Tezuka[43] who showed that methyltrifluoromethanesulfonate used in catalytic amounts was an excellent initiator for the polymerization of **178**, yielding, after propagation and termination, **182** (Scheme 35).



Scheme 35

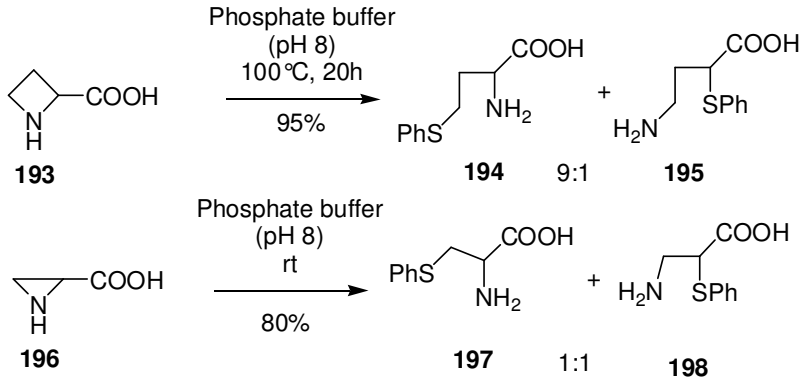


Scheme 36

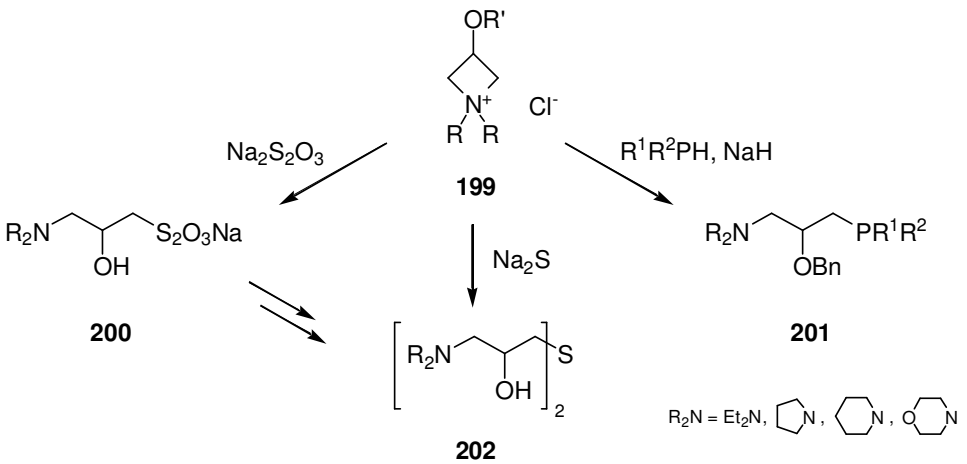
Finally, we have recently shown that azides and amines are excellent nucleophiles that can participate in the opening of functionalized azetidinium triflates, allowing a straightforward and original synthesis of enantiomerically pure diamines or azido-amines (Scheme 36).[40] Concerning the regioselectivity of the nucleophilic opening, it seems to be quite similar to the one observed with acetates: benzylamine and sodium azide react at the less substituted position with high regioselectivity for azetidinium salts such as **183** possessing an unsubstituted carbon while they react at the carbon bearing an electron withdrawing group (nitrile or ester) when the other carbon is substituted with a methyl group. In both cases however, useful levels of regioselectivities can be reached, leading to stereodefined functionalized acyclic amines with good yields and total diastereoselectivity. Some examples are shown in Scheme 36.

3.2.4. Opening with sulfur and phosphorus nucleophiles

Sulfur nucleophiles were also reported to open azetidines and azetidinium salts. To the best of our knowledge, the first publication in this area consisted of the work of Hata and coworkers who reported the reaction of azetidine-2-carboxylic acid **193** with thiophenol in phosphate buffer at 100 °C. Using these conditions, thiophenol regioselectively opens the azetidine at the less substituted position to give **194** as the major product.[44] Interestingly this reaction was found to be less regioselective with the 3-membered aziridine homologue **196** since in this case the two regioisomers were obtained in equimolar amounts. However, the aziridine was more reactive since the reaction proceeded at room temperature (Scheme 37).



Scheme 37

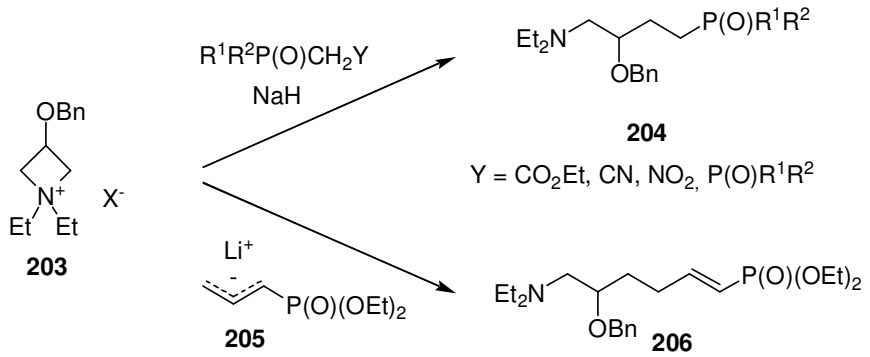


Scheme 38

More recently, Krawiecka reported that a range of sulfur[45] and phosphorous[46] nucleophiles reacted with azetidinium salts. Selected examples illustrating this ring opening with different inorganic sulfur and phosphorus salts are shown in Scheme 38.

3.3. Ring opening with carbon nucleophiles

Surprisingly, despite the high synthetic potential of these original electrophiles, a single example of ring opening of azetidinium salts with carbon nucleophiles was reported to the best of our knowledge. It involved the reaction of phosphorus-stabilized carbanions: anions derived from phosphine oxide or allylic anion **205** react with azetidinium **203** to give respectively polyfunctionalized compounds **204** and **206** (Scheme 39).[46c] Considering that synthetic methods for the preparation of enantiomerically pure, functionalized azetidines are available,[1d] studies directed to the examination of the reactivity of others organometallic reagents with azetidinium salts should appear in the near future.



Scheme 39

4. Conclusion

A conclusion to this brief review can be stated in a single sentence: the history of azetidine chemistry is quite short! Due to their poor availability, they have long been considered as lab curiosities and the reactions involving these heterocycles were often classified as "exotic" transformations. However, a growing interest for these strained heterocycles has appeared in the past two decades and some general trends in their reactivity can now be defined. In fact, many studies collected in this review compare the reactivity of azetidines with those of their lower homologues, aziridines and one general conclusion can be drawn from these compared reactivities: four-membered rings are generally less reactive in ring expansion and ring opening reactions than three-membered rings, which is due to a reduced ring strain. However, and this is quite an interesting feature also due to this reduced strain, this reactivity is easier to control which leads to highly chemo- or regioselective processes. The chemistry of this original heterocycle is only at its beginning and there is no doubt that azetidinic compounds will have the scope of their synthetic applications extended in the coming years.

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OXIDATIVE CLEAVAGE OF THE ISOXAZOLIDINE RING

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Abstract. *Mechanism, scope, and limitations of the title reaction are discussed. Emphasis is given to its role as source of the so-called second generation nitrones, which in turn are the object of a variegate array of synthetic applications.*

Contents

1. Introduction

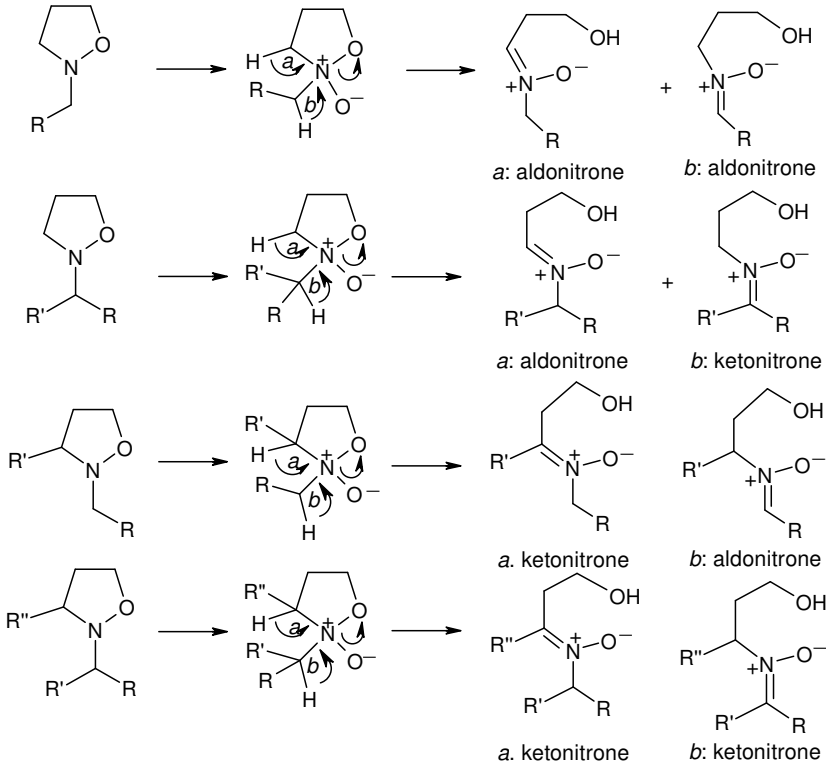
Pentatomic heterocycles have been increasingly employed in the last decades as intermediates in synthetic sequences and their use in this role is today recognized as a versatile strategy in organic syntheses. However, irrespective to the target, such a synthetic approach can be really efficient and more convenient in comparison to the alternative ones provided that the intermediate heterocycle is *i)* easily accessible with a multiform pattern of substitution and *ii)* prone towards a site-selective opening under rather mild conditions sustainable by other functionalities. Both these requisites are met by the isoxazole ring in all its degrees of oxidation. In fact, 1,3-dipolar cycloadditions of nitrones and nitriloxides to ethylenic and acetylenic dipolarophiles open the access to a practically illimited array of isoxazole, dihydroisoxazole, and isoxazolidine derivatives. On the other hand, among the endocyclic bonds of these heterocycles, the nitrogen-oxygen one is by far the most fleasible and can be broken selectively under reductive conditions, so originating a 1,3-bifunctionalized open-chain moiety. In the case of the isoxazolidines, the rupture of the same endocyclic bond can also be accomplished under oxidative conditions, giving of course different products with respect to those deriving form reductive cleavage.

The oxidative opening of isoxazolidines has been firstly reported long time ago[1] and has been later described in several papers. However, with the exception of the remarkable series of articles by Ali and coworkers,[2-10] its use appears mostly to be occasional rather than systematic. Hence, a sound rationale as well as a clear panorama of the scope and limitations of such reaction is still lacking. The present review will illustrate comprehensively and critically the literature data on the oxidative opening of isoxazolidines with the aim of facilitating the organic chemists to evaluate the synthetic potential of this reaction and at the same time with the hope of soliciting chemical researchers to further speculative and applicative investigations on this topic.

It seems advisable to state preliminarily that the oxidative opening of isoxazolidines is typically accomplished by peroxidic species, the most common of which is *m*-chloroperbenzoic acid (MCPBA). Very little is known in the literature about the behaviour of isoxazolidines towards other kinds of oxidants, perhaps because no clear and/or useful outcomes have been detected.

2. Mechanism and regiochemistry

The mechanism of the oxidative ring opening of isoxazolidines is well documented and generally accepted.



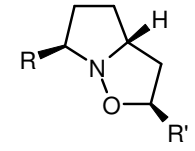
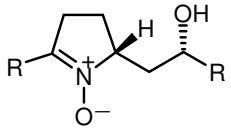
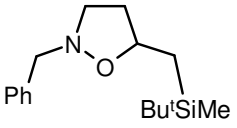
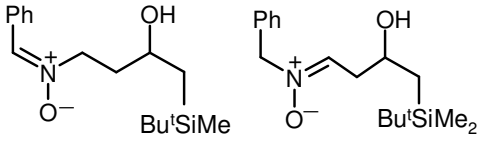
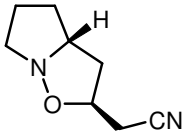
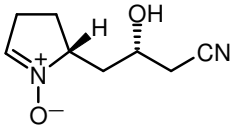
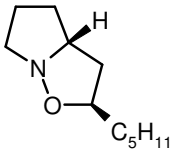
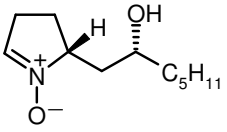
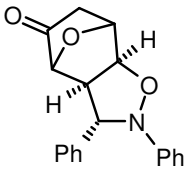
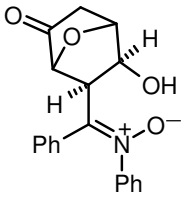
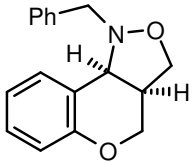
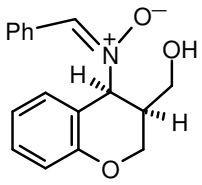
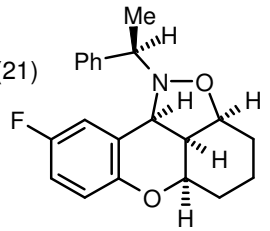
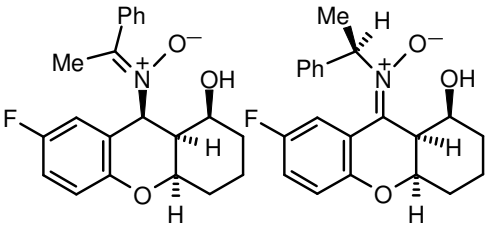
Scheme 1

As illustrated in Scheme 1, in line with the usual behaviour of the trivalent nitrogen towards peroxides, the first stage of the overall reaction is the formation of a *N*-oxide species which undergoes the heterolytic cleavage of the endocyclic nitrogen-oxygen bond followed by (or concerted with) prototropic shift to give ultimately an open-chain hydroxynitrone. Such a product, in view of the fact that isoxazolidines are typically accessible by 1,3-dipolar cycloadditions of nitrones to ethylenes, is usually referred to as a *second generation*

nitrone. However, a major problem arises about which of the two adjacent carbon atoms furnishes the migrating hydrogen so that two regioisomeric products can in principle be formed.

On empirical bases, it has been stated since long time that proton abstraction should occur preferably at the less substituted carbon, which means in other words that the formation of an aldonitrone should be preferred over that of a ketonitrone. This statement often, but not necessarily, matches the matter of fact. Furthermore, in several instances, both potential products are aldonitrones or ketonitrones and consequently the just stated rule has no sense.

Table 1. Oxidation of isoxazolidines by MCPBA in dichloromethane.

Entry (Reference)	Isoxazolidine	Product(s)	Yield(s)
a (4)	 R = H, Me; R' = Bu, Ph		95%
b (10)		 (not separated 55:45 mixture)	90% (overall)
c (12)			63%
d (15)			94%
e (19)			81%
f (20)			87%
g (21)			35% + 14%

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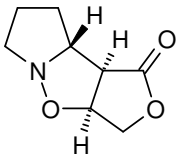
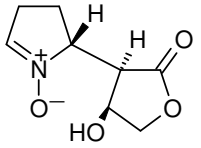
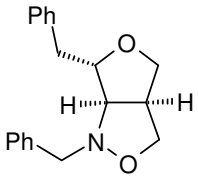
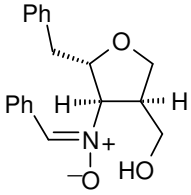
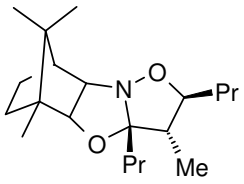
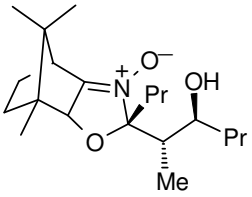
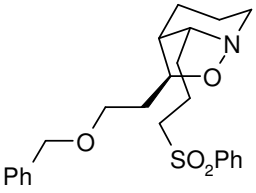
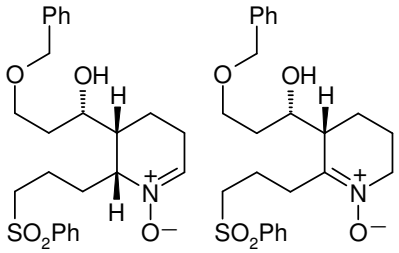
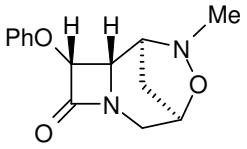
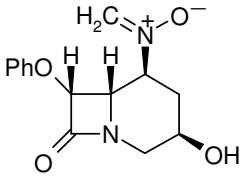
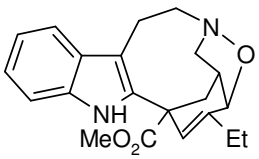
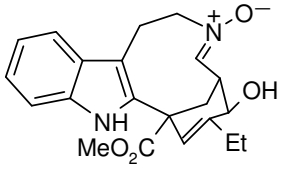
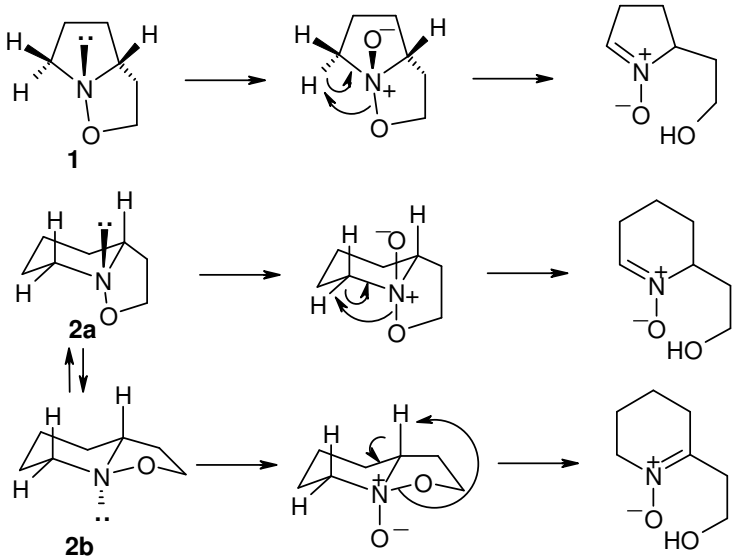
h (23)			70%
i (24)			72%
j (27)			92%
k (28)			61% + 12%
l (50)			26%
m (25)			95%

However, steric factors can affect markedly the regiochemistry of the reaction so that a full regioselective outcome is far from being a rare evenience. A selection of significant examples is given in Table 1. Mutual spatial relationships are generally important and they play a determinant role in the case of crowded and/or rigid molecules such as fused-ring isoxazolidines. In the MCPBA oxidation of the latter, Ali and coworkwers[2,5,8] have found that the regiochemistry of the reaction happens to be dictated by the orientation of the lone electron pair on the nitrogen because the proton capture by the incipient alkoxide anion proceeds intramolecularly involving the most adjacent hydrogen atom (Scheme 2). In the case of isoxazolidine **1**, existing exclusively in the *cis*-annulated conformation, the equatorial hydrogen of the endocyclic methylene group is migrating so that an aldonitrone is formed regioselectively. At variance, the related isoxazolidine **2** exists as a conformational mixture and in the *trans*-annulated conformer (**2b**) the

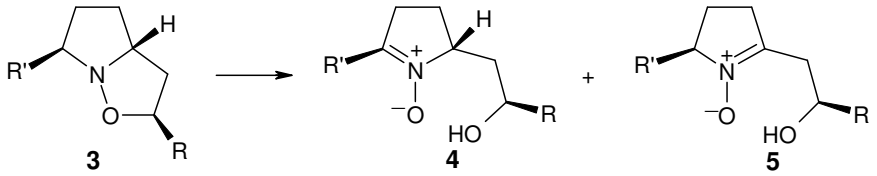
bridgehead hydrogen happens to be the most prone to migrate; consequently, a regioisomeric mixture of nitrones is produced.



Scheme 2

The regiochemistry of the isoxazolidine oxidation is also dependent on the solvent,[3-5,37,38] as clearly shown in Table 2.

Table 2. Solvent effect on the regiochemistry of MCPBA oxidation of isoxazolidines **3**.



Entry (Reference)	R	R'	Solvent	4:5 Ratio[a]
a (4)	Ph	H	CH_2Cl_2	100:0
			MeOH	20:80
			AcOH	0:100
b (4)	CH_2OH	H	CH_2Cl_2	100:0
			MeOH	50:50
			AcOH	15:85
c (4)	$CH_2OSi(Bu^t)Me_2$	H	CH_2Cl_2	100:0
			MeOH	40:60
			AcOH	0:100
d (4)	$CH_2CH_2CH_2OH$	H	CH_2Cl_2	100:0
			MeOH	50:50
			AcOH	15:85
e (3)	Ph	Me	CH_2Cl_2	100:0
			MeOH	50:50

[a]Overall yields>90%.

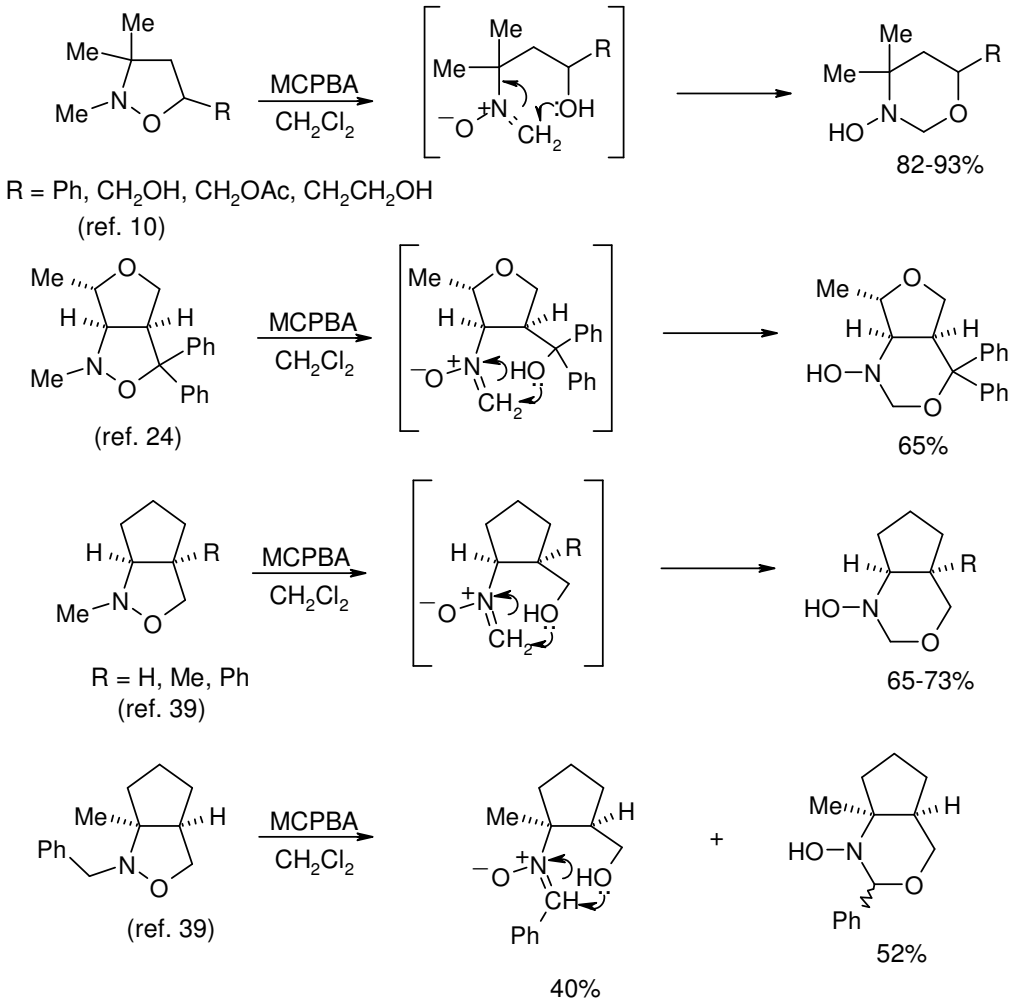
Such dramatic effect can be rationalized as follows. In aprotic solvents, the proton migration is plausibly intramolecular and involves the hydrogen atom most proximate to the transient alkoxide anion. Conversely, protic solvents act as intermediaries of the proton migration so that the process is under thermodynamic control and originates the two possible nitrones in a ratio determined by their relative stability. For the same reason, the regiochemistry may be affected by the water content of the employed oxidant.[37,38] Interestingly, the presence of a hydroxy group in the starting isoxazolidine interferes and moderates the typical effect of protic solvents (see entries **b** and **d** of Table 2).

It remains to be said that the peracid oxidation of enantiopure chiral isoxazolidines has been proven to proceed with no loss of optical activity (see entries **g**, **i**, and **l** of Table 1).

3. Transformations of the primary hydroxynitrones

3.1. Tautomerization to *N*-hydroxy-tetrahydro-2*H*-1,3-oxazines

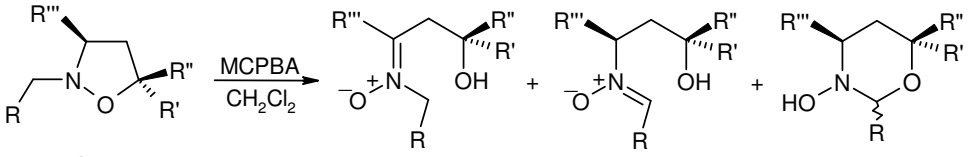
N-(3-Hydroxyalkyl)nitrones can spontaneously tautomerize to *N*-hydroxy-tetrahydro-2*H*-1,3-oxazines by way of an intramolecular Michael-type addition of the hydroxy group to the nitrone functionality (Scheme 3).[8-10,24,39-41] The tendency to the ring closure is markedly dependent on the substitution pattern and may be cancelled by steric hindrance; accordingly, *N*-methylisoxazolidines have been found the most propense ones to the intramolecular addition.



Scheme 3

The tautomeric equilibrium between nitrones and oxazines is often the reason of further complication of the product mixture deriving from the oxidative cleavage of isoxazolidines (see for instance Table 3).

Table 3. Product distribution of MCPBA oxidation of isoxazolidines **6**[a].

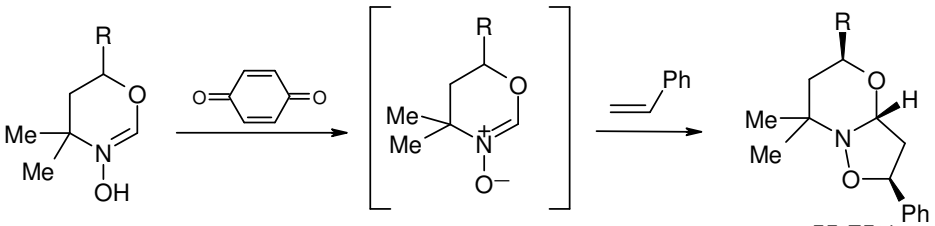


6 **7** **8** **9**

R	R'	R''	R'''	Product distribution (%)		
				7	**8**	**9**
Me	H	Ph	H	45	32	33
H	H	CH_2CH_2OH	H	32	10	58
H	H	$CH_2OSi(Bu^t)Me_2$	H	20	8	72
Me	H	Ph	Et	0	23	77
H	Me	CH_2OH	H	55	10	35

[a]Ref 10

On the other hand, whenever the equilibrium is totally shifted in favour of the ring-closed substrates, the reaction acquires synthetic usefulness because *N*-hydroxy-tetrahydro-2*H*-1,3-oxazines are the appropriate precursors, through oxidation, of a peculiar kind of nitrones, namely six-membered cyclic nitrones endowed with an ethereal function at the carbon. A synthetically fruitful application[9] of such reaction sequence is outlined in Scheme 4.



Scheme 4

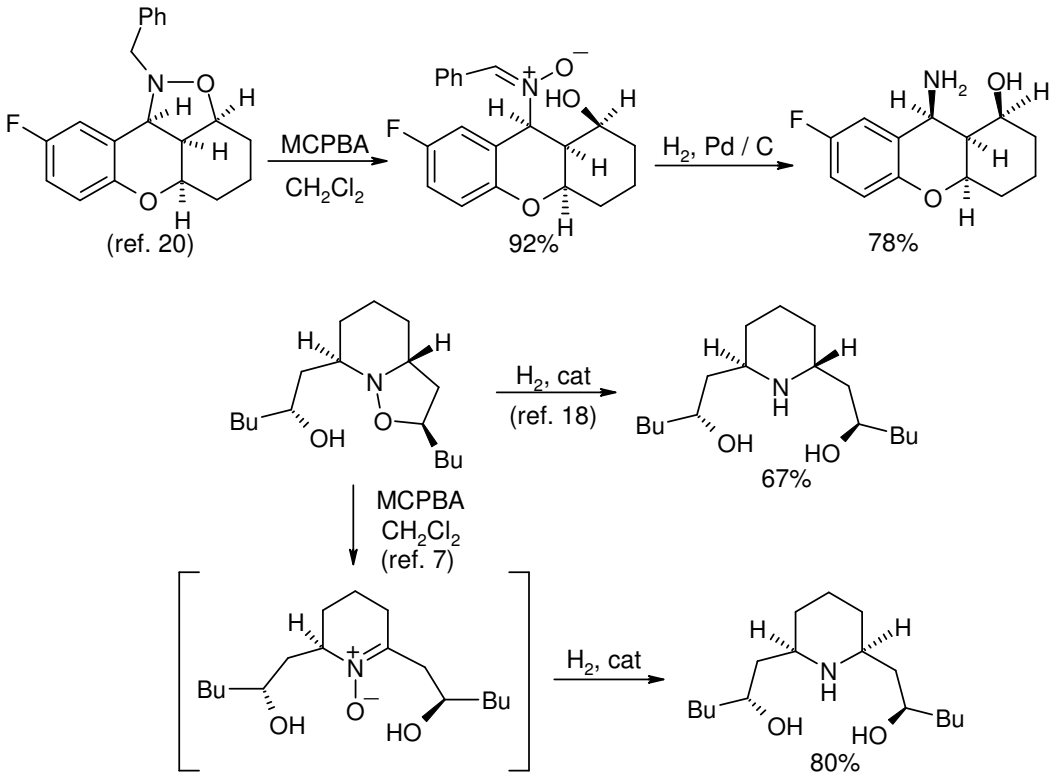
3.2. Reduction to 1,3-aminoalcohols

1,3-Aminoalcohols are the typical products of the reductive cleavage of the isoxazolidine ring. However, certain isoxazolidines have been shown reluctant to be reduced. This drawback can be circumvented by way of the oxidative cleavage of the heterocycle followed by reduction of the so-formed nitrone.[3,4,7,20,21] In cases where the isoxazolidine carbon in 3-position is a stereocentre, the latter may be destroyed during the oxidation and regenerated during the reduction, but not necessarily in a stereoselective manner. Useful applications of this two-step reaction protocol are outlined in Scheme 5.

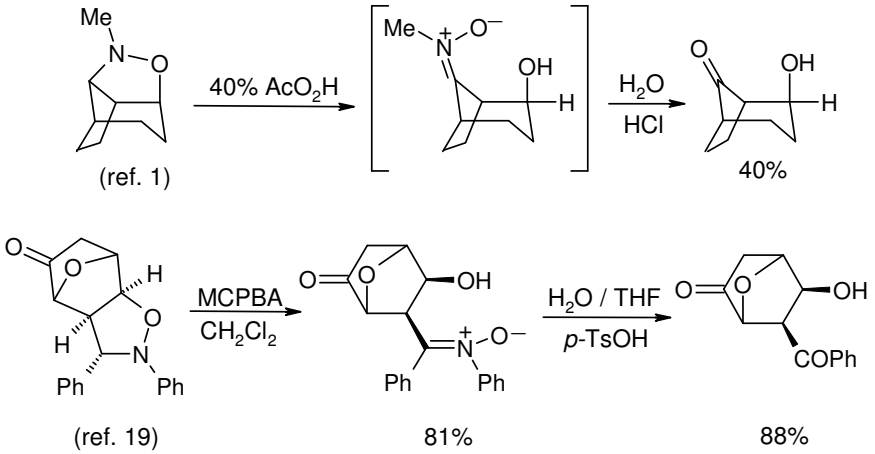
3.3. Hydrolysis to hydroxyketones

If one wishes to prepare nitrones, the most general and common procedure is the direct condensation between a carbonyl compound and a *N*-substituted hydroxylamine, eventually in the presence of a

dehydrating agent. The reverse reaction of hydrolysis of the nitrone functionality has usually no practical significance, just excepting the case of nitrones derived from oxidative cleavage of isoxazolidines. These nitrones, upon hydrolysis, produce hydroxyketones which may be not easily accessible by other routes (Scheme 6).[1,12,13,19,22,27,49] The hydrolysis can occur directly in the oxidation medium when a moist solvent or a large excess of water containing MCPBA are employed.

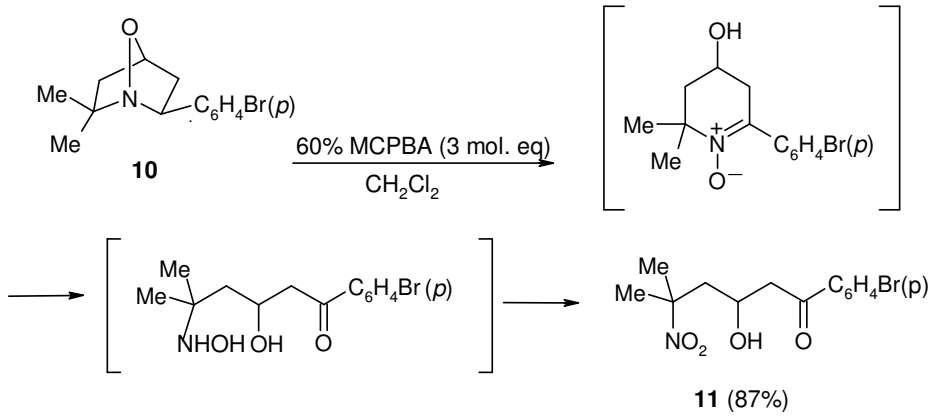


Scheme 5



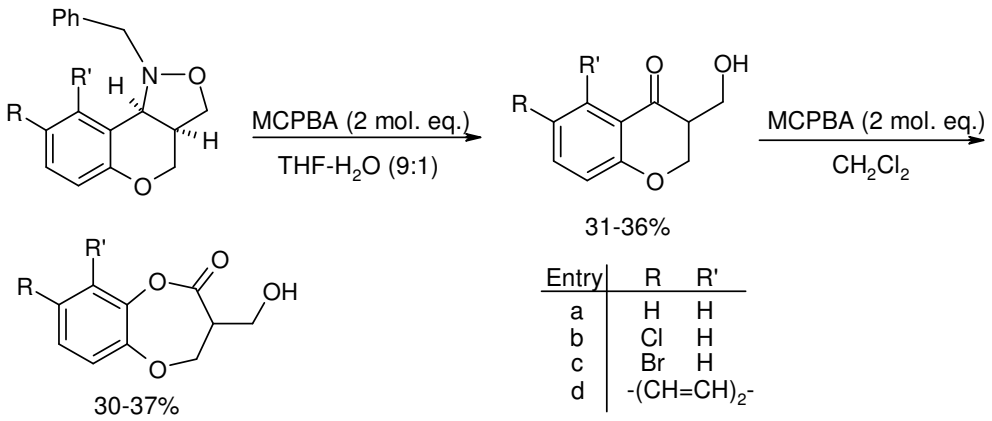
Scheme 6

It must be noted that such a hydrolytic process implies the loss of a hydroxylamine fragment. A novel and interesting outcome has been observed in the case of the bridged-ring isoxazolidine **10**, where the hydroxylamine moiety remains incorporated in the hydrolysis product and undergoes a further transformation, ultimately leading to δ-nitro-β-hydroxyketone **11** (Scheme 7).[49]



Scheme 7

On combining the hydrolytic oxidation of isoxazolidines with the Baeyer-Villiger protocol, Broggini and coworkers have developed an interesting entry to seven-membered α-(hydroxymethyl)lactones (Scheme 8).[22]



Scheme 8

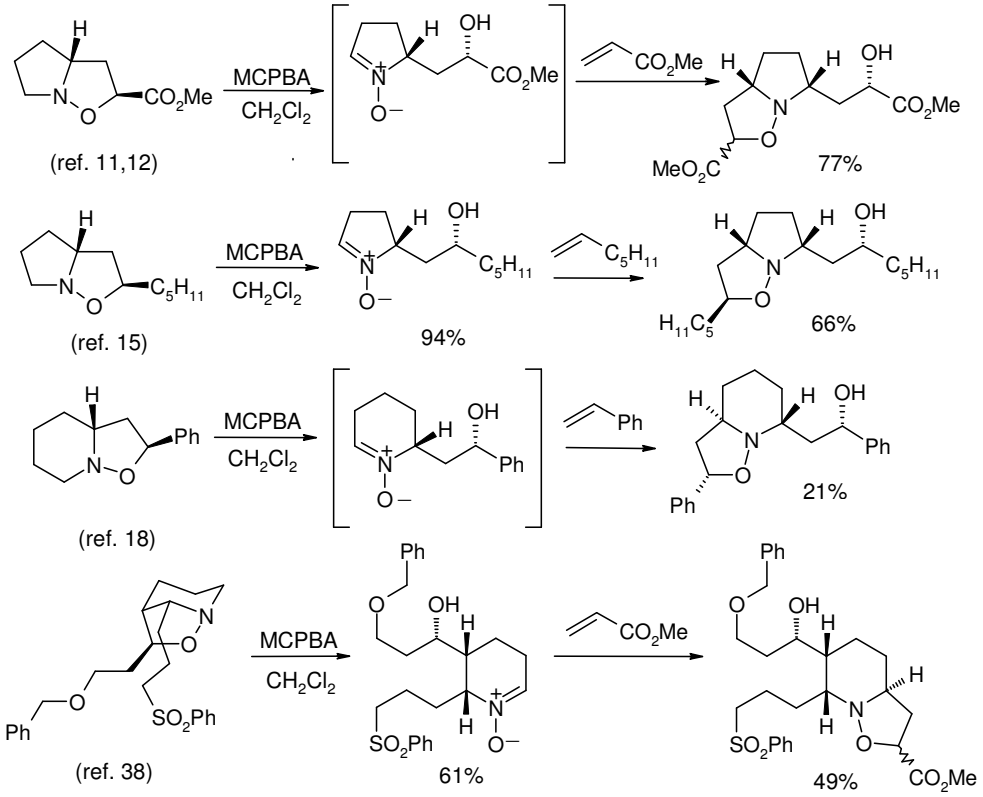
3.4. Intermolecular 1,3-dipolar cycloadditions

In line with the typical reactivity of the nitrone functionality, the so-called second generation nitrones are obviously capable of behaving as 1,3-dipoles and cycloadding to multiple bonds.[4,7,15,17,23,38,43-47] In several cases, the crude product arising from oxidative cleavage of the isoxazolidine is treated with the potential dipolarophile without isolation and purification. When two regioisomeric nitrones are formed and they are not separated, it may be that the aldonitrone is more reactive than the corresponding ketonitrone so that only one cycloadduct is usefully obtained. A few illustrative examples are reported in Scheme 9.

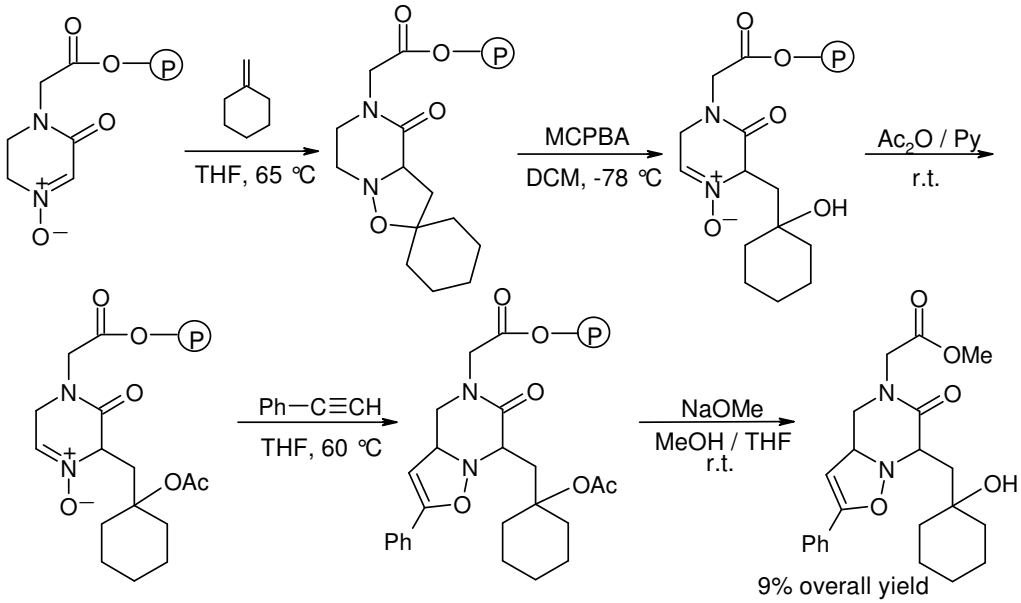
A recent paper[42] describes both preparation and reaction of a second generation nitrone anchored to a polymeric support (Scheme 10).

3.5. Intramolecular 1,3-dipolar cycloadditions

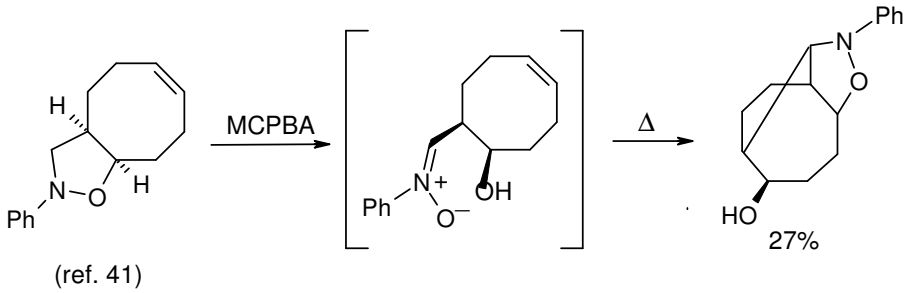
In the last two decades, intramolecular nitrone cycloadditions have become very popular due to their astonishingly versatile usefulness. If one submits to oxidative cleavage an isoxazolidine endowed with an appropriate ethylenic bond, the resulting nitrone may evolve further by way of an intramolecular 1,3-dipolar cycloaddition, as exemplified in Scheme 11.



Scheme 9

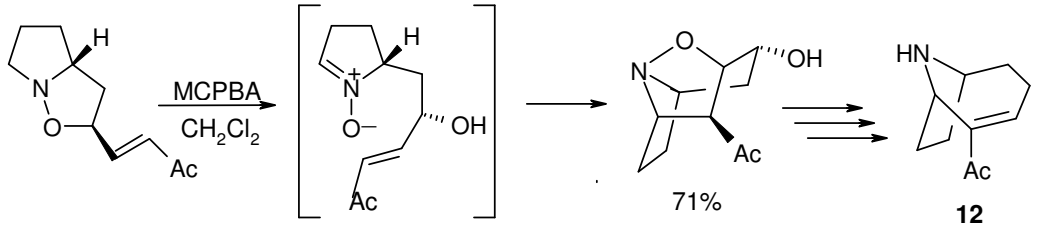


Scheme 10



Scheme 11

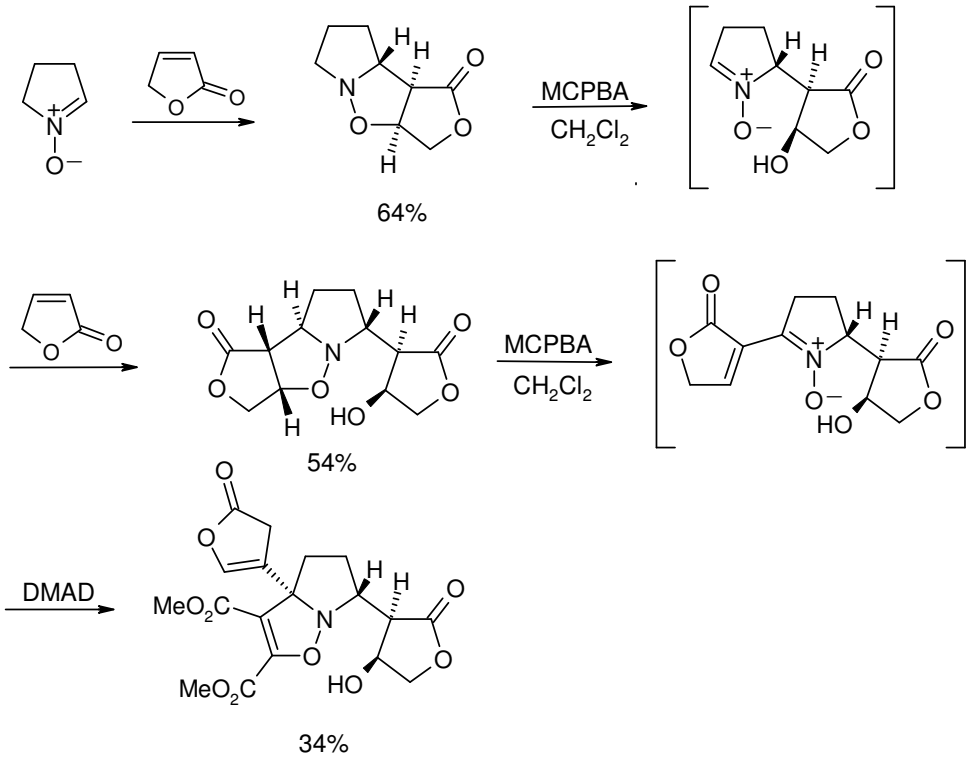
Such synthetic strategy has been elegantly applied to the total synthesis of the natural, highly toxic compound **12**, secreted by micro-algae and referred to as *anatoxin-a* (Scheme 12).[14]



Scheme 12

3.6. Access to third generation nitrones

In 1993, Ali and Wazer[3,4] described the first example of the so-called third generation nitrones, namely formed through a twice repeated sequence involving nitrone cycloaddition and isoxazolidine oxidation. The use of such nitrones in 1,3-dipolar cycloadditions has been later reported (Scheme 13).[23]

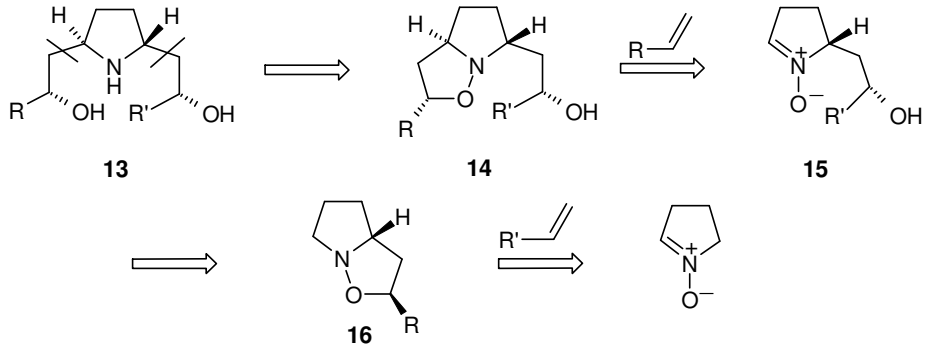


Scheme 13

4. Highlights in synthetic applications

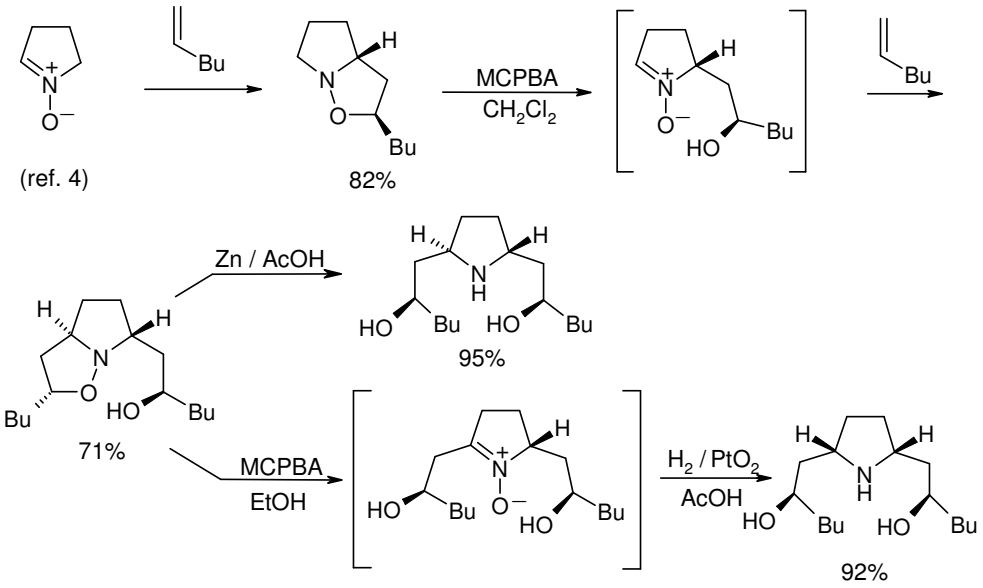
4.1. Diastereoselective synthesis of 2,5-disubstituted pyrrolidines

Different research groups[3,4,15,16,36] have developed a synthetic entry to 2,5-disubstituted pyrrolidines of general formula **13** (or derivable from them) on the basis of the disconnection line and the retrosynthetic analysis depicted in Scheme 14. Both the regioselectivity of the isoxazolidine oxidation and the diastereoselectivity of the second nitrone cycloaddition are crucial for the efficiency of the overall sequence.

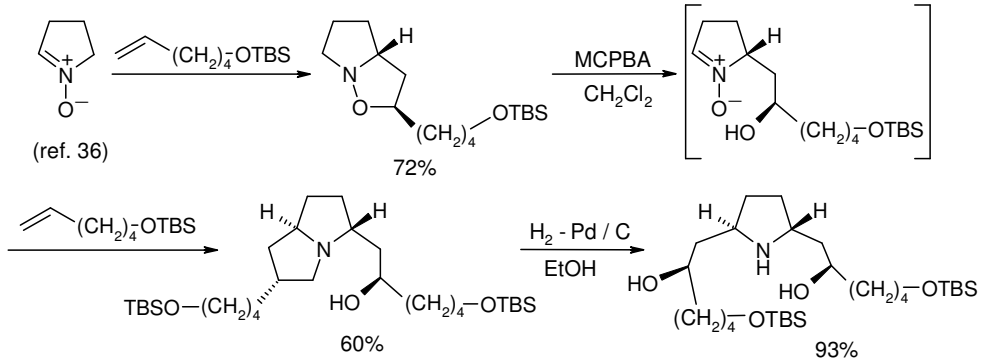


Scheme 14

Fortunately, high selectivities are usually operative. In fact, the oxidative cleavage of the bicyclic isoxazolidine **16** originates preferably an aldonitrone (**15**), which may subsequently cycloadd with total diastereofacial discrimination due to steric hindrance exerted by the bulky substituent. Furthermore, the strategy happens to be diastereodivergent because the final product may be a *trans* or *cis* 2,5-disubstituted pyrrolidine as a function of the protocol used to open the isoxazolidine ring of the second cycloaddition product **14**. Two practical examples are given in Schemes 15 and 16.

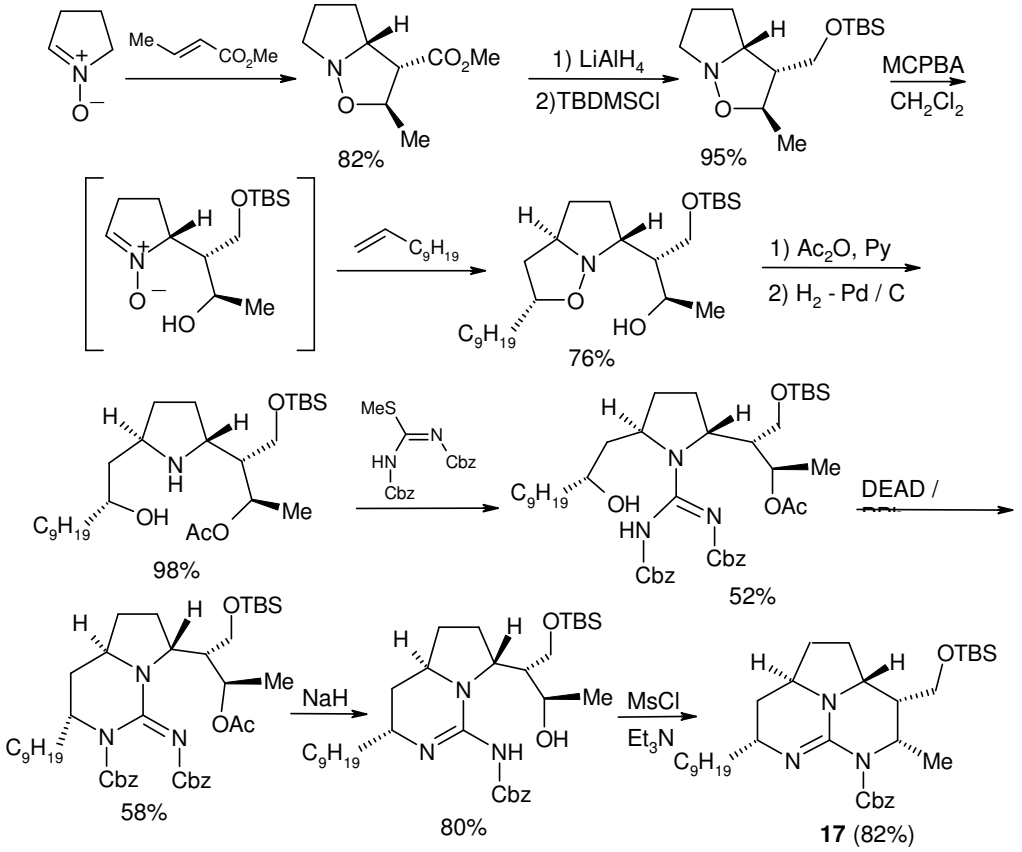


Scheme 15



Scheme 16

In the last years, Nagasawa and coworkers have brilliantly exploited the above strategy to synthesize biologically active compounds, belonging to the marine alkaloids, the structure of which contains a 2,5-annulated pyrrolidine ring.[43-48] The preparation of the tricyclic compound **17**, devised as intermediate for the total synthesis of natural *batzelladines*,[44] is outlined in Scheme 17, while Scheme 18 illustrates the total synthesis of *(-)-crambescidin 359* (**18**).[43]



Scheme 17

4.2. Asymmetric synthesis of chiral β-hydroxycarbonyl compounds

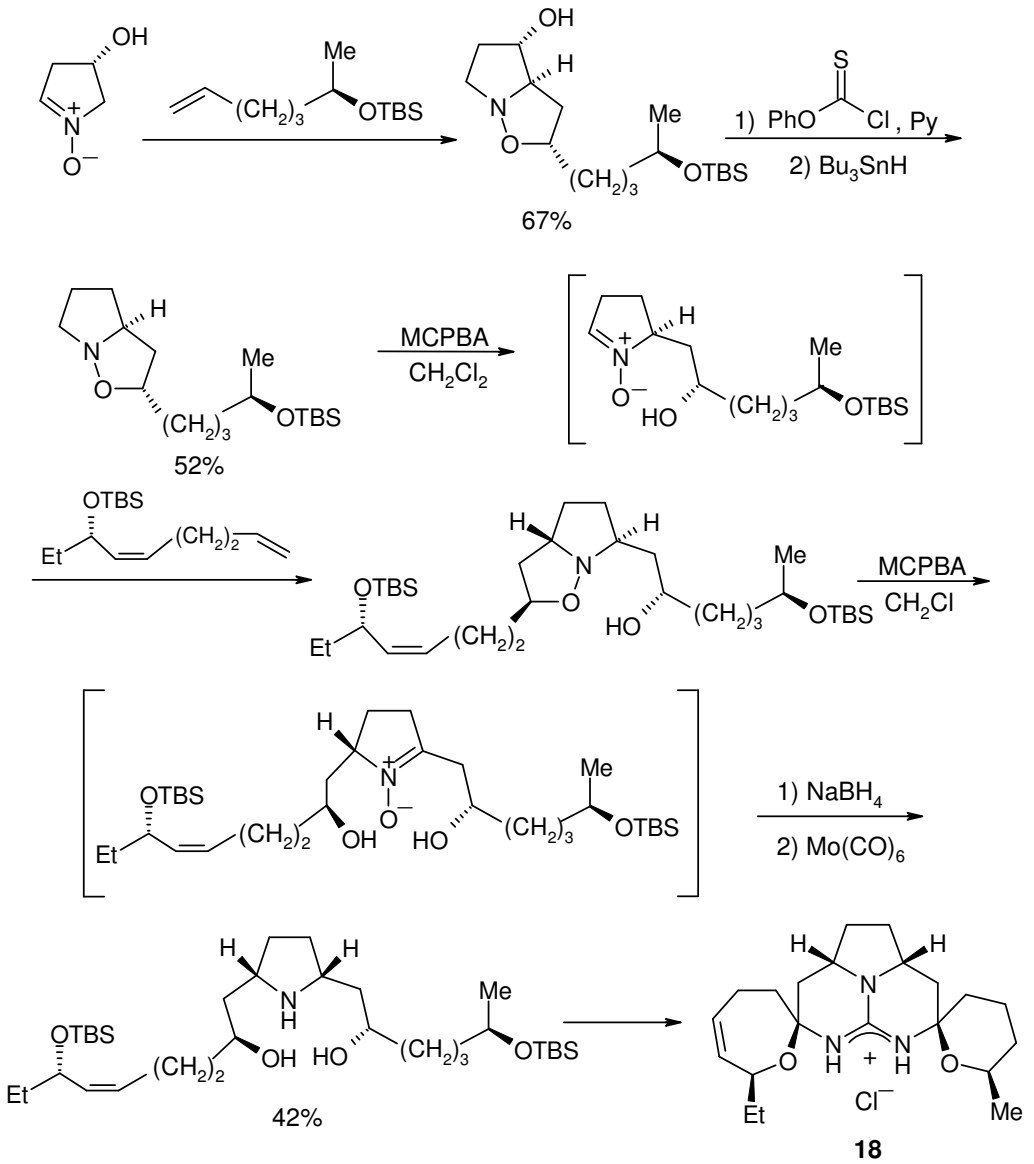
Langlois and coworkers reasoned that the oxidation of the bicyclic skeleton **19**, having each other annulated isoxazolidine and oxazolidine rings (Scheme 19), could have given the peculiar nitrone **20**, which should readily undergo the hydrolytic cleavage to give a β-hydroxycarbonyl compound (**21**) different from that due to the true hydrolysis of the nitrone functionality.[27,28]

On combining this idea with the use of enantiopure nitrones **22** derived from (+)-3-(hydroxyamino)-borneol, Langlois' research group realized a general asymmetric synthesis of β-hydroxy-carbonyl compounds (Scheme 20). Oxime **23**, formed in the final hydrolytic step, behaves as a recyclable chiral auxiliary, so greatly enhancing the efficiency of the synthetic procedure.[26-28,31,34,35]

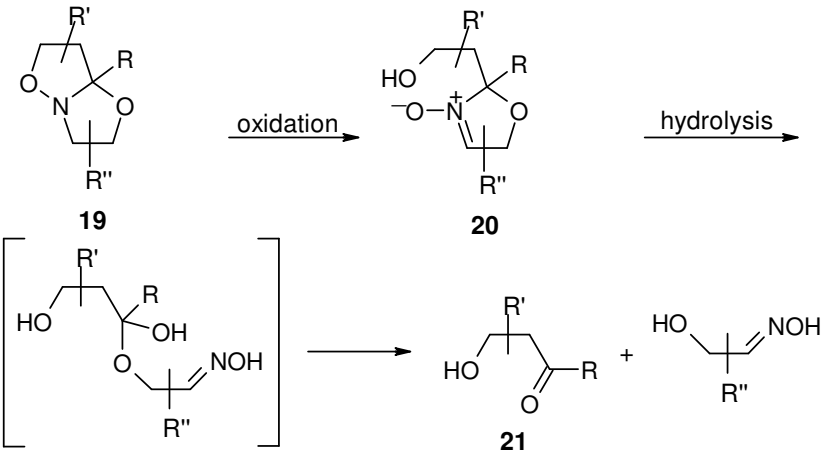
4.3. Access to non-racemic β-lactones and β-lactams

The strategy described in the precedent paragraph was successfully exploited by Langlois and coworkers, on choosing properly substituted starting materials, in order to open a general access to non-racemic chiral β-lactones[26,29-31] and β-lactams.[31-33] Schemes 21 and 22 describe useful applications to the

synthesis of pharmaceutically important targets such as *(-)-tetrahydrolipstatin* (**24**)[30] and β-lactam **25**, a known precursor of *β-methylcarbapenems*.[32,33]



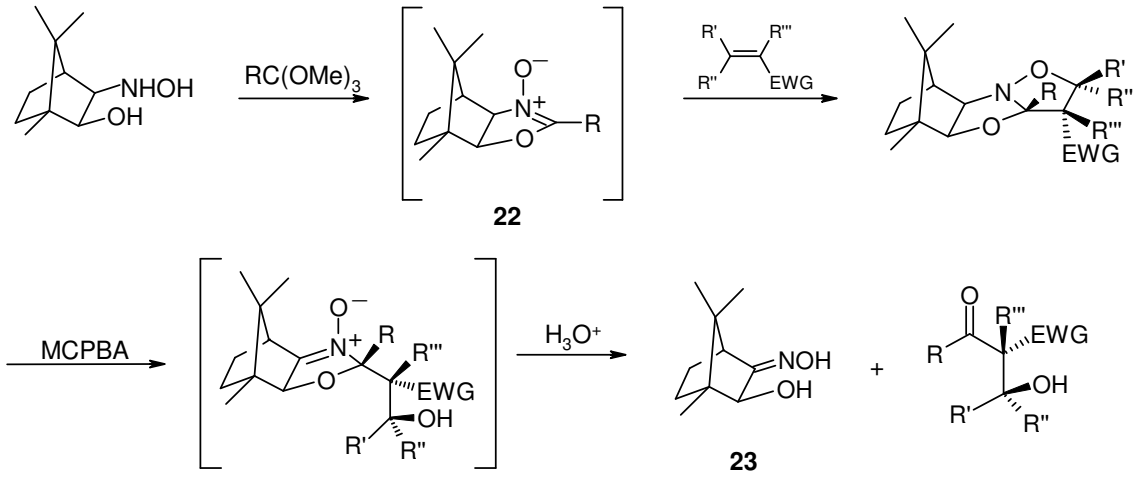
Scheme 18



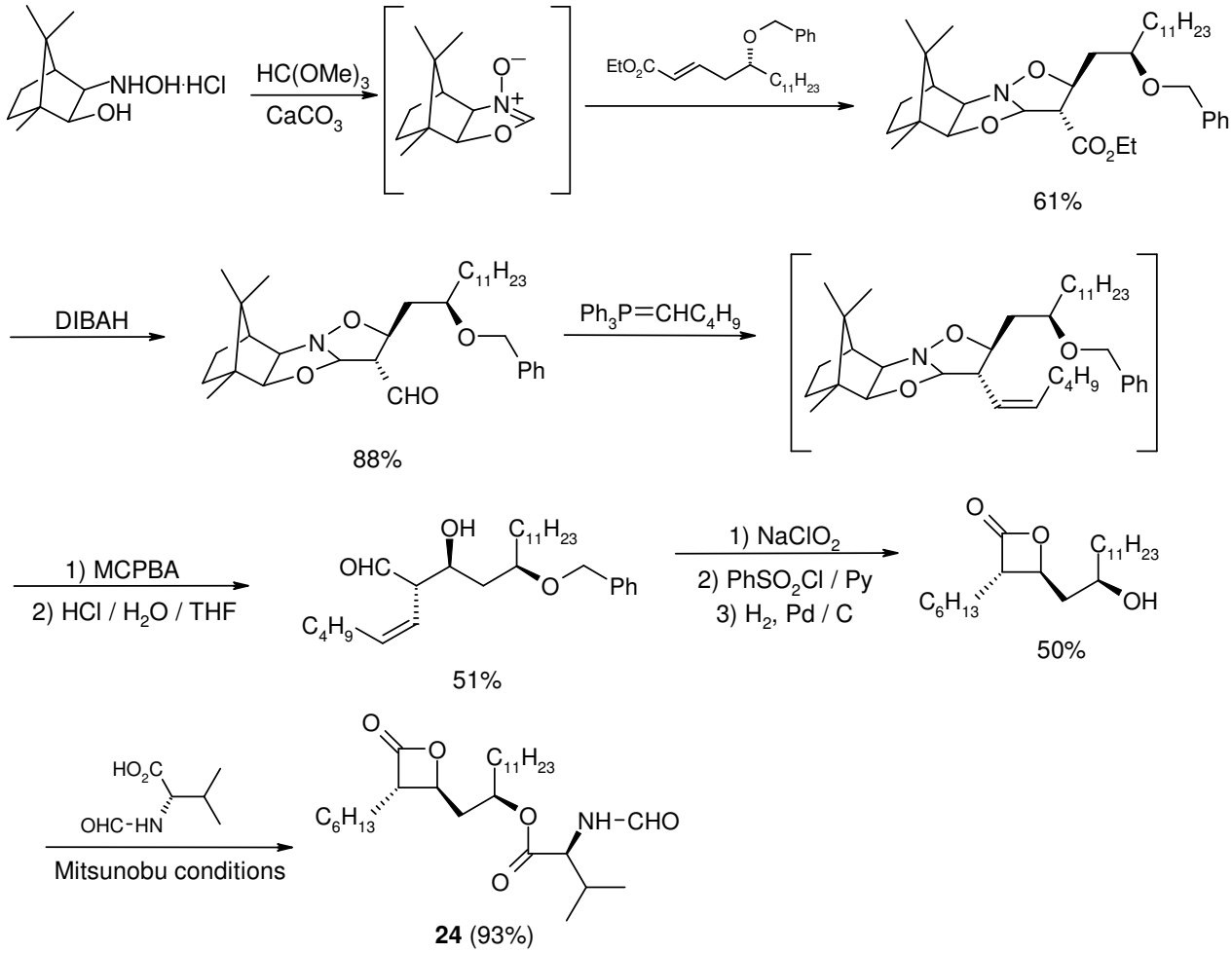
Scheme 19

5. Other oxidation protocols

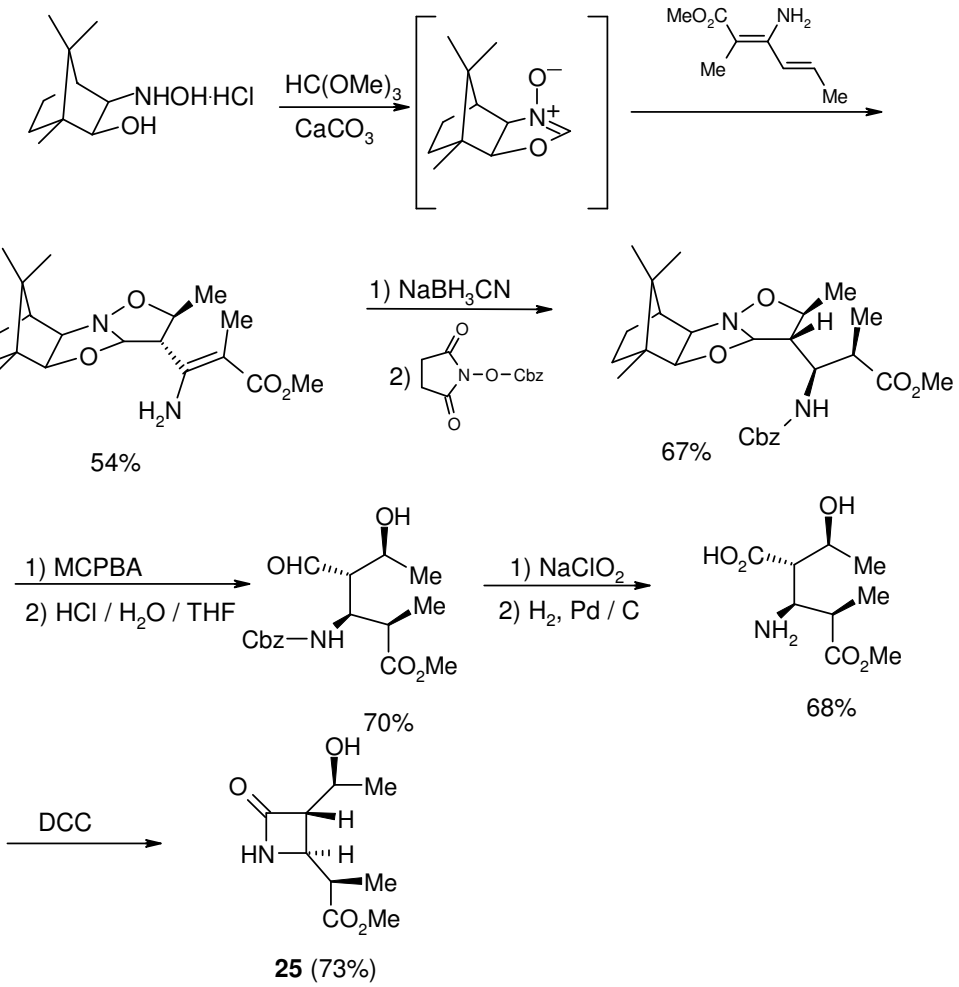
This last paragraph is concerned with the oxidative cleavage of isoxazolidines by means of oxidants other than peroxidic species. The presentation will be merely illustrative because the paucity of literature data on this subject precludes any general consideration and rationalization.



Scheme 20

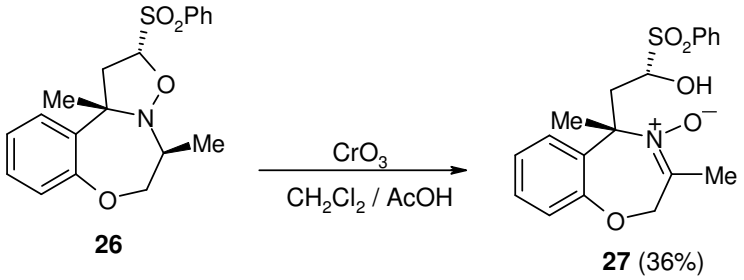


Scheme 21



Scheme 22

A paper has appeared describing the conversion of the tricyclic 1,4-benzoxazepine **26** into the hydroxynitrone species **27** by oxidation with chromium trioxide, but no reason is given for the choice of such an oxidant (Scheme 23).[51]

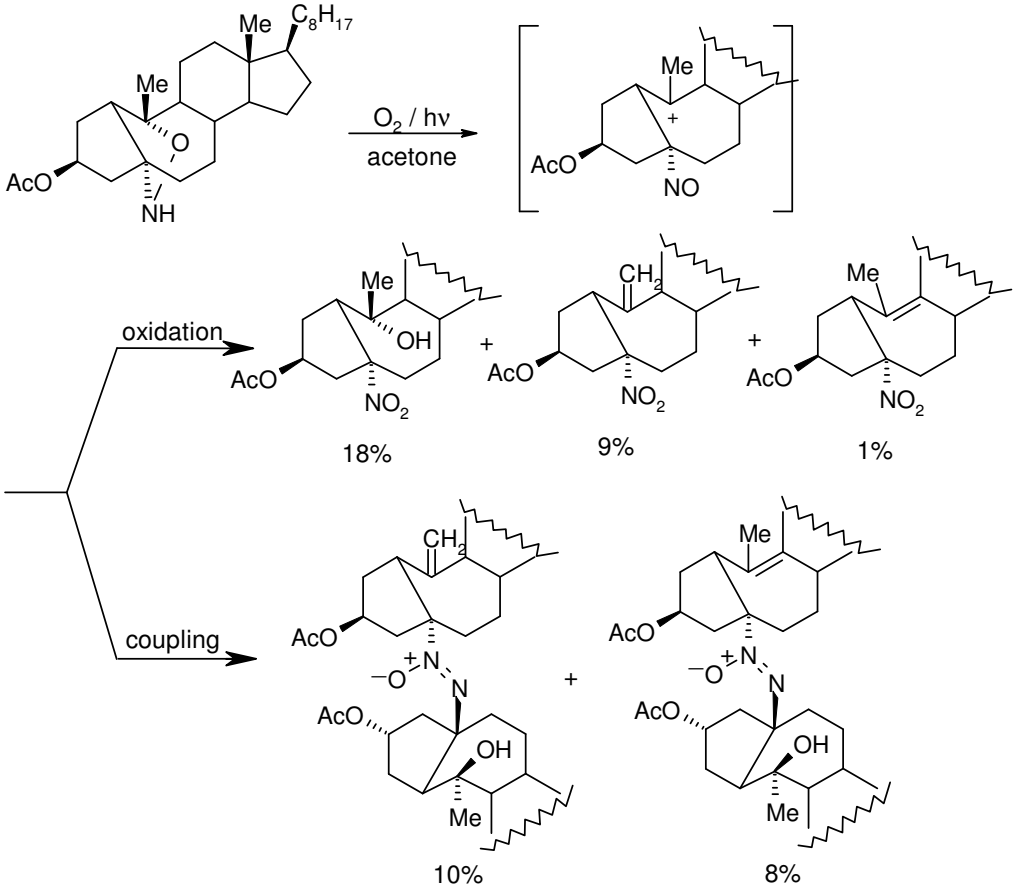


Scheme 23

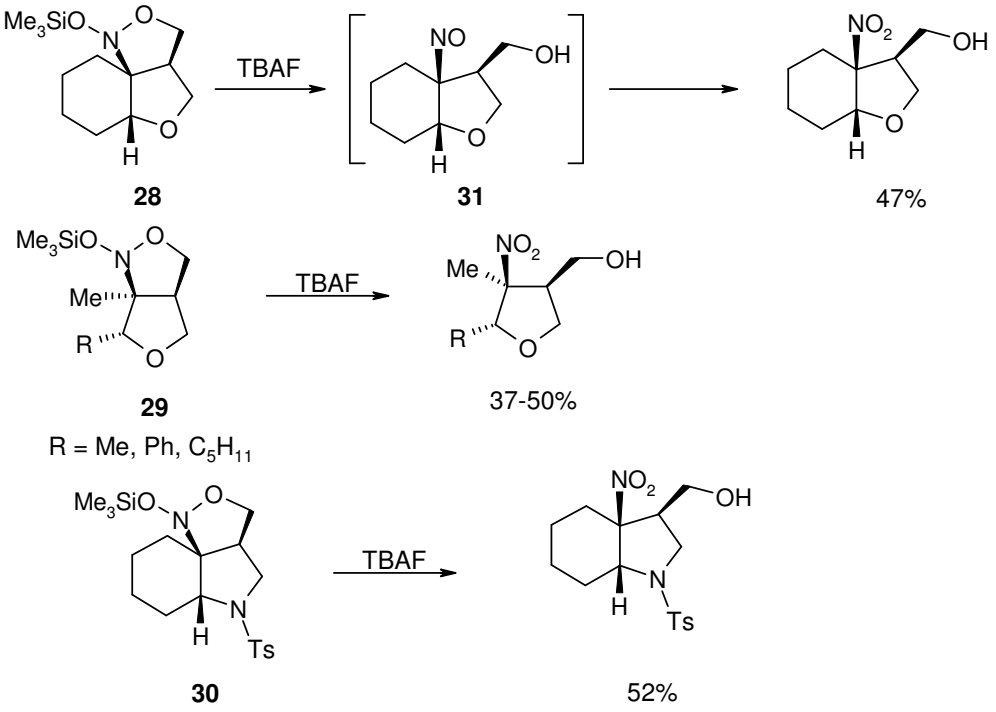
In one case,[52] the oxidative fragmentation of the isoxazolidine ring has been accomplished by molecular oxygen under photocatalytic conditions. The reaction pathway is attractive, but lacks synthetic usefulness as leading to a complex product mixture (Scheme 24).

Rodriguez and coworkers[53] have recently reported the peculiar behaviour of *N*-(trialkylsilyloxy)-isoxazolidines **28**-**30**, which under usual desilylating conditions gave an unprecedented oxidative cleavage to afford β-nitroalcohols (Scheme 25). The suggested mechanistic sequence is supported by the isolation of the

nitrosoderivative **31**, which was shown very prone towards the aerobic oxidation to give the corresponding nitroderivative.



Scheme 24



Scheme 25

It remains to be mentioned that the opening of the isoxazolidine ring is greatly facilitated *via* the preliminary protonation or alkylation of the endocyclic nitrogen.[54-58] In fact, the so-formed ammonium cations are readily opened by nucleophilic species. This procedure has been referred to by some Authors[54,55] as oxidative cleavage, but in our opinion this definition is incorrect and therefore we have not enclosed such ring-opening protocol in the present review.

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SOLID-PHASE INDOLE SYNTHESIS

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Abstract. *The indole skeleton is one of the most common heterocyclic structures found both in natural and synthetic products often having biological activity. Hence, a wide range of synthetic approaches to indole systems are used. In this review, novel approaches towards the synthesis of functionalized indoles using solid-phase chemistry are described. This chapter is divided into the different strategies: Fischer indole synthesis, Bartoli indole synthesis, Nenitzescu synthesis, Wittig indole synthesis, Madelung-Indol-syntheses, Palladium-catalyzed indole syntheses, cycloaddition strategies, C-arylation of substituted acetonitriles or 1,3-dicarbonyl compounds and finally, reduction of ortho-fluoro-nitroarenes.*

Contents

1. Introduction

Combinatorial solid-phase synthesis was initially developed for peptide synthesis, but it has been transferred since then to a broad range of non-peptide synthesis. The focus of this methodology is the use of parallel and automated techniques on solid-supports to produce large libraries of small molecules.[1] Solid-phase organic synthesis (SPOS) and the development of High Throughput Screening and Ultra High Throughput Screening have led to a dramatic increase in the number of substances which can be tested for their biological and pharmacological activities.[2] These techniques have turned out to be valuable tools for the optimization of new lead structures and are also applicable for compounds which might be less accessible with traditional liquid-phase chemistry. One of the main advantages of SPOS is the easier and faster work up of reactions.[1,2] A main aspect of SPOS is to develop strategies which allow introducing a broad range of substrates of a reagent class in each reaction to increase the diversity of the desired structures (points of diversity). Due to the efficiency of SPOS, this methodology is not only used in

pharmaceutical and medicinal chemistry,[2a,3] but also in areas such as the development and immobilization of catalysts, as well as material science and agro chemistry.[4]

In Figure 1, the principles of SPOS are depicted. Substrates, reagents or catalysts are immobilized on organic (*e.g.* polymers, dendrimers)[5] or inorganic supports (*e.g.* oxides, metals or glass).[6] For SPOS three components are required: 1) a suitable solid-support (*e.g.* polystyrene resin); 2) a suitable linker that connects the substrate to the support; 3) a suitable cleavage procedure that releases target molecules from the support.[3] The linker has to be stable under all reaction conditions, and it must be cleavable under conditions which do not destroy the desired product.[7] It is also shown in Figure 1 (electron microscopic picture) that functionalized polystyrenes for SPOS consist of spherical particles, which are called "beads".

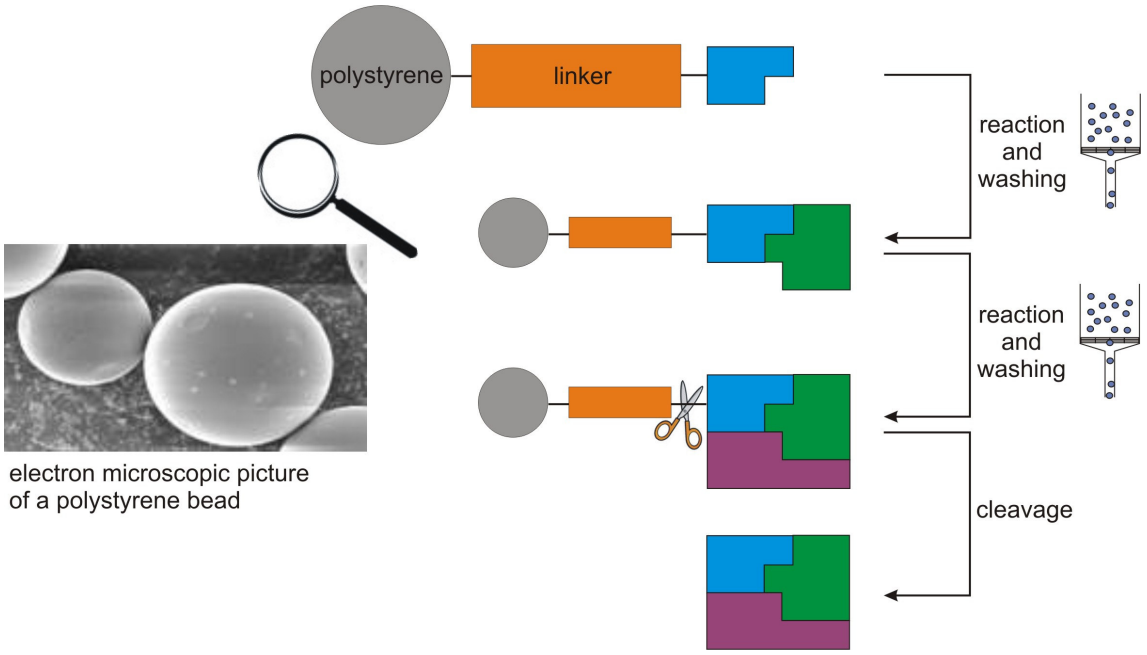


Figure 1. Principle scheme of solid-phase organic synthesis (SPOS) with an insoluble polymer. Electron microscopic image shows bead sizes of 50-150 μm.

The synthetic approach to the indole skeleton is one of the most investigated strategies in SPOS of benzoannelated heterocycles.[3b,8] For further benzoannelated nitrogen-heterocycles, *e.g.* benzodiazepines, see the review of Bräse *et al.* from 2002.[2]

Indoles have a very broad range of biological and pharmacological activities. A small selection of compounds relevant to medicine and pharmacy are depicted in Figure 2. Alongside the natural-occurring amino acid tryptophan (**8**), which is commercially available as a drug,[9] the indole core is found in the neurotransmitter serotonine (5-hydroxytryptamine, 5-HT, **1**), which is activating to 5-HT receptors.[10] The nortopsentins (**2**) show antitumor activity.[11] Martefragine A (**3**)[12] and other 5-(3-indolyl)oxazoles are inhibitors of lipid peroxidation.[13] Indololactam V (**4**) is a protein kinase C activator,[14] and fumitremorgine C (**5**) is an agent against mamma carcinomas.[15] The alkaloid hippadin (**6**) inhibits the fertility of male rats.[16]

Not only tryptophan (**8**), but also a wide range of compounds containing an indole structure are available as drugs (Figure 3). Indomethacine (**9**) is exhibited as an anti-inflammatory agent.[17] Tadalafil

(Cialis™, **10**) is a selective inhibitor of cyclic guanosine monophosphate (cGMP) type 5 specific phosphodiesterase (PDE 5).[18]

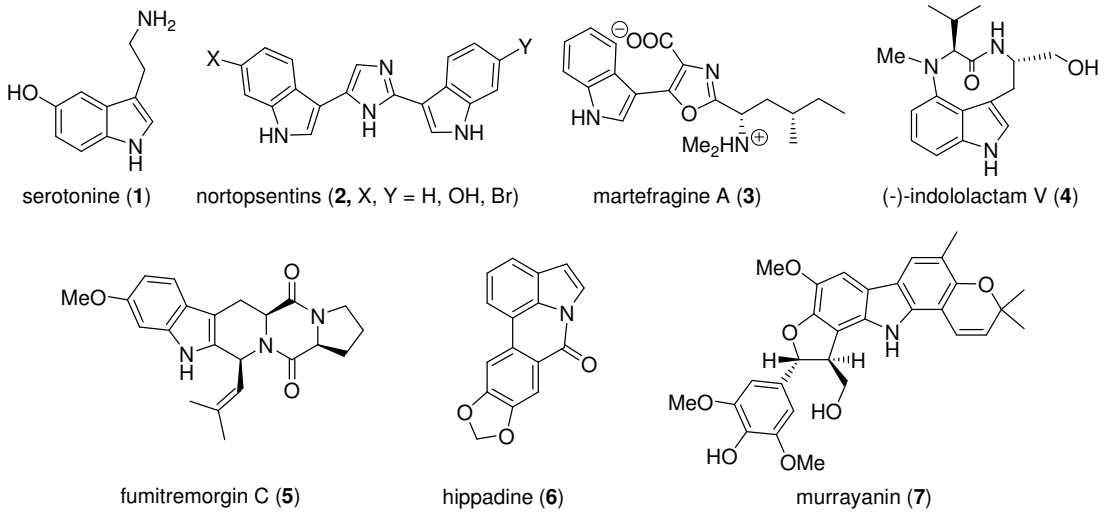


Figure 2. Selection of biologically and pharmacologically active compounds with an indole core.[9-16]

Fluvastatin (Cranoc™, Lescol™, **11**) is used for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia.[19] Sumatriptan (Imigrain™, Imitrex™, **12a**)[20] and Zolmitriptan (**12b**)[21] are serotonin agonists and are used against migraines, as well as being vasoconstrictor agents and anti-inflammatory agents. Another anti-inflammatory agent is etodolac (Lodine™, Ultradol™, **14**), which is in acute and long term use in the management of signs and symptoms of osteoarthritis and rheumatoid arthritis and is indicated for the management of pain.[22] Delaviridine (Rescriptor™, **13**) is an inhibitor of the non-nucleoside reverse transcriptase and it is used for the treatment of HIV-1 infections in combination with appropriate antiretroviral agents.[23]

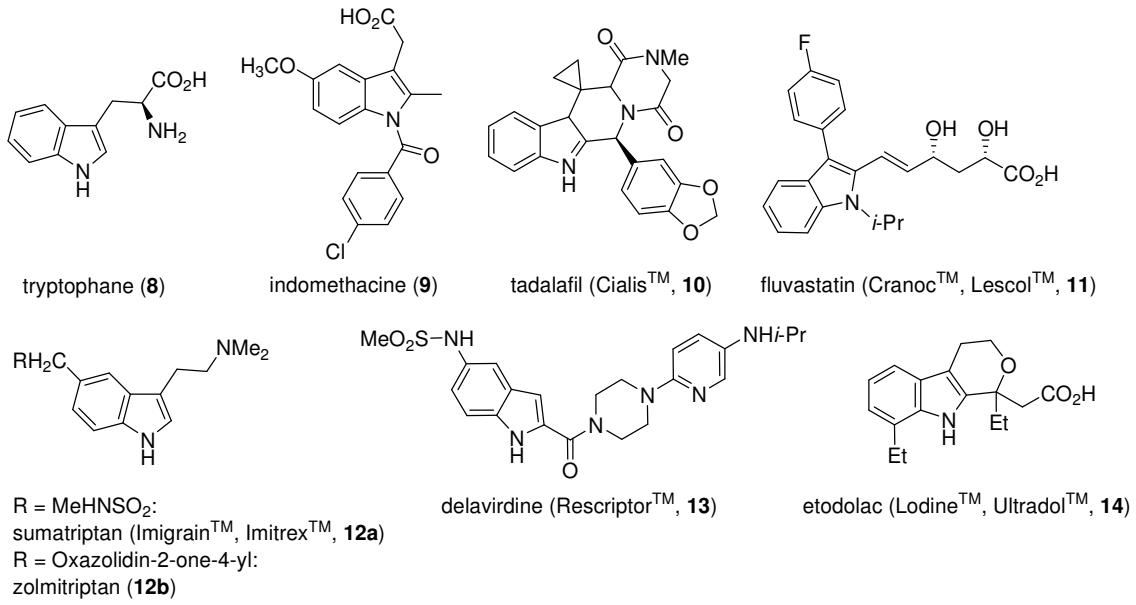
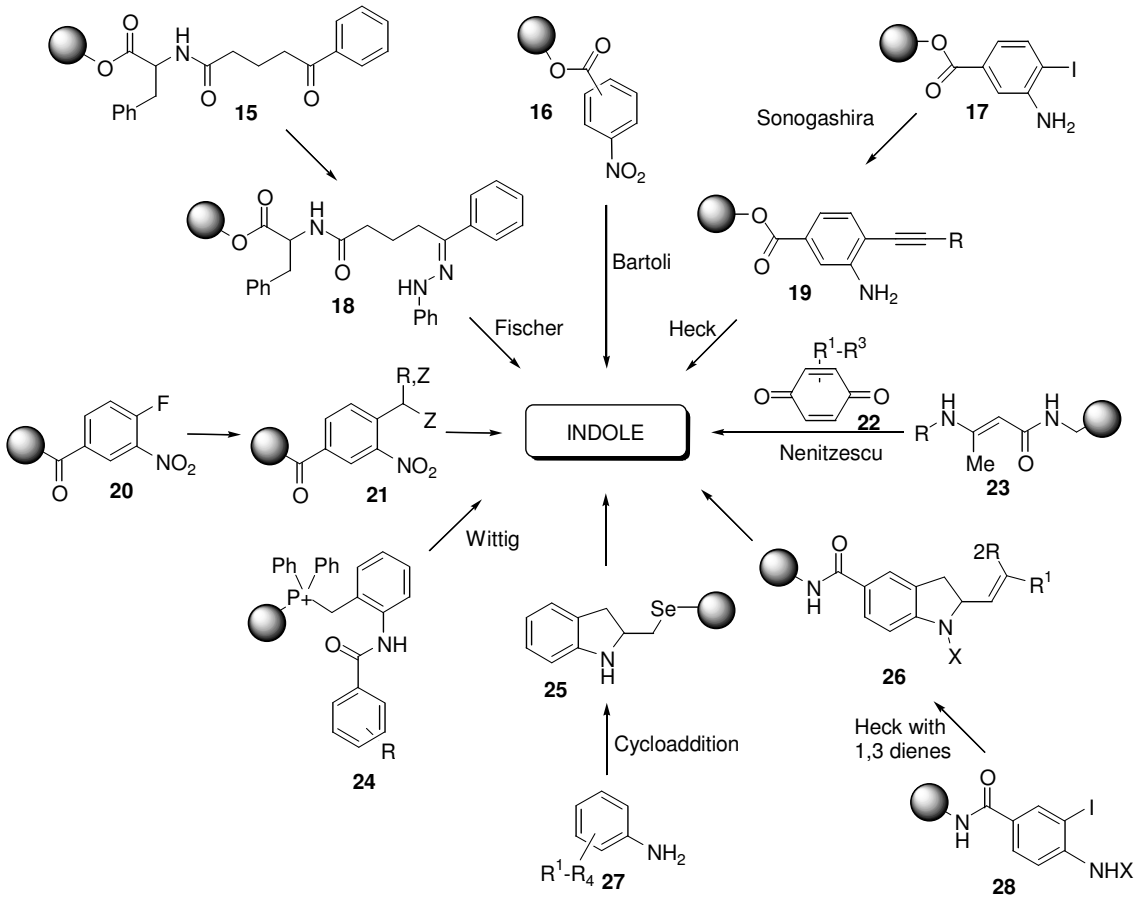


Figure 3. Commercially available drugs with an indole core structure.[17-23]

For SPOS, a wide range of synthetic approaches to indole systems are used. The different strategies are shown in Scheme 1. This chapter is divided into the different strategies: Fischer indole synthesis,[24] Bartoli indole synthesis,[25] Nenitzescu synthesis,[26] Wittig indole synthesis,[27] Madelung-Indol-Synthese,[28] Palladium-catalyzed indole syntheses,[29] cycloaddition strategies,[30] C-arylation of substituted acetonitriles or 1,3-dicarbonyl compounds[31] and finally, reduction of *ortho*-fluoro-nitroarenes.[31]

As well as the indoles, related structures with biological and pharmacological activities can also be synthesized on solid-supports. For example, the antiarrythmic agent indolizine[32] or antirheumatic effective oxoindoles[33] should be mentioned. The latter are also inhibitors of mandelonitril lyase,[34] and proteintyrosin kinase.[35] Indolines are selective 5-HT_3 receptor antagonists.[36]



Scheme 1

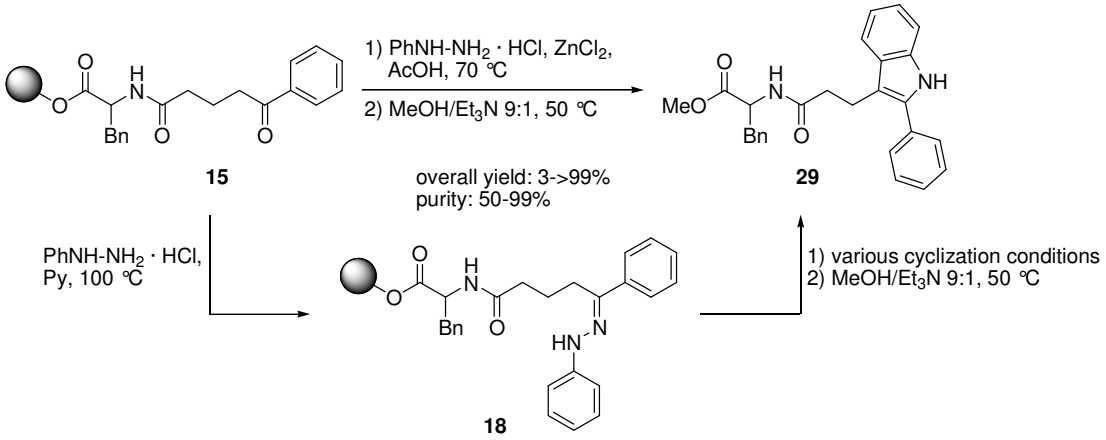
Selection of synthetic strategies for indoles on solid-supports.[24-31]

2. Fischer indole synthesis

The first SPOS of indoles was reported by the group of Chapman in 1996.[24a] Starting with the immobilized ketone **15**, they used standard liquid-phase protocols[37] for the Fischer indole synthesis (Scheme 2). The products were obtained in up to quantitative overall yields (two steps) and cleaved product purities >96%. One year later, this methodology was transferred to the synthesis of spiroindolines using Rapp TentaGel resin as solid-supports.[24b]

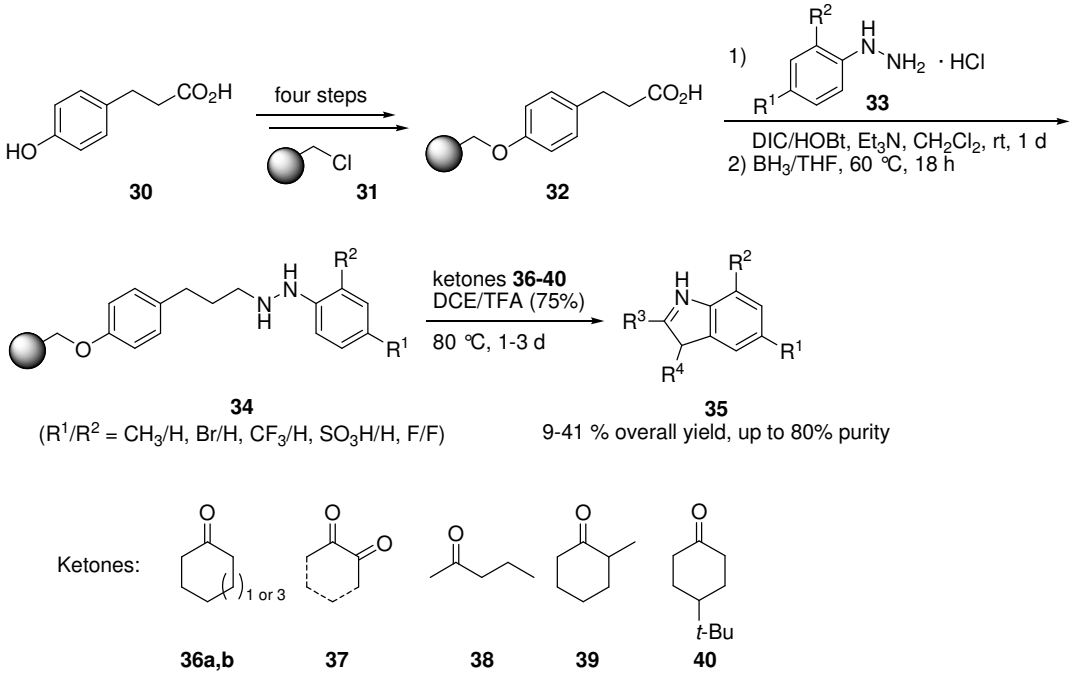
In 2003 a traceless SPOS using the Fischer indole protocol was reported by Waldmann and co-workers.[38] After the immobilization of hydrazine derivatives **33** with several functionalities like alkyl or

halogen substituents, as well as sulfonic acids on Merrifield resin (**31**), ketones **36-40** yielded eleven indoles **35** *via* a cyclization-cleavage mechanism (Scheme 3) in overall yields of 6-41% and purities up to 80%.



Scheme 2

First solid-supported Fischer indole synthesis by Chapman *et al.*[24a]

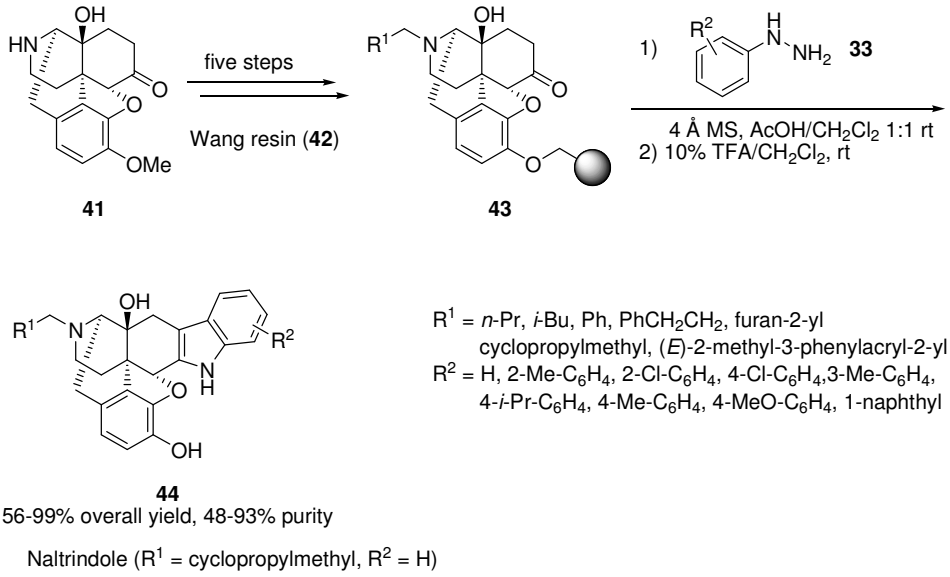


Scheme 3

Fischer indole synthesis on the solid-phase by Waldmann *et al.*[38]

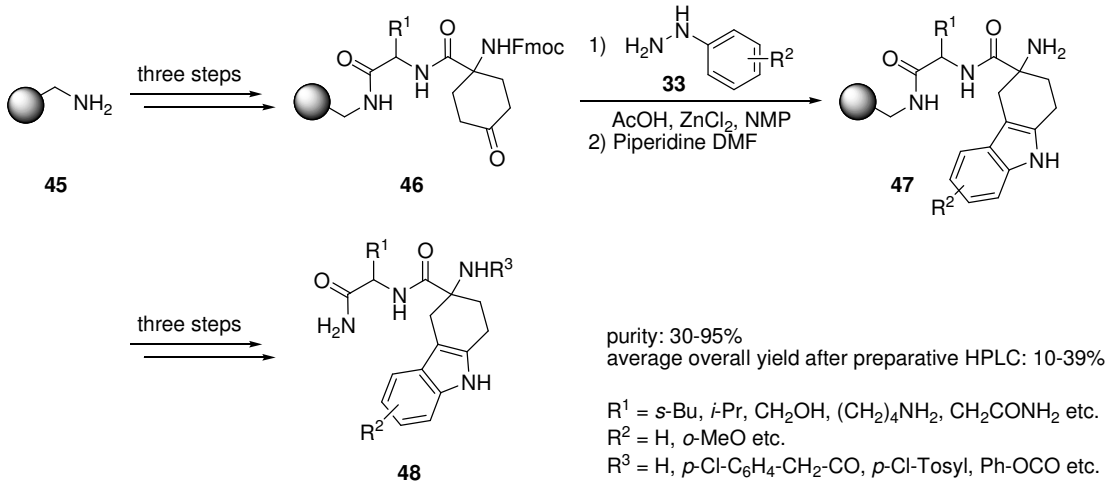
Takahashi performed the Fischer reaction in SPOS of naltrindole derivatives based on a one-pot release and cyclization methodology (Scheme 4).[39] The advantage of this strategy is the tolerance of a wide range of functional groups shown by a 40-membered indole library in good to excellent overall yields and purities of the cleavage product.

Recently, Koppitz *et al.* reported the SPOS of substituted 3-amino-3'-carboxy-tetrahydrocarbazoles.[40] They used Rink amide resin as a solid-support. In this strategy, the indole systems were also formed using standard conditions of the Fischer indole synthesis (Scheme 5).



Scheme 4

Solid-supported syntheses of naltrindole derivatives **44** by Takahashi *et al.*[39]

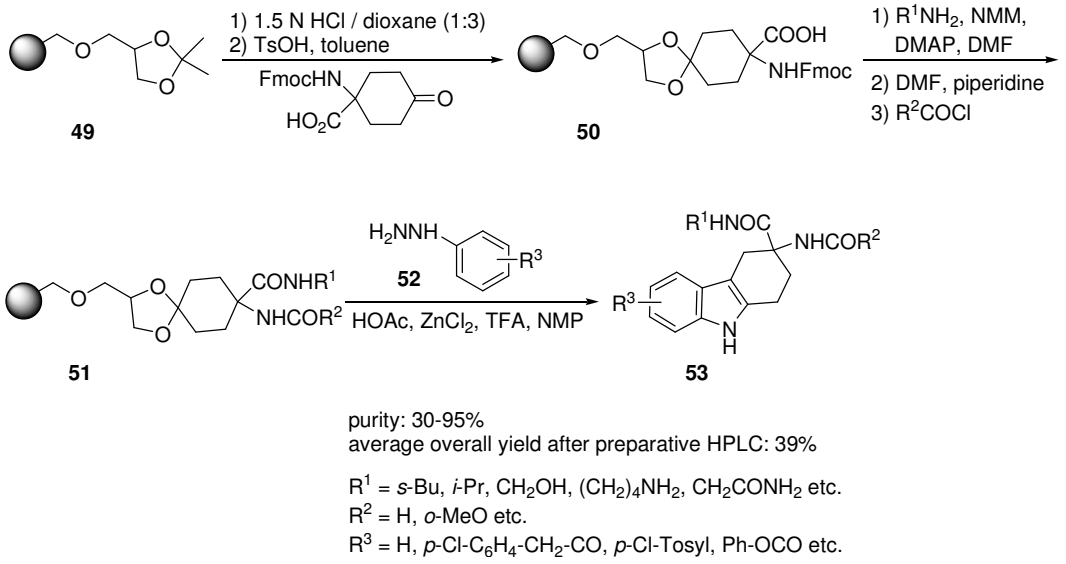


Scheme 5

SPOS of substituted 3-amino-3'-carboxy-tetrahydrocarbazoles **48** by Koppitz *et al.*[40]

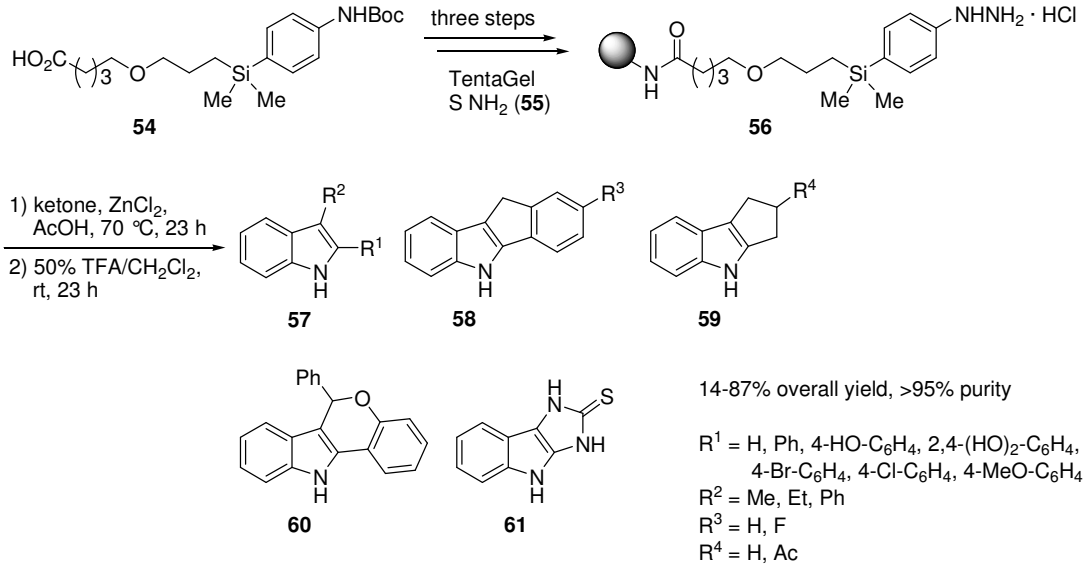
A second strategy for SPOS of tetrahydrocarbazoles **53** was described by Koppitz and co-workers.[40] Based on a patent of Ruhland *et al.*,[41] they introduced the Fischer indole synthesis as cleavage reaction to form the indole moiety (Scheme 6). As developed by the group of Ruhland, they synthesized the immobilized indole precursor **51**. A subsequent conversion with different arylhydrazines **52** lead to the cleavage of the tetrahydrocarbazoles **53** in moderate to excellent purities and reasonable overall yields. Using these two approaches, Koppitz *et al.* developed an indole library with about 1000 members in moderate overall yields (isolated) and moderate to excellent purities.

Very recently, TentaGel S NH_2 (**55**) was introduced as solid-support for the Fischer indole synthesis by Jeong and co-workers.[42] The addition of various ketones yielded the indoles **57-61** in moderate to very good overall yields and excellent purities (Scheme 7).



Scheme 6

Fischer synthesis as cleavage reaction in the SPOS of tetrahydrocarbazoles **53** by Koppitz *et al.*[40,41]



Scheme 7

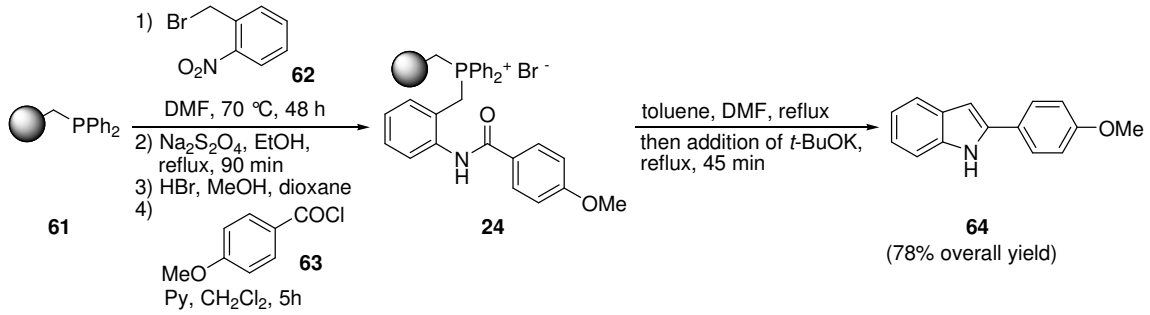
Solid-supported Fischer indole synthesis by Jeong *et al.*[42]

3. *Aza*-Wittig, Nenitzescu, Madelung and Bartoli indole synthesis

To our knowledge, there was only one example for each of the *aza*-Wittig,[27] the Nenitzescu,[43] the Madelung,[28] and the Bartoli[44] indole synthesis on solid-phase described.

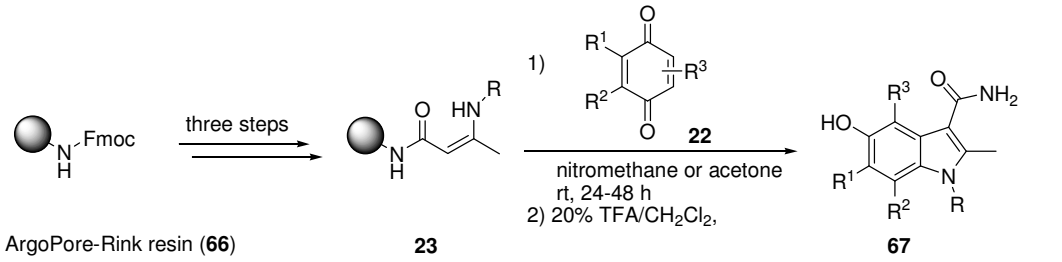
In 1996, Hughes used an *aza*-Wittig reaction to build up an indole system on a solid-support.[27] Starting from the resin-bound phosphine **62**, the phosphonium salt was prepared. The anilide **24** was synthesized by reduction of the nitro group and treatment of benzoyl chloride **64**. The indole **65** was achieved after cyclization and cleavage in 78% yield (purity is not mentioned in this manuscript).

Ketcha and co-workers used ArgoPore-Rink amine resin (**66**) as a solid-support for the Nenitzescu indole synthesis (Scheme 9).[43] After forming of the enaminone **23**, a Michael addition of benzoquinones **22** and subsequent cleavage yielded fourteen indoles **67** in up to 95% yield and purities up to >99%.



Scheme 8

Indole synthesis by solid-supported *aza*-Wittig reaction by Hughes.[27]



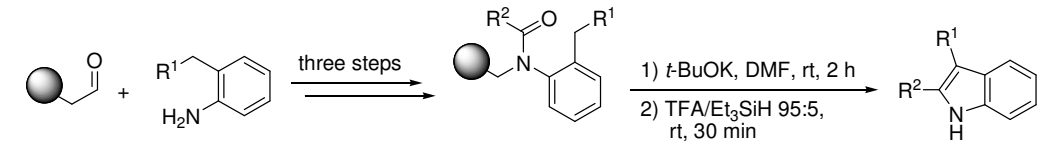
0-95% overall yield, 14->99% purity

R^1 = H, Me, Ph, MeO, Cl, Br
R^2 = H, Me
R^3 = H, Cl

Scheme 9

Nenitzescu indole synthesis on solid-phase by Ketcha *et al.*[43]

The Madelung indole synthesis was transferred to SPOS by Wacker and Kasireddy.[28] The anilins **69** were immobilized on Bal resin (**68**) and treated with various acid chlorides to yield resin **70**. Under basic conditions, the cyclization to the indole took place and after cleavage, fifteen indoles **57** were obtained in yields up to 88% and reasonable to excellent purities.



0-88% overall yield, 51-95% purity

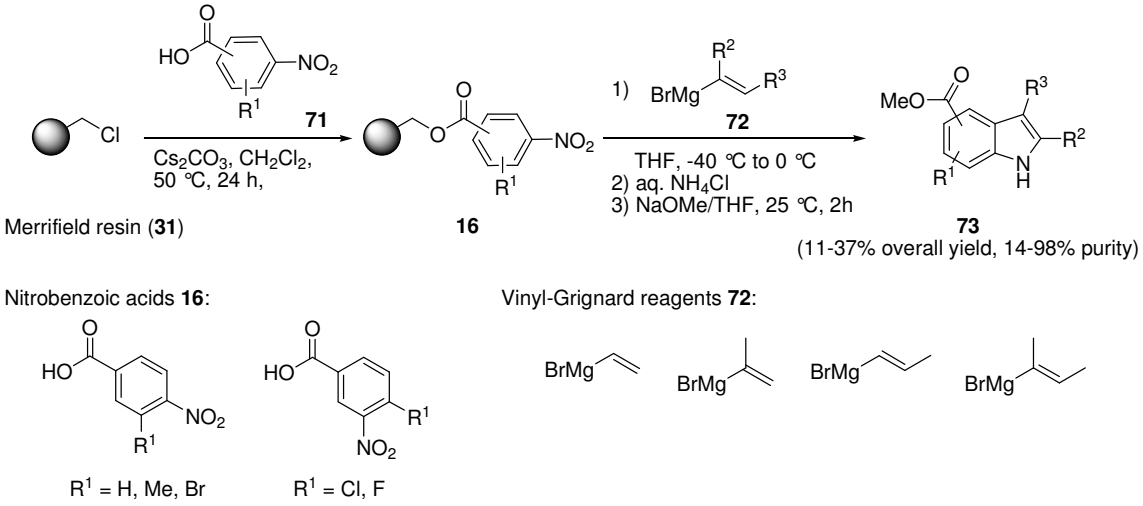
R^1 = CN, CO_2t-Bu/CO_2H, $CONMe_2$
R^2 = Et, *t*-Bu, CH_2CH, Ph, Bn, $PhCH_2CH_2$, 2-Et-C_6H_4, 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 3-Pyridyl, 5-Isoxazolyl

Scheme 10

Madelung indole synthesis on the solid-phase by Wacker and Kasireddy.[28]

Recently, Knepper and Bräse reported the first indole synthesis on a solid-support according to the Bartoli[45] protocol.[44] After immobilization of various nitro benzoic acids **71** on Merrifield resin (**31**) the

treatment with different vinyl-Grignard reagents **72** and subsequent cleavage, the methyl indolcarboxylates **68** were obtained in modest overall yields and moderate to excellent purities. Further derivatization on the solid-phase was also possible by palladium-mediated Heck and Suzuki cross coupling reactions. Nineteen different indoles were synthesized with this approach.

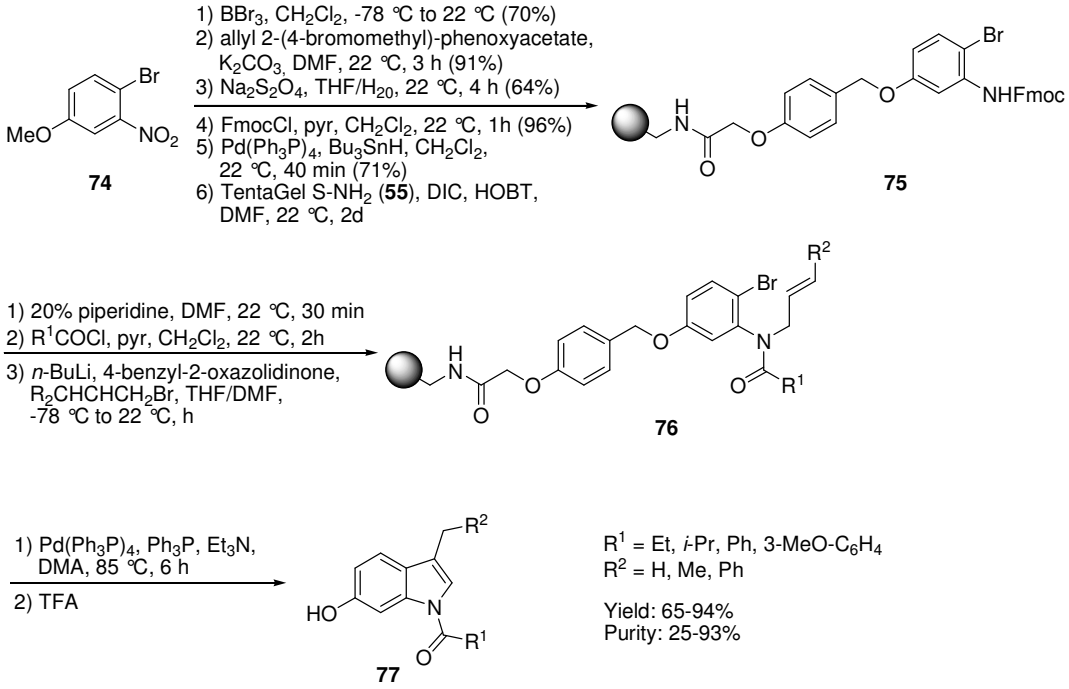


Scheme 11

Bartoli indole synthesis on a solid-support by Knepper and Bräse.[44]

4. Palladium-catalyzed indole synthesis

Palladium-catalyzed reactions offer an important approach to the synthesis of various heterocycles.[46] In the last decade, various strategies for the palladium catalyzed solid-supported indole syntheses have been developed.

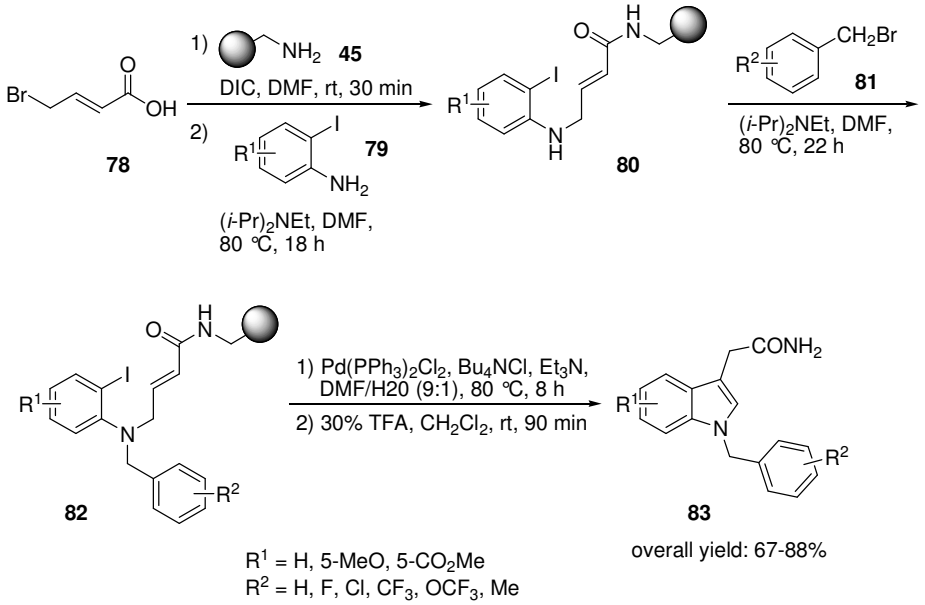


Scheme 12

Indole analogue syntheses by intramolecular Heck reaction by Yun and Mohan.[47]

An intramolecular Heck reaction on a solid-support was reported as a new approach for the syntheses of indole derivatives by Yun and Mohan in 1996.[47] The immobilized cyclization precursor **76** was synthesized in nine steps starting from anisol **74**. Resin **76** was converted *via* an intramolecular Heck reaction to the corresponding indoles **77**, which were obtained after cleavage with TFA in good to excellent overall yields and moderate to high purities (Scheme 12). Given the large pool of available acid chlorides and allyl reagents, as well as the mild reaction conditions this methodology can be transferred to automation synthesis for large substance libraries.

In 1997, Zhang and Maryanoff synthesized indole and benzofuran systems on the solid-phase *via* Palladium-mediated cyclizations.[48] After constructing the cyclization precursor **82** starting from bromocrotonic acid **78**, the cyclization took place to form twelve corresponding indoles **83** in good to very good yields (Scheme 13). This strategy offers the opportunity to introduce two diversity points into the target molecule. It also showed that more complex molecules could be built up in this way. Another strategy using a Pd-mediated heteroannulation of internal alkynes lead to the solid-supported synthesis of trisubstituted indoles.[49]



Scheme 13

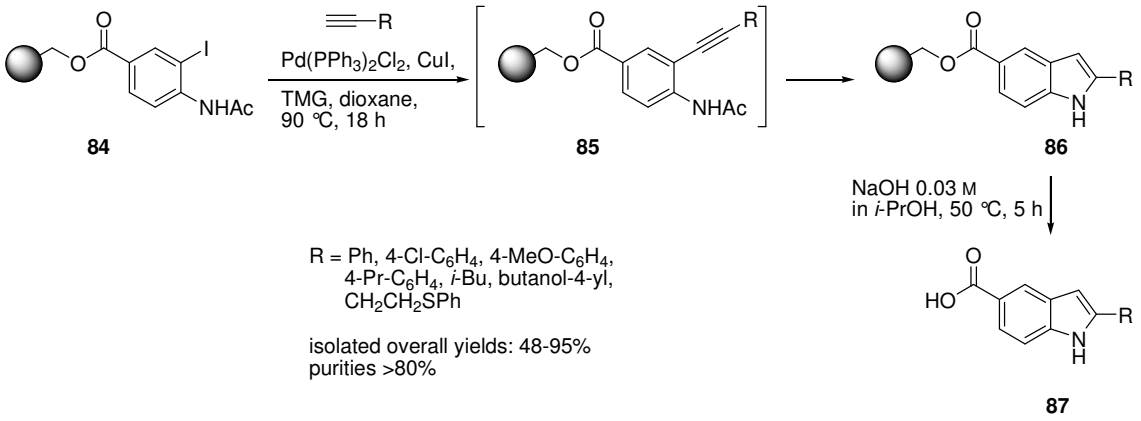
Palladium-mediated indole syntheses on a solid-support by Zhang and Maryanoff.[48]

Bedeschi and co-workers reported a Sonogashira coupling reaction with *ortho*-iodo anilines with subsequent cyclization to sixteen corresponding immobilized indoles **86** in the same year.[29b] As support, TentaGel-S^{TM} was used. After cleavage, twelve carboxylated indoles **87** were obtained in yields of up to 95% and purities of >80% (Scheme 14).

A similar synthesis was developed by Collini and Ellingboe.[29a] In contrast to Bedeschi *et al.,* they could introduce two points of diversity. As a solid-support, chlorinated Wang resin (**42**) was used. They also showed that an *N*-alkylation under standard conditions is possible before cleavage. The tri-substituted carboxy indoles **88** were obtained in 34-76% yield (Scheme 15).

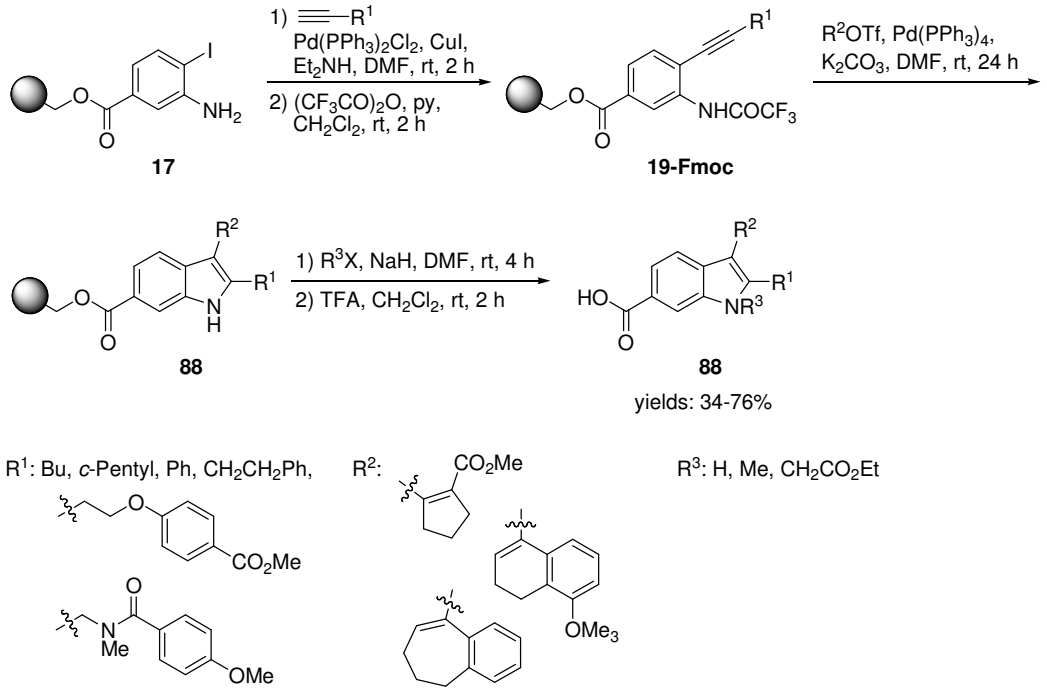
In 1998, another pathway under Heck reaction conditions was introduced by Wang and Huang starting with a solid-supported *ortho*-iodo aniline derivative **28-R^1** and 1,3-dienes **89**.[29e] Twelve indolines **90** were

synthesized by Pd-mediated annulation. After cleavage, the indolines **90** were obtained in very good overall yields and reasonable to excellent purities. This strategy was also transferred to the synthesis of benzoannelated pyrans and tetrahydroquinolines.



Scheme 14

Pd-catalyzed indole synthesis on a solid-support by Bedeschi *et al*.[29b]

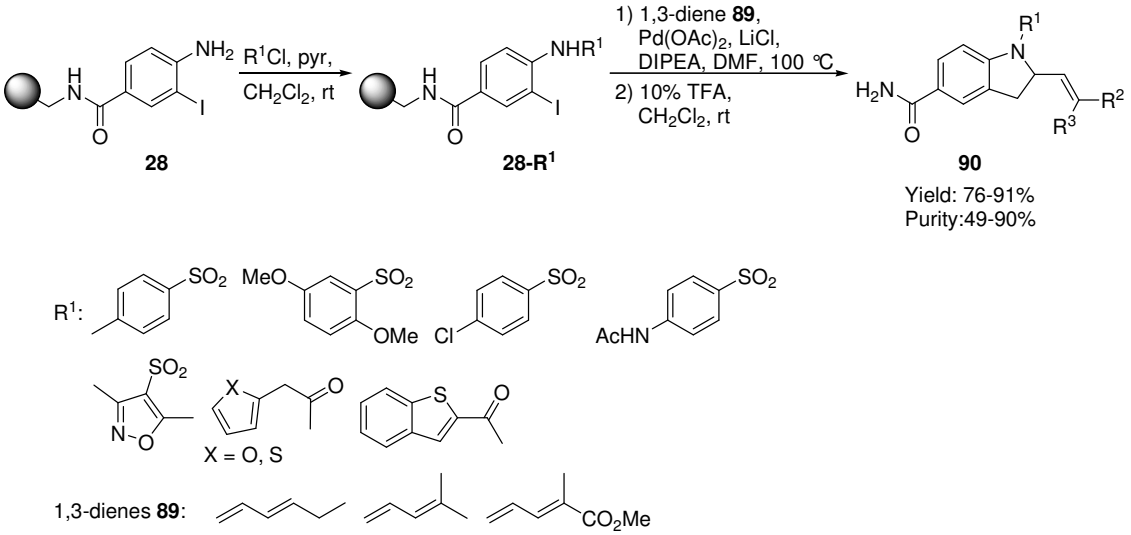


Scheme 15

Pd-catalyzed indole synthesis on a solid-support by Collini and Ellingboe.[29a]

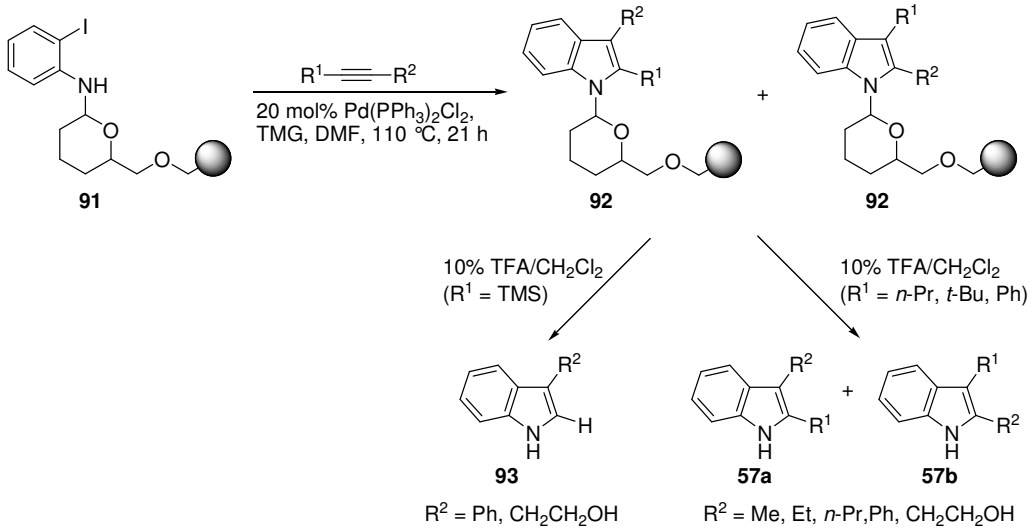
A traceless solid-phase synthesis of 2,3-disubstituted indoles was developed by the group of Smith using Ellman's THP resin in 1998.[29d] Following a cross-coupling reaction, a cyclization to form the indole ring took place. After traceless cleavage, the indoles **57a,b** and **93** were found (Scheme 17). The results of conversion (crude products), isomeric ratio (**57a**:**57b**) and mass recovery are given in Table 1. In the case of

trimethylsilylalkynes only one regioisomer was found. Clean protodesilylation was observed during cleavage giving rise to the pure 3-substituted indoles **93**.



Scheme 16

SPOS of indolines *via* Pd-catalyzed annulation by Wang and Huang.[29e]



Scheme 17

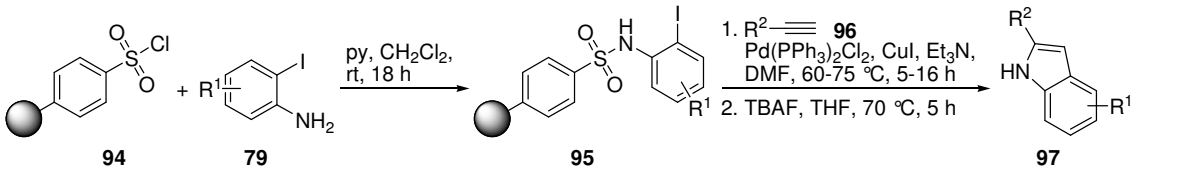
Traceless indole synthesis on a solid-support by Smith *et al.*[29d]

Table 1. Solid-supported traceless indole synthesis by Smith *et al.*[29d]

Entry	R^1	R^2	Conversion [%][a]	Isomeric ratio **57a**:**57b** [%]	Mass recovery [%]
1	Ph	Et	100	84:15	63
2	TMS	CH_2CH_2OH	100	100:0	82
3	Ph	Ph	93	-	97
4	TMS	Ph	100	100:0	73
5	*n*-Pr	*n*-Pr	100	-	53
6	*t*-Bu	Me	48	100:0	55

[a]Determined by HPLC analysis of crude cleavage products.

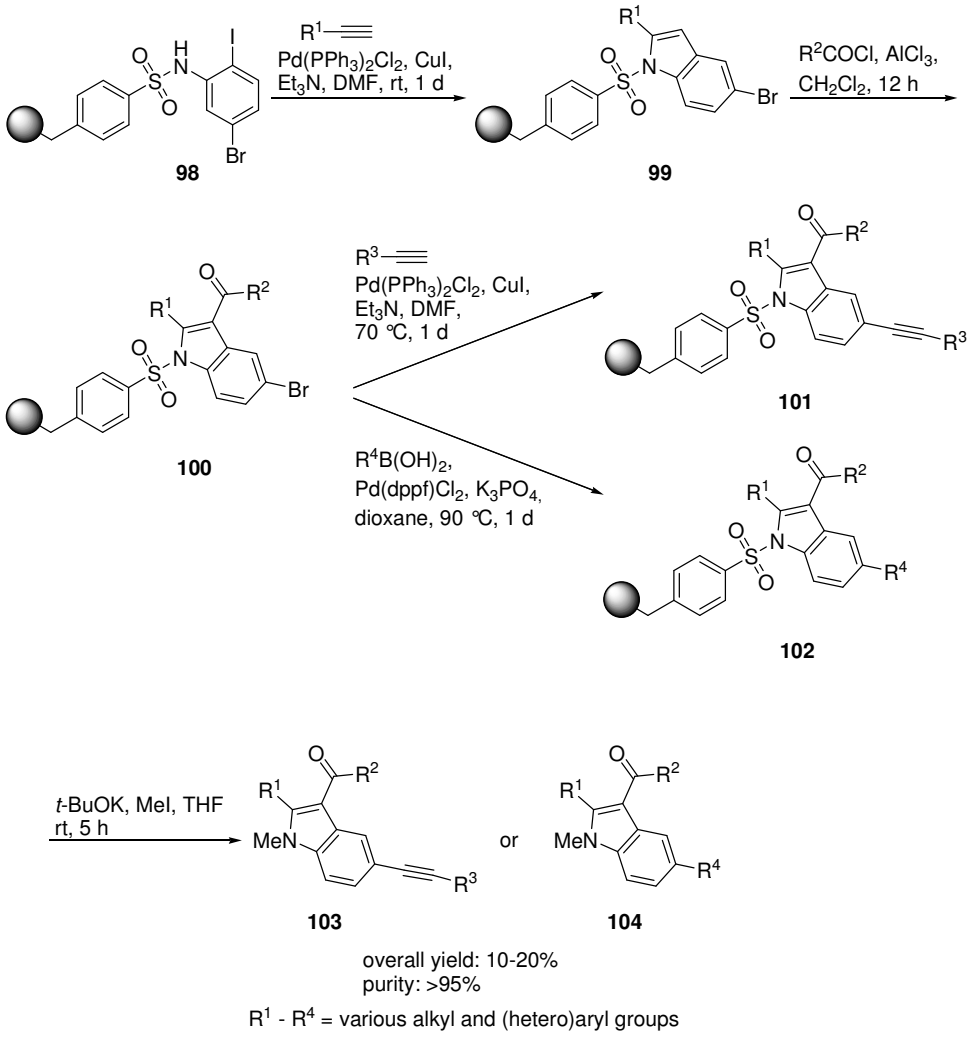
In 2000, Zhang *et al.* developed a facile solid-phase construction of indole derivatives based on a traceless, activating sulfonyl linker.[50] Various *ortho*-iodo anilines **79** were immobilized on a sulfonyl chloride resin **94** and converted under Pd-catalysis with various terminal alkynes **29** to seventeen corresponding indoles **97**, which were then released from the solid-support with TBAF in excellent overall yields and purities (Scheme 18). A further derivatization *via* immobilized 3-indolmercury species was possible.



R^1 = H, 6-F, 6-MeO, 5-CO_2Me
R^2 = Bu, Ph, $MeOCH_2$, $HOCH_2CH_2$, $(EtO)_2CH$, 4-Me-C_6H_4, 4-F-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, $PhSCH_2$, 6-MeO-2-Np, 2-pyridyl

Scheme 18

Facile solid-phase construction of indole derivatives by Zhang *et al.*[50]



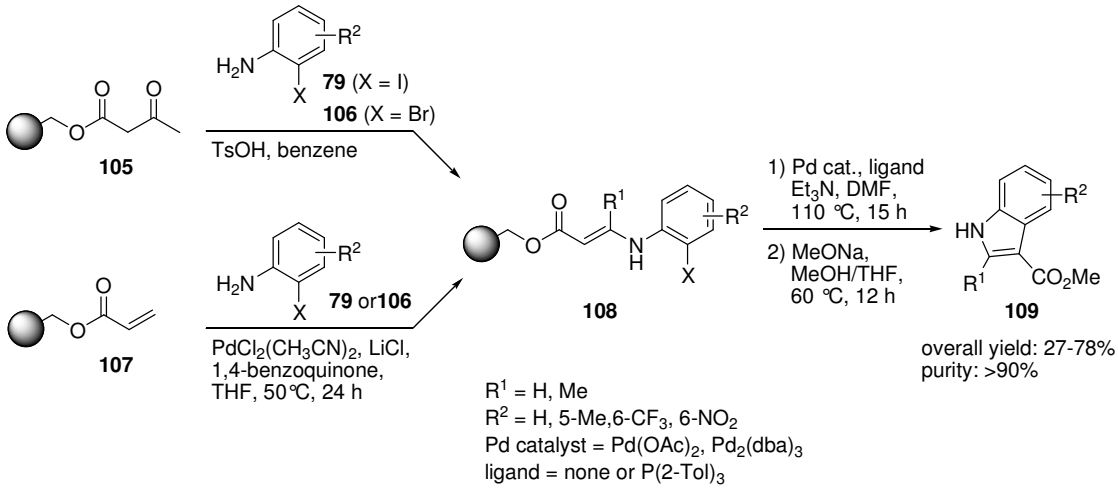
R^1 - R^4 = various alkyl and (hetero)aryl groups

Scheme 19

SPOS of 2,3,5-trisubstituted indoles by Schultz *et al.*[51]

Another SPOS of 2,3,5-trisubstituted indoles was published by Schultz and co-workers in 2001.[51] After immobilization of 4-bromo-2-iodo-aniline on resin **94** and cyclization to the indoles **99** as shown by Zhang *et al.* (Scheme 18), further derivatization was carried out by Lewis-acid catalyzed acylation, Sonogashira or Suzuki cross-coupling reactions as well as during subsequent cleavage. The trisubstituted indoles **103** and **104** were obtained in modest overall yields, but in excellent purities (Scheme 19). Six R^1-alkynes, thirteen acid chlorides (R^2) and eight R^3-alkynes were introduced in the indole library synthesis.

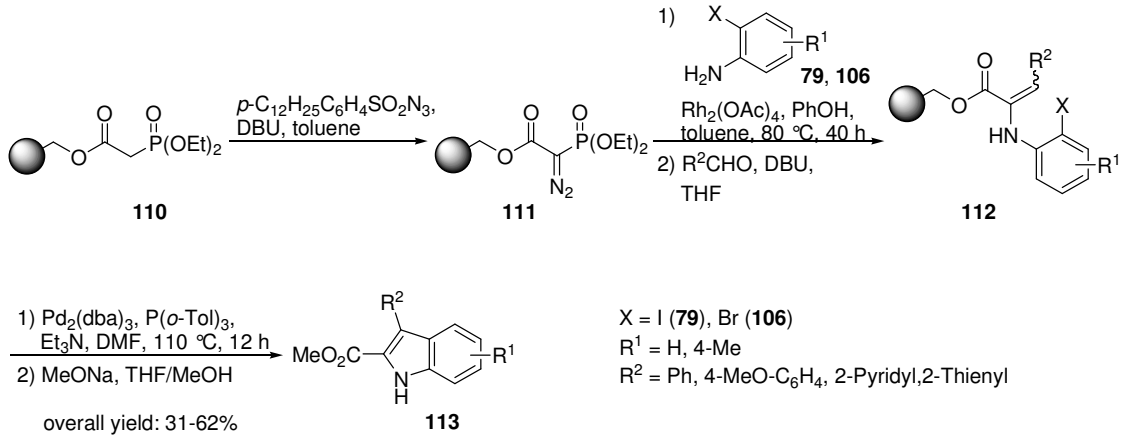
In 2002, Yamazaki and Kondo reported the Pd-catalyzed synthesis of indole 3-carboxylates on a solid-support.[52] Starting from two different resins **105** and **107**, the *ortho*-halide anilines **79** or **106** were immobilized and than converted to eighteen indole 3-carboxylates **109** under Pd-catalysis in moderate to good overall yields and excellent purities.



Scheme 20

Pd-catalyzed SPOS of indole 3-carboxylates **109** by Yamazaki and Kondo.[52]

Other palladium catalyzed reactions to yield indoles were developed by Kondo *et al.*. They reported immobilized α-diazophosphonoacetate **111** as a versatile key precursor for palladium catalyzed indole synthesis on a polymer support.[53]

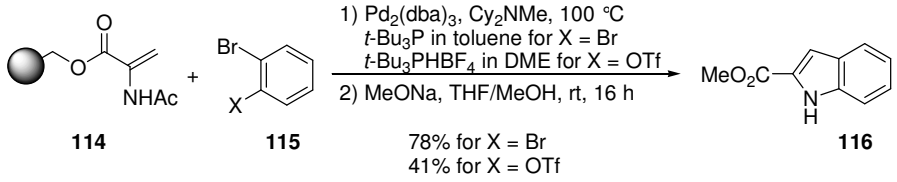


Scheme 21

α-Diazophosphonoacetate **111** as precursor for Pd-catalyzed indole synthesis on a polymer-support by Kondo and Yamazaki.[53]

Following diazo transfer to the immobilized phosphonoacetate **110** and rhodium-catalyzed N-H insertion, the precursors **112** were cyclized under palladium catalysis. The corresponding indoles **113** were obtained in 31-62% yields after cleavage with methanolate (Scheme 21).[53] Details concerning the purities of the cleavage products were not given.

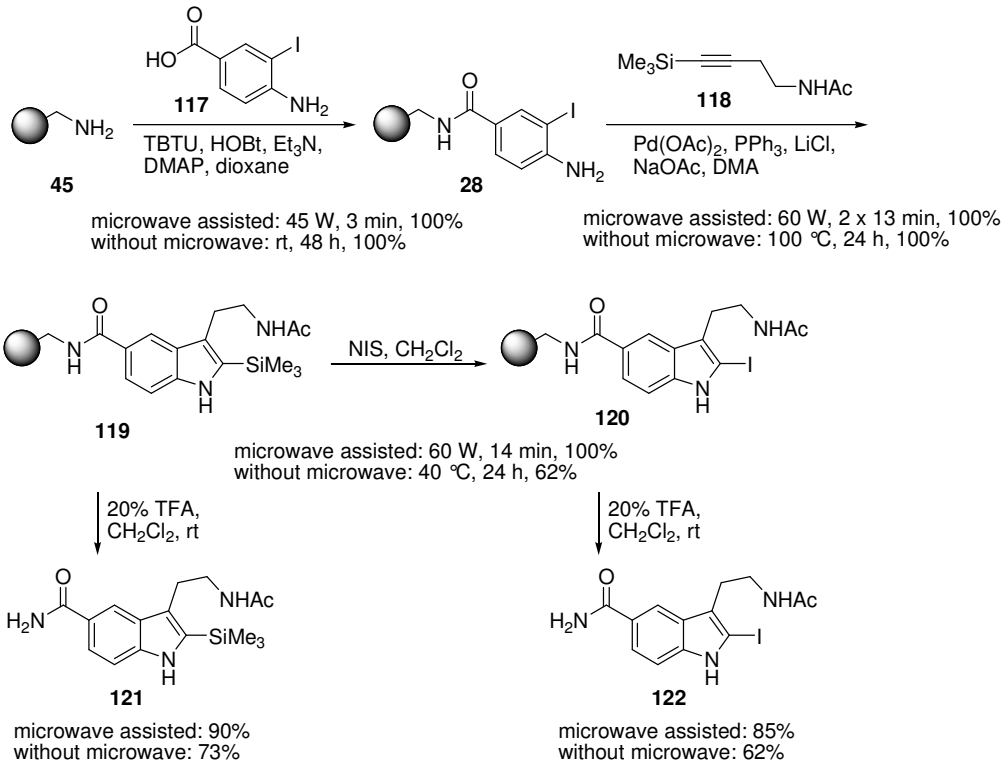
Based on their previous results,[52-54] the same group investigated a palladium catalyzed tandem *C,N*-arylation of immobilized enamine **114** for solid-phase indole synthesis.[55] In this case the *N*-arylation and subsequent cyclization took place in a one pot-reaction to give the indoles **116** in reasonable to good yields (Scheme 22, purities are not described).



Scheme 22

C,N-Arylation of immobilized enamine **114** for solid-phase indole synthesis by Kondo *et al*.[55]

The transposition of the solid-supported synthesis of the indole core of melatonin analogues under microwave irradiation were reported by Berteina-Raboin *et al*..[56] They used a combination of the Sonogashira and the Heck cross-coupling reaction (Scheme 23).

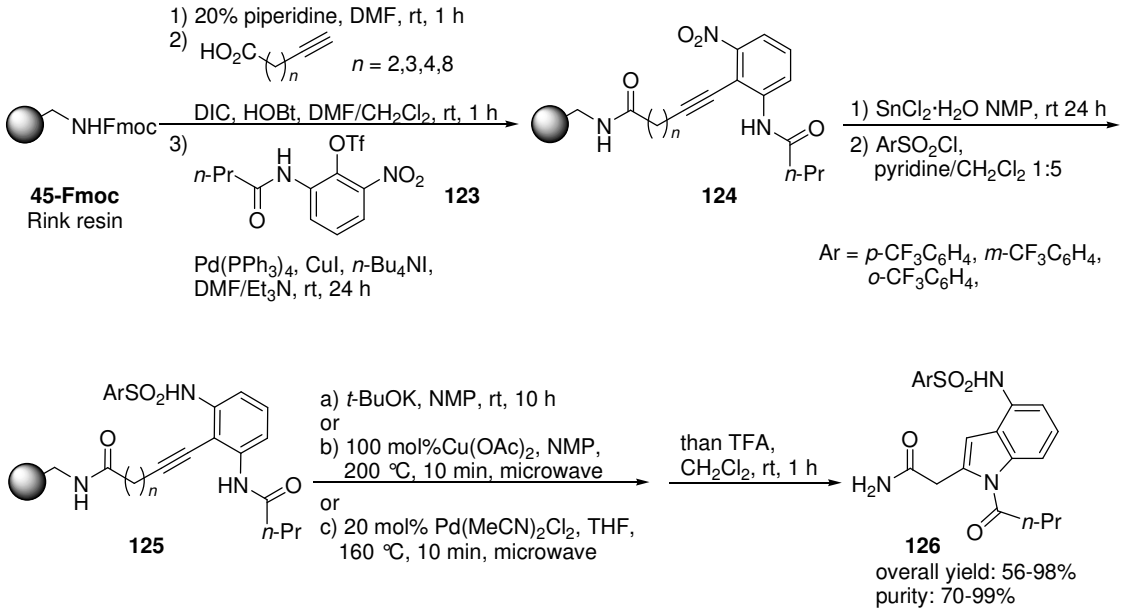


Scheme 23

Microwave-assisted indole synthesis on a solid-support by Berteina-Raboin *et al*.[56]

After immobilization of the *ortho*-iodo aniline **117**, a Pd-mediated cross-coupling with silyl alkynes **118** and subsequent cyclization reaction led, after cleavage, to the indole **121**. In all steps, shorter reaction times were observed under microwave irradiation. The yields were comparable to the reactions without microwave irradiation (62-85%).

A further synthesis using microwave assisted solid-phase organic synthesis as the key step for an indole library construction was reported by Dai *et al.* in 2003.[57] The immobilized cyclization precursor **125** was synthesized in five steps starting from Rink resin **45-Fmoc** (Scheme 24). Under different cyclization conditions twelve indoles **126** were obtained after cleavage in good to high yields and good to excellent purities. In the Cu- or Pd-mediated cyclization the microwave assisted reactions were completed after 10 min (reactions without microwave 3 to 24 h).

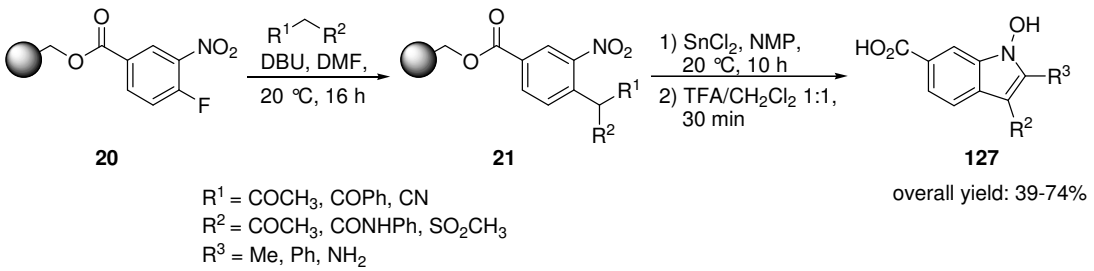


Scheme 24

SPOS indole library construction by Dai *et al.*[57]

5. Miscellaneous synthetic strategies

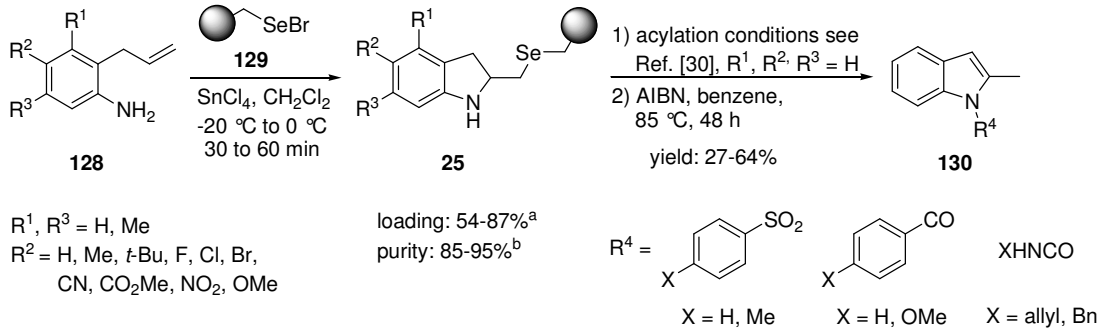
In 1999, Stephensen and Zaragoza reported a SPOS of *N*-hydroxyindoles **127** by *C*-arylation of substituted acetonitriles and 1,3-dicarbonyl compounds with polystyrene-bound aryl fluorides **20**.[31] Three indoles were formed under reductive conditions using tin(II)chloride. After cleavage, the hydroxyindoles **127** were obtained in moderate to good yields and as analytically pure products after recrystallisation.



Scheme 25

SPOS of *N*-hydroxyindoles **127** by Stephensen and Zaragoza.[31]

The solid-supported cycloaddition reaction strategy, using selenium resin **129** as an indoline approach, was developed by Nicolaou *et al.*.[30] The *ortho*-allyl anilines **128** and selenium resin **129** were suspended in dichloromethane and treated with tin(IV)chloride as Lewis-acid to give the immobilized indolines **25** in high purities and loadings of 87% as determined by weight of cleavage product. A further *N*-acylation and conversion to fourteen indoles **119** was performed. This strategy was also introduced to the syntheses of the natural-product like indole structures, namely 2-methyl indolines, polycyclic indolines, 2-methyl indoles, and 2-propenyl indolines.[58]

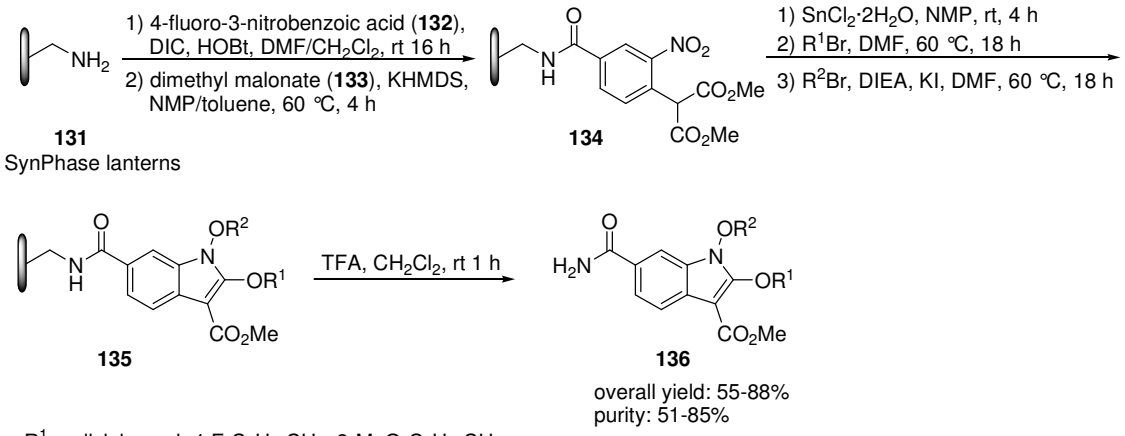


[a] as determined by weight of cleavage product
[b] estimated by cleavage (*n*-Bu_3SnH, AIBN, 90 °C), polarity-based purification, and ^1H NMR analysis

Scheme 26

Solid-supported cycloaddition reaction as indoline approach and further derivatization by Nicolaou *et al.*[30,58]

In 2003, a SPOS of 1,2-dialkoxyindoles on SynPhase lanterns (**131**) was described by Wu and Ede.[59] After immobilization of 4-nitro-3-nitrobenzoic acid (**132**) on the solid-support and reaction with dimethyl malonate (**133**), a reductive cyclization yielded the indole core **135**. After further alkylation, a library of 64 1,2-dialkoxyondoles **136** was constructed in reasonable to very good overall yields and purities. This approach is comparable with Stephensen's and Zaragoza's strategy as shown in Scheme 25.

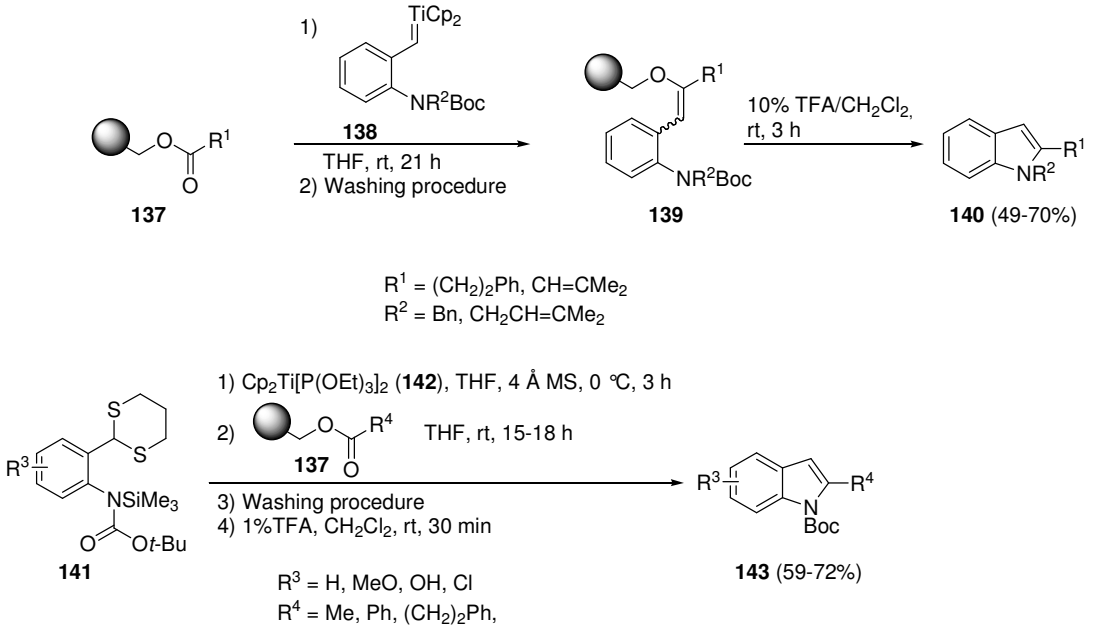


R^1 = allyl, benzyl, 4-F-C_6H_4-CH_3, 3-MeO-C_6H_4-CH_3, 4-Me-C_6H_4-CH_3, 4-Br-C_6H_4-CH_3, 3-Cl-C_6H_4-CH_3, 3,5-F_2-C_6H_4-CH_3
R^2 = allyl, propyl, benzyl, 3-Cl-C_6H_4-CH_3, 4-*t*-Bu-C_6H_4-CH_3, 4-F-C_6H_4-CH_3, 3-MeO-C_6H_4-CH_3, 3-Me-C_6H_4-CH_3,

Scheme 27

1,2-Dialkoxyindole syntheses on SynPhase lanterns (**131**) by Wu and Ede.[59]

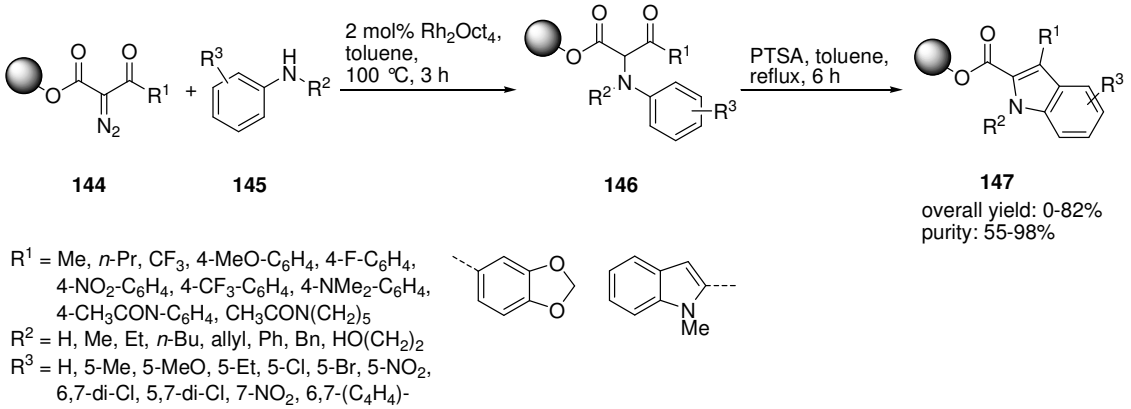
In the same year, Hartley and co-workers developed a solid-supported synthesis of 2-substitueted benzofurans and indoles using functionalized titanium benzylidene reagents **138**.[60] The titanium benzylidene reagents **138** can be generated from the titanium precursors **142** by the reduction of the corresponding thioacetals **141**.[61] Using these strategies, Hartley *et al.* created an indole library in good overall yields (Scheme 28).



Scheme 28

Solid-phase indole synthesis using benzylidene reagents **138** by Hartley *et al.*[60]

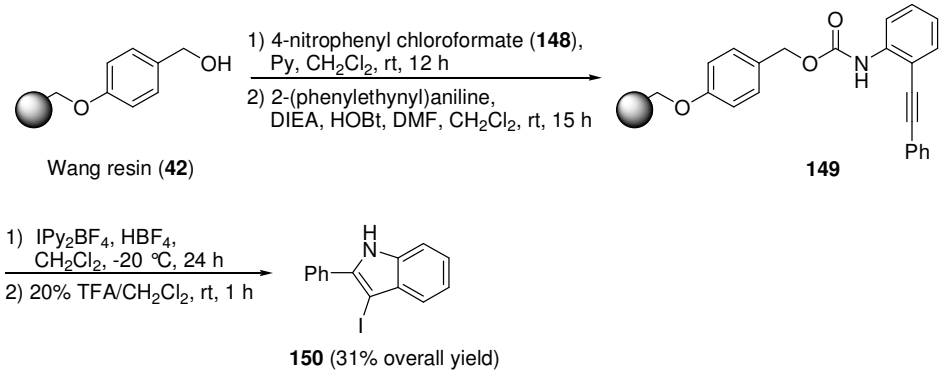
A SPOS variant of the Bischler indole synthesis based on a rhodium carbenoid N-H insertion was developed by the Janda group in 2003.[62] In this synthesis (Scheme 29), *J*anda*J*el resin was used as support and the key step is an N-H insertion of *N*-alkylanilines **145** into a polymer-bound rhodium carbenoid intermediate to yield the corresponding α-arylamino-β-ketoester **146**. Treatment of these amino acid derivatives **146** under acidic conditions gave the indole library **147** *via* a cyclodehydration reaction in 0-82% overall yield and 55-98% purity.



Scheme 29

Rhodium catalyzed indole synthesis using *J*anda*J*el resin as support by Janda *et al.*[62]

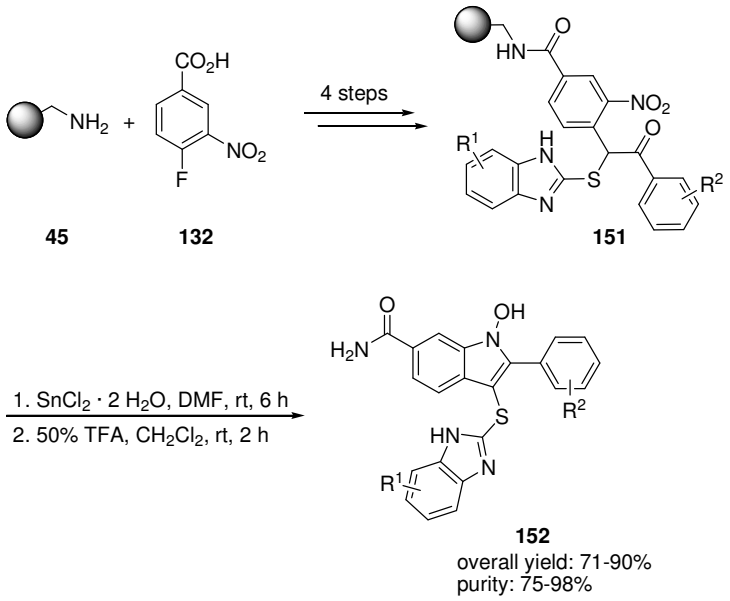
The first iodocyclization reaction on a solid-support for the synthesis of 3-iodoindoles was developed by the group of Barluenga in 2003.[63] Starting from Wang resin (**42**) they synthesized the cyclization precursor **149** *via* activation with 4-nitrophenyl chloroformate (**148**) (Scheme 30). Treatment of resin **149** with IPy_2BF4 led to the corresponding iodoindole **150** which was released in 31% overall yield from the solid-support.



Scheme 30

Solid-supported iodocyclization to iodoindole **150** by Barluenga *et al.*[63]

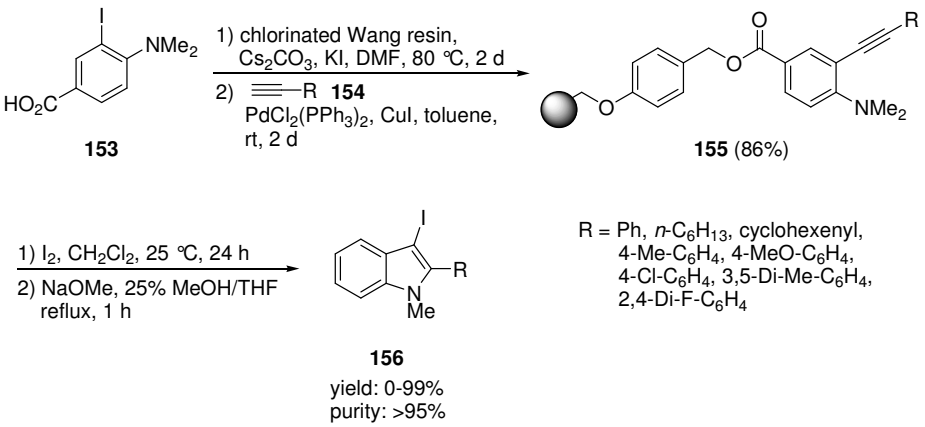
In 2004, Roy *et al.* reported a novel SPOS of highly substituted *N*-hydroxy indoles (**152**) *via* intramolecular rearrangement.[64] The indole cyclization precursor **151** can be synthesized in four steps starting from Rink resin (**45**) and 4-fluoro-3-nitro-benzoic acid (**132**). Reductive cyclization and subsequent cleavage yielded the highly substituted *N*-hydroxy indoles **152** in good to excellent yields and up to 98% purity. The strategy can be used for the generation of large libraries using automated synthesizer.



Scheme 31

Solid-supported intramolecular rearrangement for the synthesis of biheterocyclic indole-benzoimidazole derivatives **151** Roy *et al.*[64]

Recently, Larock and co-workers developed another iodocyclization reaction on a solid-support for the synthesis of 1,2,3-trisubstituted indoles **157** and 2,3-disubstituted benzofurans.[65] They used chlorinated Wang resin (**42**) as a solid-support. After immobilizing the benzoic acid **153**, a Sonogashira cross-coupling reaction with various terminal alkynes **154** yielded the cyclization precursor **155** (Scheme 32). Instead of using IPy_2BF_4, they performed the iodocyclization reaction with iodine to obtain the eight iodoindoles **156** after cleavage with methanolate in no to excellent yields and >95% purities. A further derivatization by Sonogashira or Suzuki cross-coupling reactions was also possible.

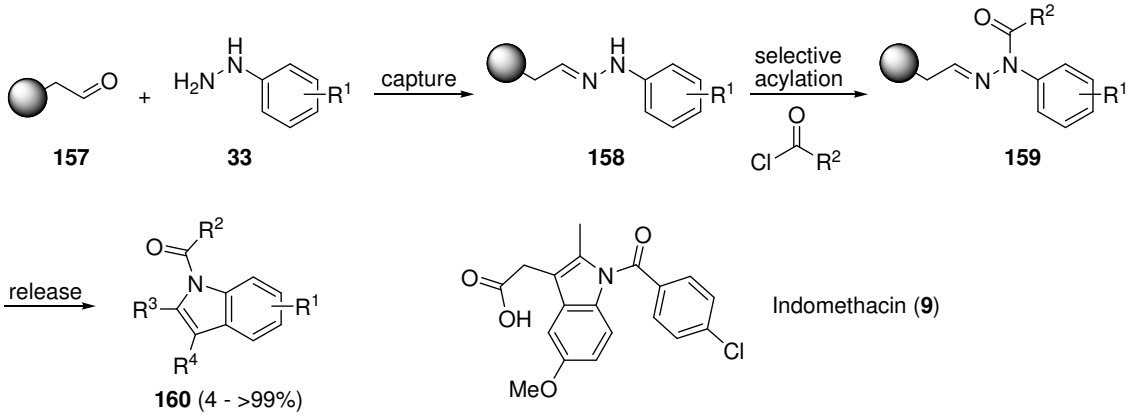


Scheme 32

Iodocyclization reaction as indole syntheses by Larock *et al.*[65]

6. Natural products synthesis

To our knowledge, only one solid-phase synthesis of a natural product including formation of the indole core structure on a solid-support has been reported so far.[66] In 2004, Waldmann *et al.* synthesized an indomethacin library with 134 compounds, which were than evaluated for biological activity. The general synthetic strategy is shown in Scheme 33. During their synthesis they could introduce four points of diversity into the indomethacin derivatives **160**. Six members of this library showed an inhibition of angiogenesis-related receptor tyrosine kinases.



Scheme 33

Strategy for the SPOS of an indomethacin library by Waldmann *et al.*[66]

7. Conclusions

The SPOS of indoles that have been reported to date illustrate several different approaches to the challenge of preparing libraries of bioactive products containing the indole moiety. Due to the impressive pharmacological activities of a large number of indoles, the indole synthesis is still of great interest. Therefore not only the development of new combinatorial syntheses on solid-supports increases, but also the application of combinatorial approaches in solution-phase is under further development.

List of abbreviations

Ac: Acetyl
Bu: Butyl
cGMP: Cyclic Guanosine Monophosphate
DCE: Dichloroethane
DIC: Diisopropylcarbodiimide
DIPEA: Diisopropylethylamine
DMAP: *N*,*N*-Dimethylaminopyridine
DMF: *N*,*N*-Dimethylformamide
DMSO: Dimethylsulfoxide
Et: Ethyl
Fmoc: 9-Fluorenylmethyloxycarbonyl
HATU: 2-(1*H*-9-Azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS: Hexamethyldisilazane
HOBT: *N*-Hydroxybenzotriazole
Me: Methyl
NMM: *N*-Methylmorpholine
NMP: 1-Methylpyrrolidine
Np: Naphthyl
Oct: Octyl
OTf: Triflate
PDE: Phosphodiesterase
Ph: Phenyl
Pr: Propyl
TsOH: *p*-Toluenesulfonic acid
Pro: Proline
rt: room temperature
Py: Pyridine
TBAF: Tetrabutylammonium fluoride
THF: Tetrahydrofuran
TMG: Tetramethylguanidine

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TRANSITION METAL CATALYSIS AS METHODS FOR THE ELABORATION OF PHOSPHORUS HETEROCYCLES

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Abstract. *Among the heterocyclic compounds, phosphorus heterocycles are still scarcely studied although they seem to hold promises in term of biological potential. The last few years were the witness of remarkable developments and strategies for their synthesis. In this context, organometallic chemistry, using coupling reactions, C-C insertion or ring closing metathesis appears to be valuable and general approaches to achieve the formation of phosphorus heterocycles.*

Contents

1. Introduction

Heterocyclic compounds offer excellent opportunities to exploit their chemical diversity for the development of new biologically active molecules. The recent emergence of phosphorus heterocycles over the past fifty years, with more than ninety ring system described, can be considered as the testimony of the unique versatility of the phosphorus element.[1] Moreover, the fundamental role of phosphorus in biological processes deserves to be highlighted as components of the essential structure of life (ribo- and deoxyribonucleic acids are the support of heredity) as well as constituents of membrane cells (phospholipids).[2] Adenosine triphosphate, a phosphorus derivative can be considered as the universal carrier of chemical energy. Due to the extremely rich biological profile of phosphorus compounds[3,4] new and general synthetic methods for their elaboration are required.

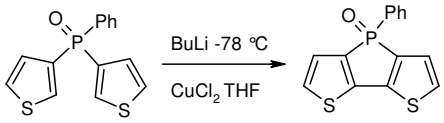
Organometallic chemistry appears as one of the recent methodology to build carbon-carbon bonds as well as phosphorus-carbon bonds.[5] Its successes, either in palladium chemistry or in the recently nobelized metathesis, often offer simple and straightforward ways to obtain complex structures.

The present reviews deals with the formation of phosphorus heterocycles using transition metal couplings or reactions.

2. Copper catalyzed reactions

2.1. Carbon-carbon formation from organolithium precursor

The first example of the formation of a phosphorus heterocycle involving a copper catalyzed reaction was described by Lampin and Matthey[6] in 1974. They studied the reactivity of the anions obtained by the reaction of *n*-butyllithium on thienyl and dithienylphosphines oxides. Based on the previous works of Gronowitz *et al.*,[7,8] the resulting dianions of **1** gave dithienophosphole **2** in the presence of catalytic amount of copper (II) chloride (Scheme 1).



1 **2** (10%)

Scheme 1

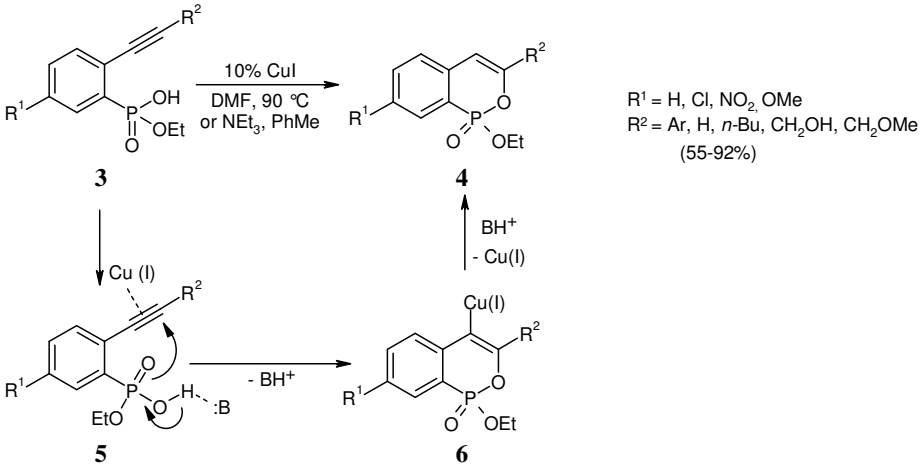
2.2. Catalytic cyclization of *o*-ethynylphosphonic acid monoesters

Transition metal catalyzed reaction of alkynes with nucleophile is one of the best methods to build heterocycles by an intramolecular process. Phosphaisocoumarins **4** are obtained by a Cu(I) catalyzed cyclization of *o*-ethynylphenylphosphonic acids monoesters **3** in 55 to 92% yields.[9] The reaction is very tolerant to functional groups and compounds bearing hydroxy, nitro, chloro, or methoxy groups can be used.

As a soft electrophile, copper(I) chloride can coordinate to the alkyne **3** to form a π-complex **5**. In the second step, the phosphoryl group traps the activated alkyne to form the Phosphaisocoumarin copper

intermediate **6**. The presence of a base such as triethylamine is requested to enhance the nucleophilicity of the phosphoryl oxygen. Polar aprotic solvent can also promote the reaction. Reprotonation of **6** induces the formation of **4** and the regeneration of the copper catalyst.

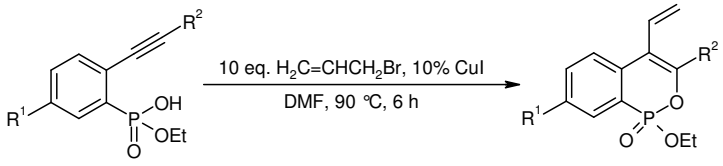
In contrast to the cyclization of alkynoic acids which proceeds mainly by a *5-exo-dig* cyclization, this reaction is highly regioselective and only the *6-endo-dig* product is formed (Scheme 2).



3 **4** **5** **6**

Scheme 2

More recently, Ding and coworker exploited the organocopper intermediate **6** in a tandem cyclization-allylation reaction for the synthesis of 4-allylphosphaisocoumarins **7** (Scheme 3).[10]



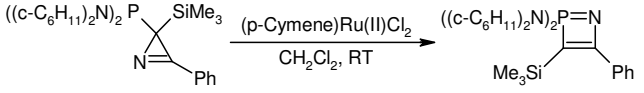
3 **7** (70-95%)

R^1	R^2	Yield (%)
H	Ph	86
H	*p*-EtC_6H_4	89
H	*p*-ClC_6H_4	92
H	$MeOCH_2$	90
Cl	Ph	95
Cl	*p*-EtC_6H_4	85
Cl	H	70
MeO	Ph	78
4,5-benzo	Ph	90

Scheme 3

3. Ruthenium catalyzed phosphorus insertion

The addition of a catalytic amount of (*p*-cymene)ruthenium(II) chloride to 3-phenyl-2,2-[(bis(dicyclohexylamino)phosphino)](trimethylsilyl)-2H-azirine **8** in dichloromethane at room temperature led to the 1,2λ^5-azaphosphete **9** in 95% yield (Scheme 4).[11,12]



8 **9** (95%)

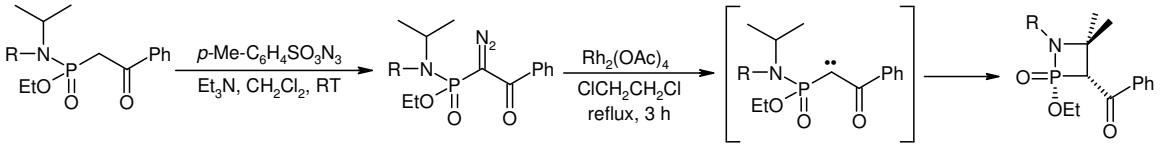
Scheme 4

4. Rhodium catalyzed carbene insertion

Rhodium catalysts are probably among the more versatile transition metals for the formation of heterocyclic phosphorus derivatives by intramolecular insertion reactions.

2-Oxo-1,2-azaphosphetidines **12** presents a specific interest as close structural analogues of β-lactams. The key step of their formation is the rhodium catalyzed decomposition of α-diazo-β-ketophosphonamides **11** followed by an intramolecular C-H insertion of the resulting carbenes intermediates.[13]

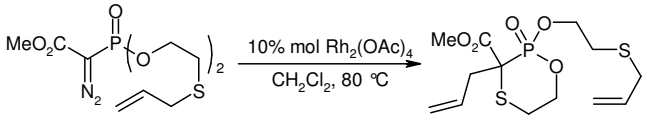
Diazo-ketophosphonamide precursors **11** were obtained by diazo transfer to the active methylene group of **10**. Low yields of 1,2-azaphosphetidines **12** were observed as the consequence of competition with the Wolff rearrangement. However, **12a** and **12b** were formed stereoselectively in a ratio of about 10:1 favouring the *cis* ethoxy-benzoyl product (Scheme 5).



10 **11** (75-98%) **12a-b**
R = *i*-Pr (33%)
R = $PhCH_2$ (16%)

Scheme 5

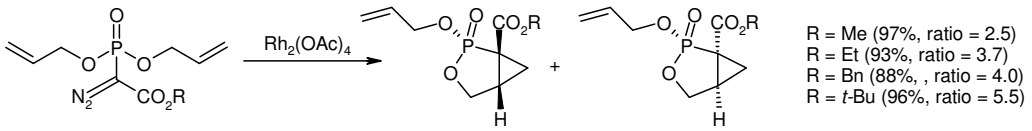
Diazophosphonates **13** bearing an allylthioether group are also subject to insertion reactions in the presence of rhodium. Moore *et al.*[14] obtained oxathiaphosphinane **14** when **13** was reacted in the presence rhodium acetate catalyst in dichloromethane in 80% yield using a pressure tube (Scheme 6). However, the diastereoselectivity of the reaction was modest with a *cis-trans* ratio of 1.7.



13 **14** (80%)

Scheme 6

Interestingly, intramolecular cyclopropanation of diallyl α-diazophosphonacetates **15** led to the fused bicyclic phospholanes in good yields.[15] Diastereoselectivity of the reaction is influenced by the size of the R group and the highest ratio **16a**:**16b** was observed for the bulkiest *t*-butyl group (Scheme 7).

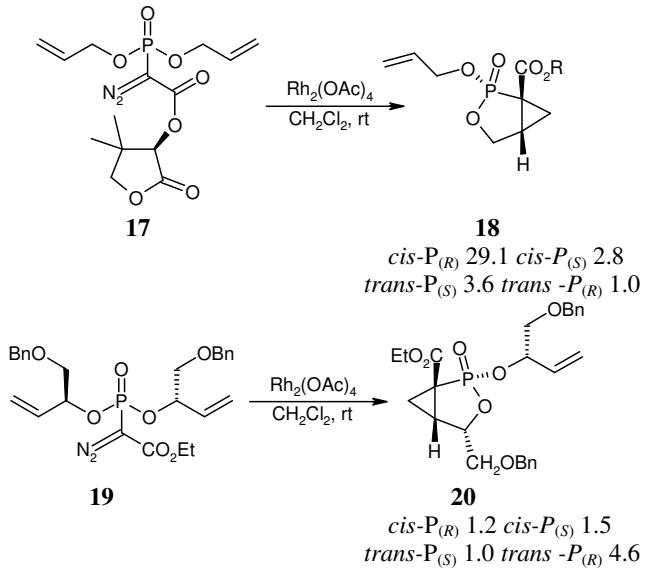


15 **16a** (*cis*) **16b** (*trans*)

Scheme 7

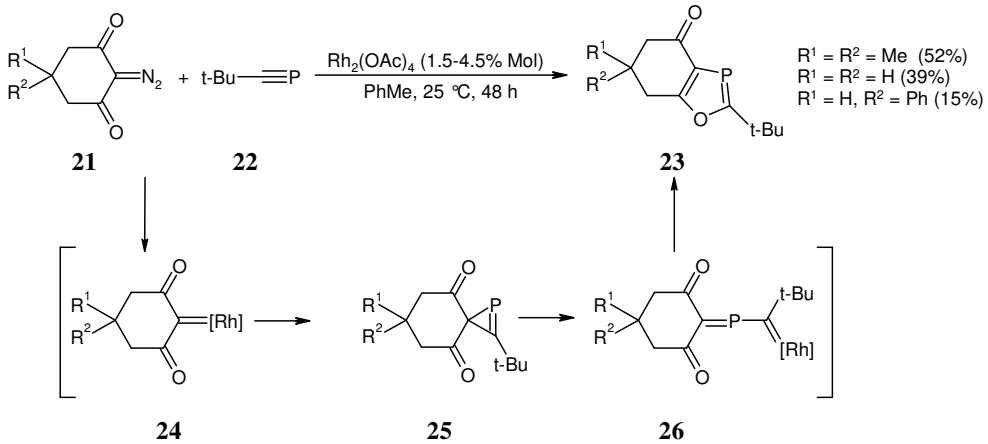
Hanson extended this approach to the synthesis of enantio-enriched bicyclic phospholanes **18** and **20**.[16] The chiral diallyl α-diazophosphonoacetates bearing (*R*)-pantolactone as an auxiliary within the carboester functionality **17** gave good levels of olefin selectivity (10.4:1) and diastereofacial-selectivity (6.9:1). In a

second reaction, chiral non racemic allylic alcohols incorporated into the phosphonate moiety **19** also led less efficiently to enantio-enriched bicyclo-[3.1.0]phospholanes **20** (Scheme 8).

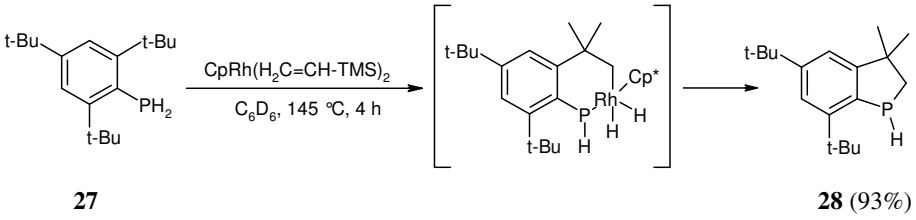


Scheme 8

Low valency phosphorus derivatives such as *tert*-butylphosphaacetylene **22** also reacted with α-diazoketones **21** and gave 1,3-oxaphospholes **23** in 15 to 52% yield when catalytic amounts of rhodium (II) acetate were used.[17] Mechanistically, the first step involves the formation of the reactive rhodium carbenoid **24** from the diazoketone and rhodium(II) acetate. Then, a [2+1] cycloaddition reaction occurs to afford the 2*H*-phosphirene **25** which rearranges into oxaphosphophole **23** with the possible participation of rhodium on the last step (Scheme 9).



Scheme 9



Scheme 10

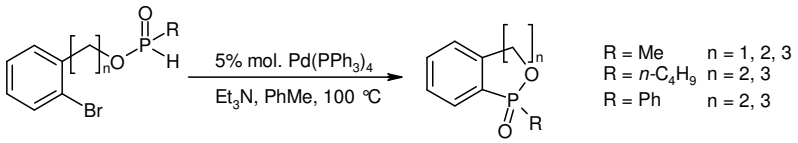
Insertion of rhodium in the phosphorus-hydrogen bond of primary or secondary phosphines is also suitable for the preparation of phosphorus heterocycles. Brookhart *et al.*[18] realized the dehydrocoupling reaction of the 2,4,6-tri-*tert*-butylphosphine **27** and obtained the phosphaindane **28** in 93% yield as the result of a double insertion reaction (Scheme 10).

5. Palladium catalyzed reactions

5.1. Arylation and vinylation of P-H compounds

Palladium-catalyzed cross-coupling reaction of P-H phosphorus compounds and aryl halides was first reported by Hirao *et al.* Mixing dialkylphosphites with arylhalides or vinyl halides in the presence of base such as triethylamine and catalytic amount of palladium tetrakis(triphenylphosphine) gave the corresponding aryl or vinyl phosphonate.[19,20]

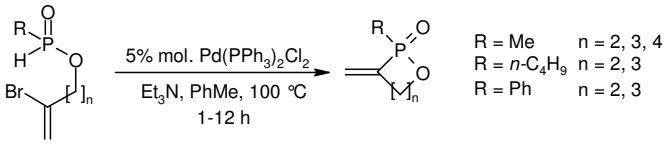
Intramolecular cyclization, using palladium-catalyzed coupling reactions afforded benzoxaphospha-cycloalkanes **30** when various 2-bromoarylalkyl phosphonous acid monoesters **29** were reacted with palladium tetrakis(triphenylphosphine) as catalyst (Scheme 11).[21] Yields are moderate and are ranging from 39% for the seven-membered ring to 51% for the six-membered rings. It also can be noticed that the reaction can be carried out with a palladium (II) catalyst such as dichlorobis(triphenylphosphine)palladium without significant yield modifications.



29 **30** (39%-51%)

Scheme 11

Extension of this methodology to bromovinylalkyl phosphonous acid monoesters **31** gave oxaphosphacycloalkanes **32** with an exocyclic methylene group (Scheme 12).[22] These structures can be considered as analogues of α-methylenelactones which represent a major class of biologically active products.[23]



31 **32** (17%-69%)

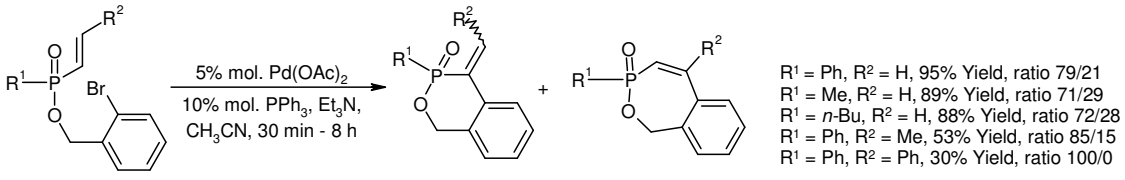
Scheme 12

5.2. Intramolecular Heck reactions

Intramolecular Heck reaction of 2-bromobenzyl vinylphosphinates **33** furnished the six or seven membered ring benzoxaphosphacyclophanes (**34a** or **34b)** with a strong preference to the *6-exo* process in comparison to the *7-endo* one (Scheme 13).[24] The substituent directly linked to the phosphorus atom had little effect both on the yield and on the ratio **34a/34b**. However, β-substituted vinylphosphinates **33** exhibited higher *6-exo* selectivity with ratio **34a/34b** ranging from 85/15 to 100/0.

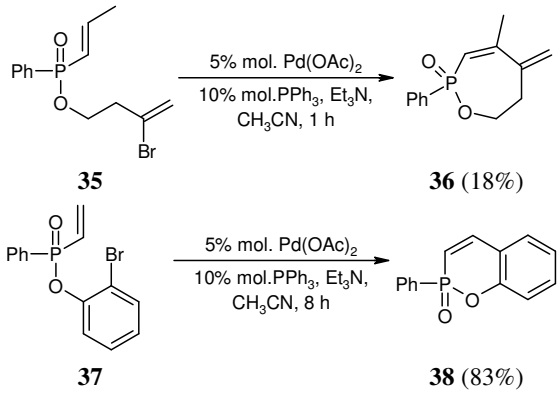
Interestingly, Heck coupling reaction was also observed from a bromovinyl phosphinate **35**. The yield was quite low (18%) but only the seven-membered ring **36** was isolated. Finally, the 2-bromophenyl

vinylphosphinate **37** gave exclusively the benzoxaphospholene **38** by a *6-endo-trig* process in 83% yield (Scheme 14).



33 **34a** **34b**

Scheme 13



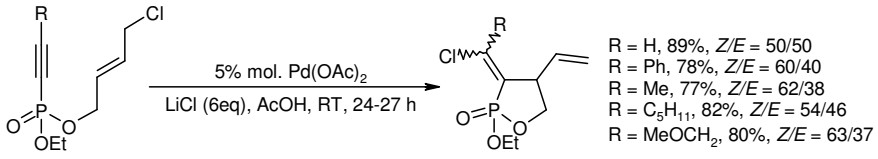
35 **36** (18%)

37 **38** (83%)

Scheme 14

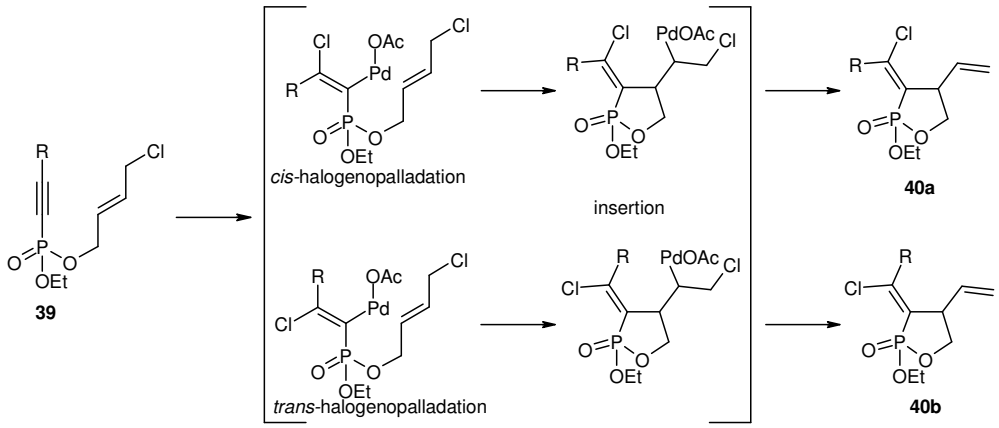
5.3. Tandem palladocyclization reactions

Palladium catalyzed cyclization of 4-chlorobut-2-enyl ethyl alkynylphosphonates **39** led to 2-ethoxy-3-methylidene-1,2λ^5-oxaphospholan-2-ones **40** in 77 to 89% yields (Scheme 15). They can be considered as phosphorus analogues of α-methylidene-γ-butyrolactone.[25]



39 **40**

Scheme 15



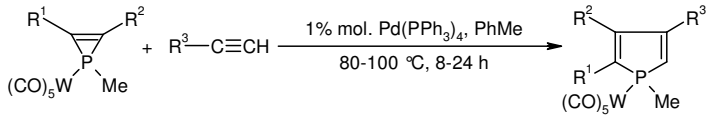
39 **40a** **40b**

Scheme 16

Relating to their previous work,[26-28] the authors made the hypothesis that the reaction takes place in three steps: firstly, the substrate **39** undergoes a *cis* or *trans* halogenopalladation of the triple bond, followed by insertion of the double bond into the newly carbon-palladium bond to form the organopalladate. Then, the final products **40a-b** arised from a dehalopalladation reaction with regeneration of palladium acetate catalyst (Scheme 16).

5.4. Alkynes insertion into phosphirenes ring

In the presence of catalytic amounts of palladium tetrakis triphenylphosphine, terminal alkynes readily inserted into the ring of phosphirene-$W(CO)_5$ complex **41** to give the corresponding phosphole complexes **42** in 33 to 85% yields (Scheme 17).[29] In the same reaction conditions, internal alkynes failed to give the expected phosphole.

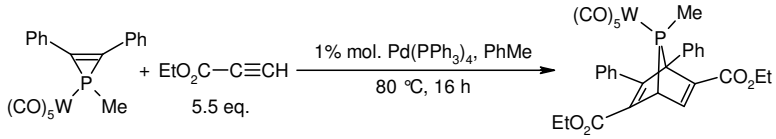


41 **42**

R^1	R^2	R^3	Yield
Ph	Ph	Ph	45%
Ph	Ph	EtO	33%
Ph	Ph	CO_2Et	85%
Et	Et	CO_2Et	50%
Ph	CO_2Et	Ph	61%

Scheme 17

Interestingly, when the previous reaction was carried out with an important excess of terminal alkyne bearing an electron withdrawing group, 7-phosphanorbornadiene **43** was isolated in 42% yield as the result of a [4+2] cycloaddition (Scheme 18).[30]

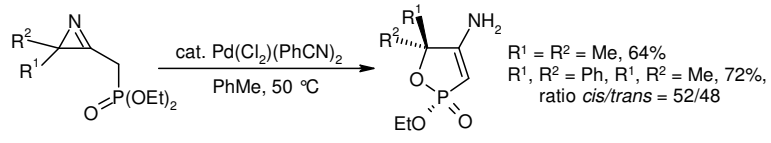


42 **43**

Scheme 18

5.5. Pallado-catalyzed cyclizations of azirinylmethylphosphonates

2-Azirinylmethylphosphonates **44** rearranged into 4-amino-2-ethoxy-1,2-oxaphosphol-3-ene 2-oxides **45** in 64 to 72% yields when they were heated in toluene containing catalytic amounts of palladium(II) dichloride dibenzonitrile (Scheme 19).[31]

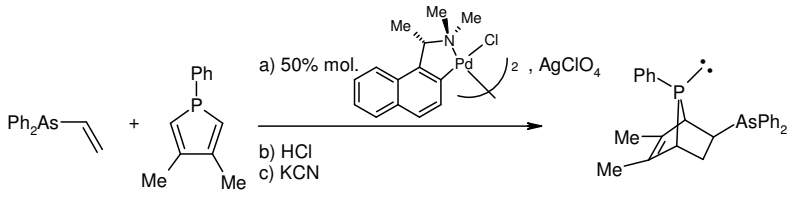


44 **45**

Scheme 19

5.6. Asymmetric Diels-Alder reactions

Addition of 1-phenyl-3,4-dimethylphosphole **47** to the complex obtained by the coordination of diphenylarsine **46** to the chiral palladium(II) complex containing ortho-metallated dimethyl[1-(2-naphthyl)ethyl]amine gave the Diels-Alder reaction to form the chiral (-)-**48** in 33% overall yield (Scheme 20).[32] The palladium complex acted probably more as a promoter than as a catalyst and no Diels-Alder reaction was observed in its absence.



46 **47** **48** (33%)

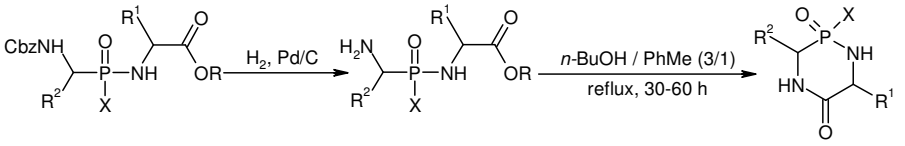
Scheme 20

Compound **48** can be considered as a chiral bidentate ligand. However, owing to the configurational instability of the uncoordinated bridgehead phosphorus stereogenic center, the ligand is stored after recoordination with selected metal ions.

5.7. Hydrogenolysis followed by cyclization

Palladium catalyzed hydrogenation or hydrogenolysis can be used to generate nucleophilic species which can consecutively undergo a cyclization reaction. Then, cyclophosphonodipeptides **51**, analogues of diketopiperazines, can be obtained in 32 to 70% yields by deprotection of the corresponding N-benzyloxycarbonyl-aminoalkylphosphinamide **49** followed by the cyclization (Scheme 21).[33]

The reaction seemed to exhibit some diastereoselectivity. So, product **51c** was obtained as a single diastereomer where the R^2 and X substituent are in *cis* position.



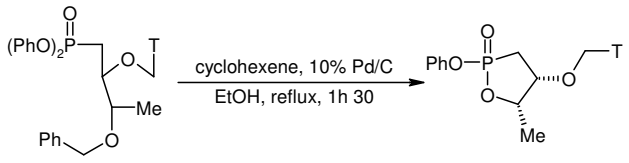
49 **50** **51**

X = Ph, OEt

	R^1	R^2	X	Yield
50a	Me	Me	OEt	37
50b	H	Me	OEt	32
50c	H	Me	Ph	61
50d	Me	Me	Ph	70
50e	CH_2Ph	Me	Ph	40
50f	H	*n*-C_3H_7	Ph	41
50g	H	*n*-C_4H_9	Ph	33
50h	Me	*n*-C_4H_9	Ph	48

Scheme 21

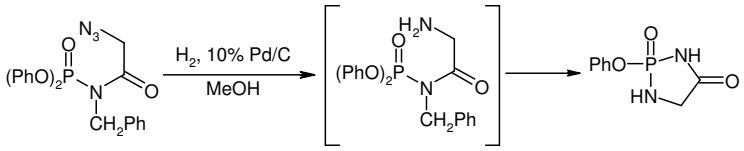
With this in mind, Panzica and coworkers synthesized 1',2'-seconucleophosphonate analogue **53** as a mixture of diastereomers by hydrogenolysis followed by intramolecular transesterification with the loss of phenol (Scheme 22).[34] This reaction takes place only with phenyl esters, since subjecting the corresponding diethylester only resulted in the isolation of the starting material.



52 **53** (65%)

Scheme 22

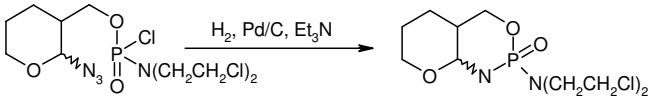
Reduction of azides **54** gave the corresponding amines which could undergo consecutively a cyclization to form phosphorus heterocycles. Mulliez exploited this approach for the synthesis of 4-keto-1,3,2-diazaphospholane **56** from azidophosphoramide **54** (Scheme 23).[35]



54 **55** **56** (65%)

Scheme 23

Similarly, reduction of the azido group of 2-azido-3-phosphoramidylmethyl-tetrahydropyranyl chloride **57** led to the bicyclic analogue **58** of cyclophosphamide as a mixture of four diastereomers in 60% yield separated by preparative HPLC (Scheme 24).[36]

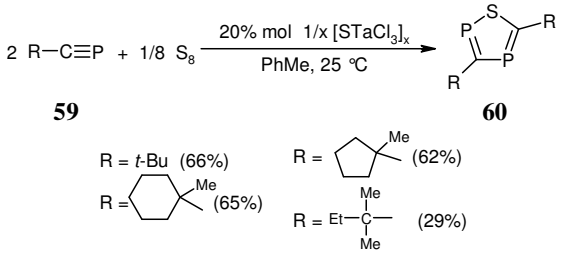


57 **58** (60%)

Scheme 24

6. Tantalum catalyzed synthesis of 1,2,4-thiadiphospholes

Phosphaalkynes **59** reacted with catalytic amounts of polymeric trichlorotantalum sulfide at room temperature in a heterogeneous reaction to afford 1,2,4-thiadiphospholes **60** (Scheme 25).[37]

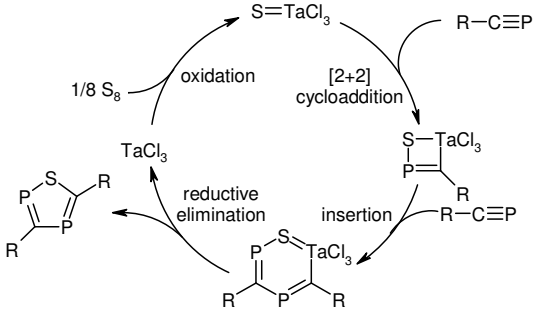


59 **60**

Scheme 25

The catalytic mechanism of formation of 1,2,4-thiadiphospholes involves in the first step a [2+2] cycloaddition between trichlorotantalum sulfide and the phosphaalkynes. Then, the resulting four-membered ring metal species undergoes a phosphaalkyne insertion into the metal carbon bond to give a six membered

ring intermediate which leads to the 1,2,4-thiadiphosphole and tantalum chloride through a reductive elimination. The later is reoxidized with sulphur (Scheme 26).

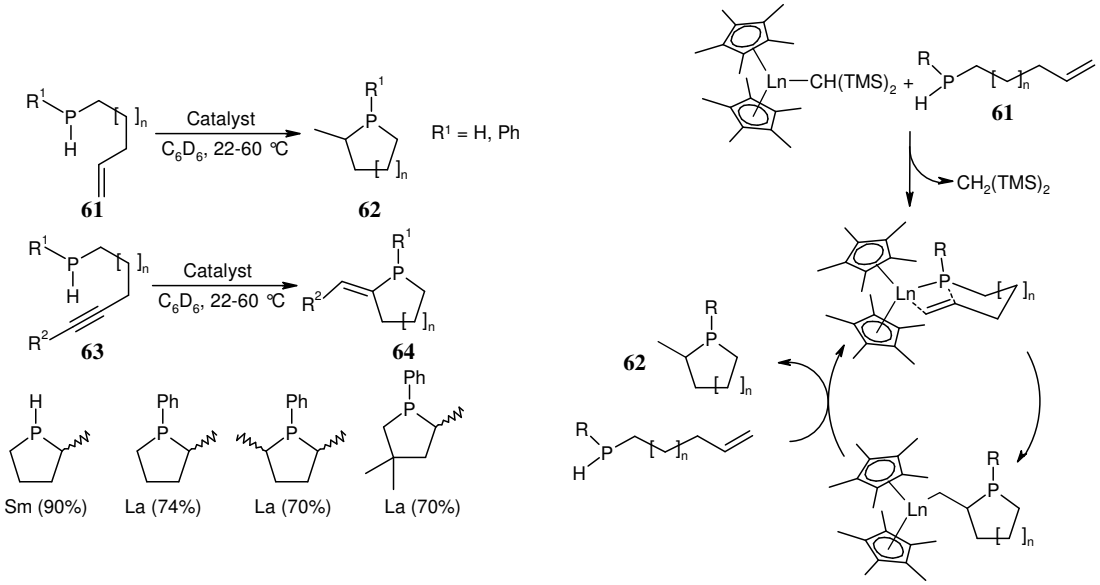


Scheme 26

7. Lanthanides catalyzed reactions

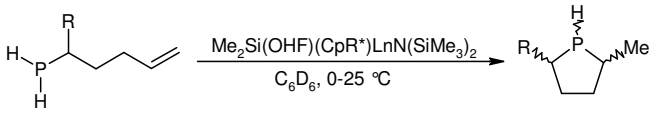
Organolanthanides mediated intramolecular hydrophosphination/cyclization of primary or secondary phosphino alkenes **61** or alkynes **63** were recently exploited as an extension of the corresponding hydroamination of aminoalkenes or aminoalkynes. The resulting phosphorus heterocycles **62** and **64** belong to a class of ligands (Scheme 27).[38]

Lanthanide complex of the type $Me_2Si(Me_4C_5)(t\text{-BuN})SmN(SiMe_3)_2$ and $(\eta^5\text{-}C_5Me_5)_2LnCH(SiMe_3)_2$ where the lanthanide cation could be lanthanum, samarium or ytterbium gave the cyclic phosphines in 70 to 90% yields, generally with no diastereoselectivity.



Scheme 27

More recently, Marks *et al.* extended their methodology to the stereoselective synthesis of phosphino heterocycles **66** from the corresponding phosphinoalkenes **65** using a chiral menthyl or neomenthyl substituted lanthanide complex with diastereomeric excess ranging from 77% to 96% (Scheme 28).[39] Qualitatively, the turnover of the reaction was higher when the ionic radius of the lanthanide increased. The reaction showed some diastereoselectivity with the preferential formation of the *trans* isomers.



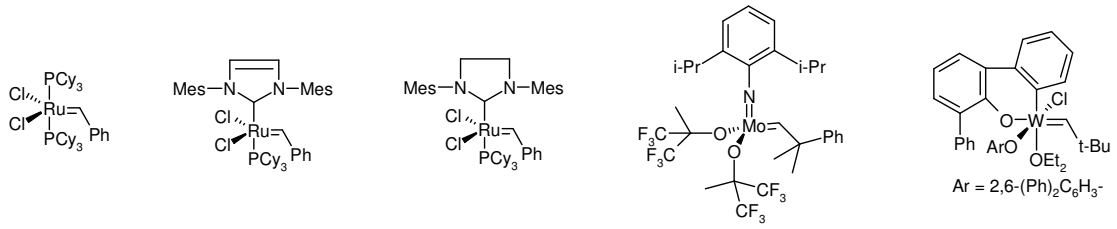
65 **66**

R	Ln	%(cis + trans)	T°C	de (%)
H	Sm	81	25	88
H	Y	75	25	78
H	Lu	78	25	83
Me	Sm	82	0	96
Me	Sm	86	25	91
Me	Y	68	25	77
Me	Lu	72	25	90

Scheme 28

8. Ring closing metathesis

Olefin metathesis was widely used for the elaboration of cyclic structures and represents a powerful tool for carbon-carbon bond formations. Through the last years, the extensive development of this methodology was following the use of more stable and efficient catalysts. As a consequence, the following part will not deal only with one kind of metal but with one reaction, ring closing metathesis RCM using either Ru, Mo or W catalyst (Figure 1).[40,41]



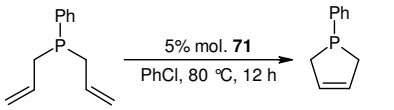
67 **68** **69** **70** **71**

Figure 1

8.1. From P^{III} dienes and their protected borane derivatives

8.1.1. From phosphines and derivatives

Phosphines are known to be good metal ligands, so they could inhibit the RCM by binding to the metal. Surprisingly, diallylphenylphosphine **72** was converted into 1-phenyl-3-phospholene **73** when the tungsten-based catalyst **71** was used (Scheme 29).[42,43]



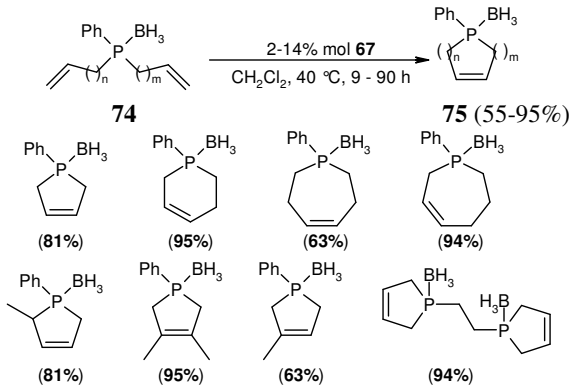
72 **73** (95%)

Scheme 29

Recently, using the same substrate, Gouverneur *et al.* demonstrated that the ruthenium catalysts **67-69** were inefficient.[44] In fact, deactivation of the catalysts is the result of a competitive binding between the phosphine and the olefin. Indeed, in the catalytic cycle, the phosphine dissociation occurs prior to the olefin binding.[45] This is also supported by Nolan's work: he reduced by 75% the activity of catalyst **68** in the RCM

reaction of the diethyldiallylmalonate only by adding 0.06 equivalent of tricyclohexylphosphine per equivalent of catalyst.[46] Only the molybdenum catalyst **70** led to the formation of the 1-phenyl-phosphol-3-ene.[44]

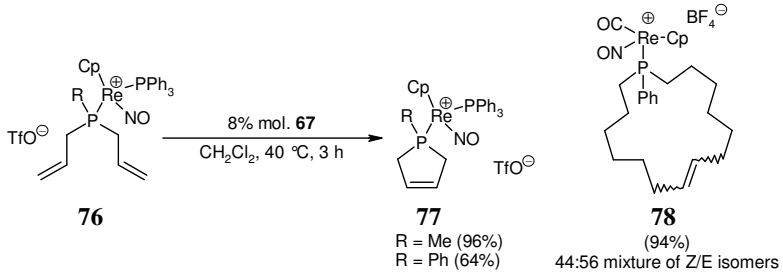
To override this problem, phosphine-borane adducts can be used. The RCM reaction using the Grubb's first generation catalyst **67** gave cyclic phosphine-borane derivatives in 55% to 95% yields.[47] The most obvious problem was the synthesis of the phosphino diene precursors owing to the presence of double bonds that are known to be sensitive to hydroboration. As a consequence, borane protecting group was introduced earlier in the synthesis, directly by reaction with dichlorophenylphosphine. The desired diene patterns were then obtained subsequently by double P-substitution by the allyl Grignard reagent (Scheme 30).



Scheme 30

As with phosphine-borane adducts, diallylphosphine-metal complexes **76** can undergo RCM.[48] Conceptually, it is possible to envision several type of starting material combinations where the metal cation is a part of the heterocycle or not.

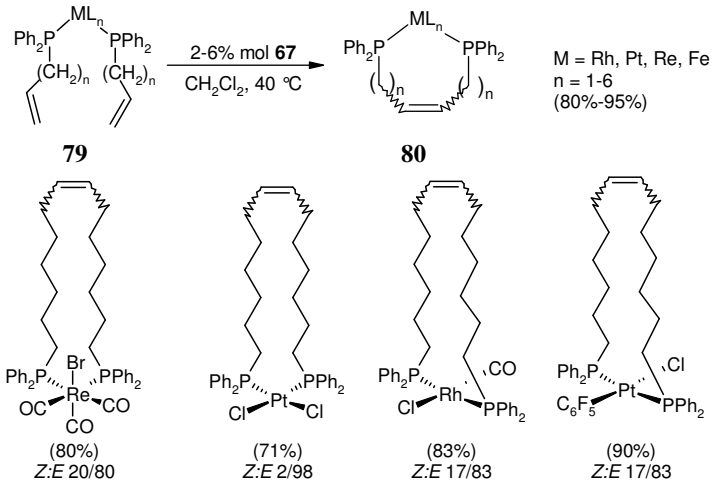
Reaction of the cationic rhenium di(allyl)phosphine complexes **76** in the presence of 8% mol. of the Grubb's first generation catalyst **67** led to the dihydrophosphole **77** in 64% to 96% yields. Similarly, the corresponding fifteen-membered macrocyclic phosphine **78** was obtained in 94% yield as a 44:56 mixture of *cis*- and *trans*-isomers (Scheme 31).[49]



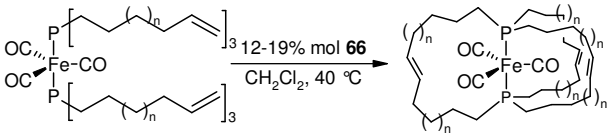
Scheme 31

Interestingly, the metal atom can also be a part of the final heterocycle. Exploiting the relative insensitivity of metathesis catalysts towards coordinated phosphines Gladysz *et al.* synthesized various metallo-macrocycles with rhodium or platinum[50,51] and rhenium[52] atoms (Scheme 32).

Molecular "gyroscopes" based on iron metallocycles **82** were obtained in 60% to 81% yields by multiple RCM reaction. High loading of metathesis catalyst are requested due to the formation of three double bonds (Scheme 33).[53,54]



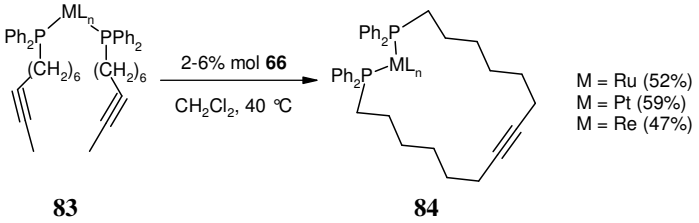
Scheme 32



n = 4 (60%, *EEE*)
n = 5 (73%, *E/Z* mixture)
n = 6 (81%, *E/Z* mixture)

Scheme 33

Tungsten-catalyzed alkyne metatheses in transition-metal coordination sphere also allowed to the formation of the corresponding diphospha-alkynes metallo macrocycles **84** with various transition metals leading to the seventeen-membered rings macrocycles in yields ranging from 47% to 59% (Scheme 34).[55,56]



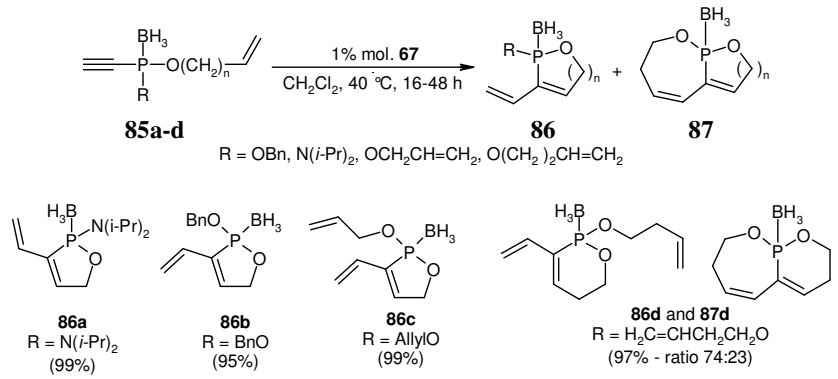
Scheme 34

Such target structures have potential applications in the development of molecular scale devices and nanochemistry.[57]

8.1.2. From phosphinites or phosphonites and derivatives

Enynes derivatives of phosphonite and phosphinite boranes **85** underwent ring-closures using **67** as catalyst in almost quantitative yields.[58] Unsymmetrical phosphinates and phosphonites gave exclusively the five or six-membered oxaphospha-heterocycle **86**.

By contrast, with symmetrical phosphonites (R = allyl or homo-allyl) group, formation of [5,4,0] bicyclic phosphonite-borane **87** from a tandem yne-diene transformation could be considered. Unfortunately, only **85d** gave the bicyclo adduct **87d** as a minor product in addition to the major product **86d** (Scheme 35).



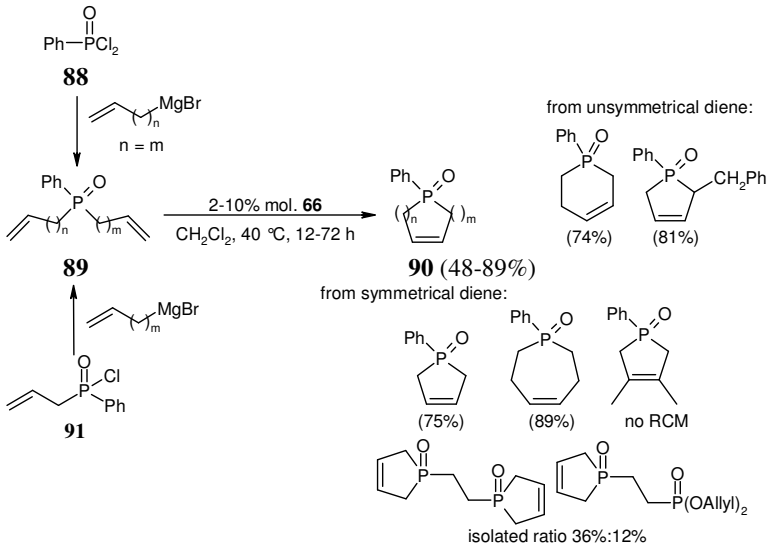
Scheme 35

8.2. From P^{IV} derivatives

8.2.1. Phosphine oxides

Phosphine oxides **89** can be used successfully for RCM to obtain cyclic phosphine oxides **90** in 48% to 89% yields.[59] The corresponding precursors, symmetrical dienes were synthesized by the addition of Grignard reagents to phenylphosphonic dichloride **88**. The unsymmetrical ones were prepared from allylphenylphosphic chloride **91** by the addition of the Grignard reagent (Scheme 36). Deprotonation of diallylphosphine oxide at -78 °C using *sec*-BuLi followed by alkylation with benzyl bromide also furnished unsymmetrical dienes.

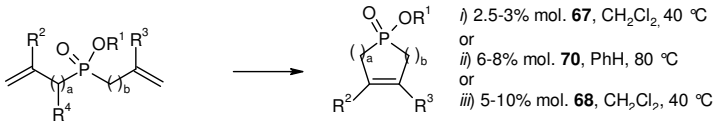
When substituted olefin was used, no RCM was observed as the consequence of unfavourable steric effects.



Scheme 36

8.2.2. Phosphinic acids and their derivatives

Mioskowski *et al.* easily prepared symmetrical and unsymmetrical unsaturated phosphinic acids or phosphinates **92** and consecutively proceeded to their ring closing metathesis reaction, using the first generation Grubb's catalyst **67** in 50 to 97% yields.[60] Under those conditions, free phosphinic acids were unreactive and as already mentioned hindered dienes too. To circumvent this problem, reaction using N-heterocyclic carbene catalyst **68** allowed the formation of **93** in nearly quantitative yields (**93a**, **93h**, **93i**) (Scheme 37).[61]

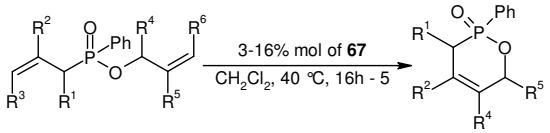


92 **93**

Entry	a	b	R^1	R^2	R^3	R^4	Conditions	Yield (%)
93a	1	1	H	H	H	H	*i* *iii*	No RCM >99
93b	1	1	Bn	H	H	H	*i* or *ii*	80
93c	1	2	Bn	H	H	H	*i*	96
93d	2	2	Bn	H	H	H	*i*	97
93e	1	1	Bn	Me	H	H	*i* or *ii*	50
93f	1	1	Bn	H	H	Me	*i*	77
93g	1	1	Bn	H	H	Bn	*i*	66
93h	1	1	Bn	Ph	H	H	*iii*	>99
93i	1	1	Bn	Me	Me	H	*iii*	88

Scheme 37

1,2-Oxaphosphin-4-ene **94** can be obtained by the same approach. The reaction of allyl allylphenylphosphinates gave **95** in 31 to 95% yields using catalyst **67** (Scheme 38).[62]



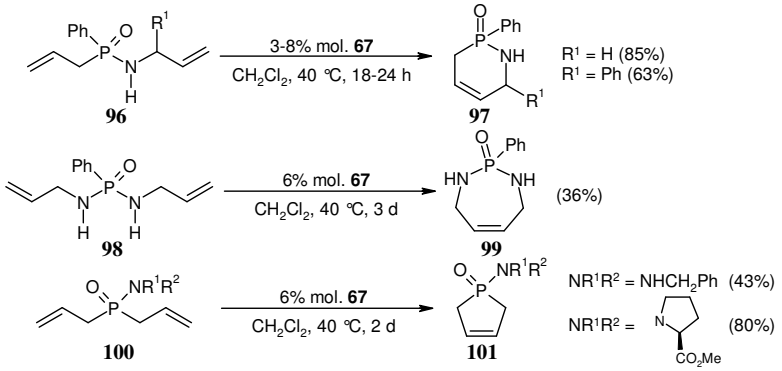
94 **95**

R^1	R^2	R^3	R^4	R^5	R^6	Catalyst	Time	Yield
H	H	H	H	H	H	4%	16h	92%
H	H	Me	Me	H	H	8%	21h	84%
Me	H	H	H	H	Me	8%	72h	95%
H	H	H	H	Me	H	10%	72h	31%
H	Me	H	H	Me	H	6%	120h	0

Scheme 38

Having established the formation of cyclic phosphinates, Gouverneur *et al.* turned their attention to the synthesis of cyclic phosphinamides from the corresponding dienes. As expected, the RCM proceed generally smoothly even for the free NH open chain precursors.[62]

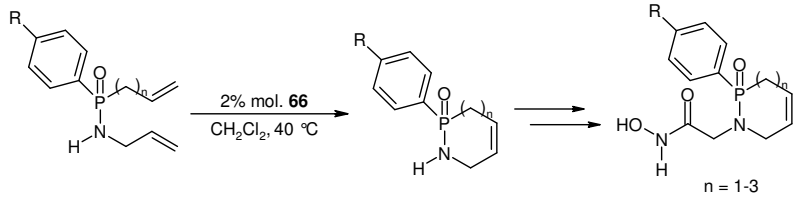
Seven-membered ring heterocycles such as in 1,3,2-diazaphosphacycloheptene **99** were obtained in low yield (36% yield). The crude mixture only showed unreacted starting material (Scheme 39).



96 **97** **98** **99** **100** **101**

Scheme 39

Sorensen and coworkers applied such reactions in order to design new matrix metalloproteinases inhibitors such as cyclophosphinamide hydroxamic acids **104** (Scheme 40).[63]



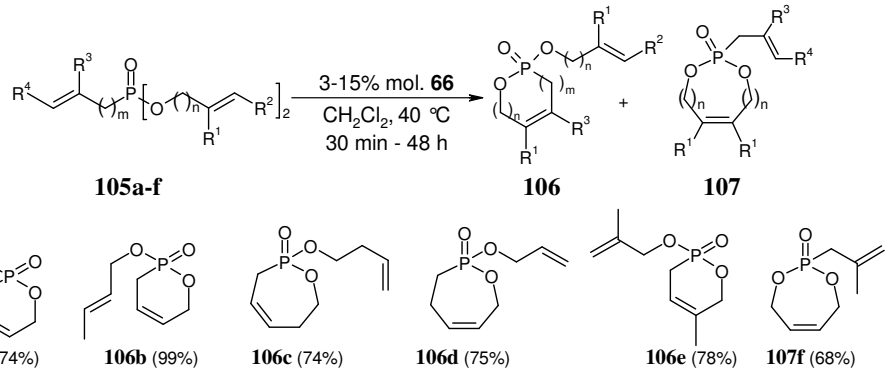
102 **103** **104**

Scheme 40

8.2.3. Phosphonic acids and their derivatives

2-Alkoxy-1,2-oxaphosphinenes **106** were obtained predominantly by ring closure from symmetrical diallyl allyphosphonates **105** using the Grubb's catalyst **67**.[64] The ring closure was generally chemioselective leading to 2-alkoxy-1,2-oxaphosphinenes **106** (**106a**, **106b**) rather than 1,3,2-dioxaphosphacycloheptenes **107**. This could be attributed to the preferential formation of the six-membered ring in comparison to the seven-membered one. The same observation can be made for **106c** and **106d** which the formation competed with those of nine-membered heterocycles **107**.

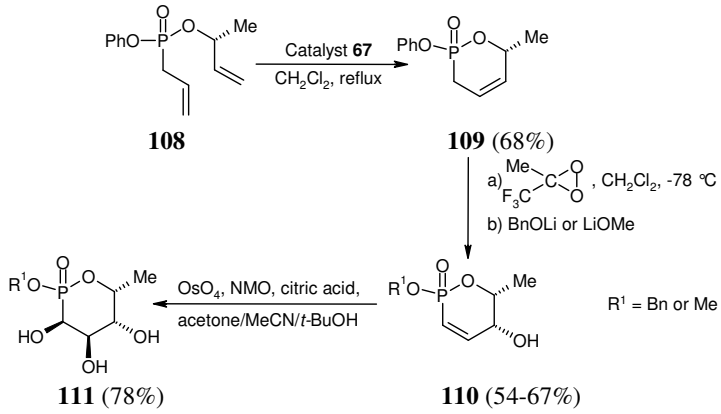
On the contrary, when the P-allyl group was substituted in α-position, the seven membered ring was predominating and the corresponding 1,3,2-dioxaphosphacycloheptene **107f** was obtained in 68% yield (Scheme 41).



105a-f **106** **107**

106a (74%) **106b** (99%) **106c** (74%) **106d** (75%) **106e** (78%) **107f** (68%)

Scheme 41



108 **109** (68%)

111 (78%) **110** (54-67%)

Scheme 42

Cyclic unsaturated phosphinates **109** were used to generate phostones **111** as analogues of carbohydrates containing a phosphorus atom at the anomeric position from RCM reaction.[65,66] Subsequent epoxidation of the double bond in the RCM product **109** led to the epoxide with a (4:1) diastereoselectivity. Reaction of the major epoxide with alkoxide gave the formation of the 5-hydroxy-1,2-oxaphosphin-3-ene **110**. Finally, dihydroxylation reaction in the presence of OsO_4/NMO was very sluggish and gave mainly the expected phostone **111**, with sometimes some amounts of epoxide (Scheme 42).

This strategy relying on the use of stereoselective additions to diphenyl allylphosphonates and RCM-hydroxylation allowed an access to a large set of P-chiral scaffolds (Figure 2).

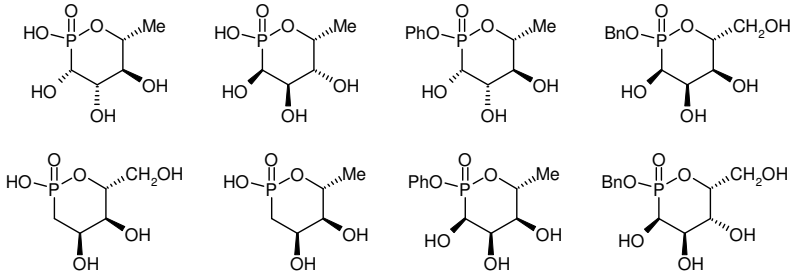
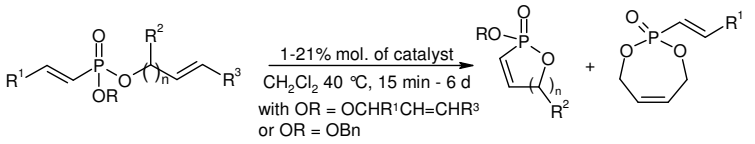


Figure 2

Further extension involved vinylphosphonates as substrates for RCM. Using Grubb's first generation catalyst **67**, Hanson *et al.* demonstrated the effectiveness of this approach to generate five or six membered rings.[67] Improved reaction conditions were used by Boom *et al.* with the Grubb's second generation catalyst **69** where a substantial increase the rate was revealed.[68] It can be noticed that the main side reaction was the formation of the 1,3,2-dioxaphosphacycloheptene **114** which was sometimes the main product, particularly when the vinylphosphonate moiety is substituted (Scheme 43).

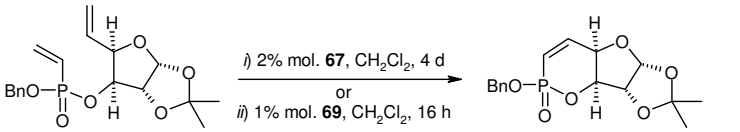


112a-i **113** **114**

R^1	R^2	R^3	n	Conditions	113 (Yield)	114 (Yield)	Ref
H	H	H	1	6% mol **67**, 6 h	44%	31%	67
				1% mol **69**, 30 min	100%	-	67
H	H	Me	1	18% mol **67**,	54%	6%	67
Me	H	H	1	6% mol **67**, 7 h	16%	54%	67
H	H	Ph	1	21% mol **67**, 144 h	30%	-	67
H	H	H	2	3% mol **67**, 2 h	79%	-	67
H	$R^1 = R^2 = H$			2% mol **67**, 96 h	25%		68
	n = 1, R = Bn			1% mol **69**,15min.	100%		68
H	R^1 = Me, R^2 = H			2% mol **67**, 48 h	65%		68
	n = 1, R = Bn			1% mol **69**, 30 min	92%		68
H	$R^1 = R^2 = H$			2% mol **67**, 96 h	85%		68
	n = 2, R = Bn			1% mol **69**, 20 min	100%		68

Scheme 43

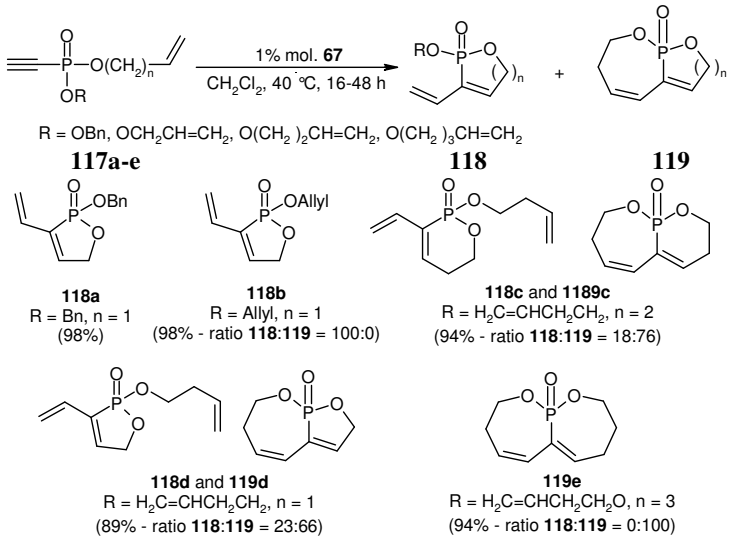
Similarly, RCM reaction of functionalized phosphonate **115** gave high conversion of the more sterically demanding *cis*-fused heterocyclic phosphonate **116** (Scheme 44).



115 **116** (*i*: 76%) (*ii*: 86%)

Scheme 44

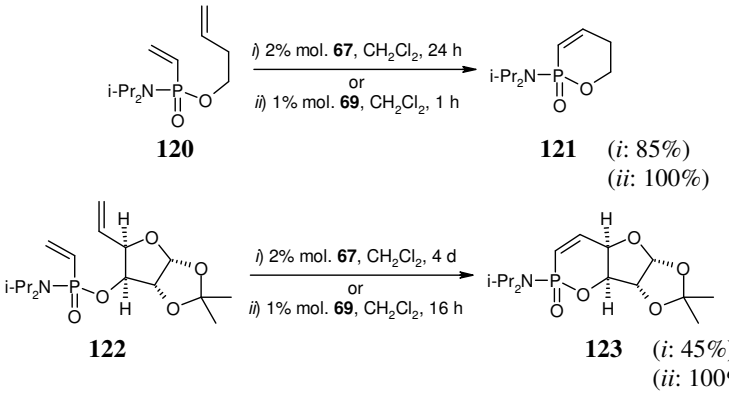
Cyclization of O-unsaturated ethynylphosphonates **117a-e** can lead to exo-vinyl heterocyclic phosphonates **118** or bicyclic products **119** by a tandem double RCM reaction.[58] When it was possible, the tandem cyclization was observed in all cases and the bicyclic products were generally obtained as the main products with exception for **117b** precursor. For the dissymmetrical phosphonates **117d** (R = H_2C=$CHCH_2CH_2$, n = 1) exclusive formation of the oxaphospholene **118d** and the bicyclo [5.3.0] product **119d** occurred (ratio 1:3) (Scheme 45). No trace of the corresponding six-membered and bicyclo [4.4.0] ring products were observed indicating that the metathesis reaction is a regioselective process.



Scheme 45

8.2.4. Phosphonamidates and phosphonamides

As their P^{III} analogues, unsaturated phosphonamidates and phosphonamides can be involved in RCM reactions.



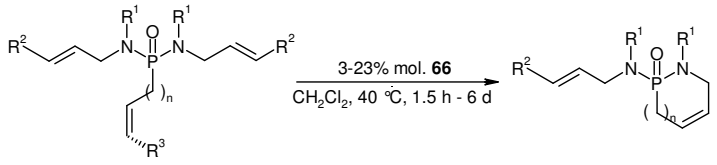
120 **121** (*i*: 85%) (*ii*: 100%)

122 **123** (*i*: 45%) (*ii*: 100%)

Scheme 46

The Grubb's second generation catalyst **69** was particularly efficient for the synthesis of cyclic phosphonamidates giving **121** and **123** in quantitative yields in comparison with the first generation catalyst **69** (Scheme 46).

Cyclization reactions of both N-H and N-Me phosphonamides **124** gave generally good yields of the expected five- or six-membered rings **125** (Scheme 47). It was only for sterically hindered unsaturated systems that low yielding reactions were generally observed.[62,67]



124 **125**

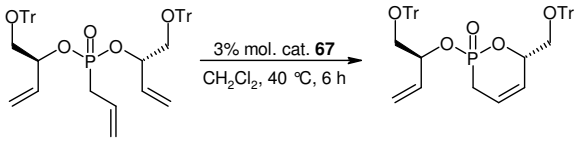
R^1	R^2	R^3	n	Conditions	Yield
H	H	H	0	9% mol. **67**, 6 h	74%
Me	H	H	0	3% mol. **67**, 5 h	76%
H	Ph	H	0	9% mol. **67**, 1 d	68%
Me	Ph	H	0	21% mol. **67**, 6 d	13%
Me	H	Me	0	3% mol. **67**, 2 h	87%
Me	Ph	H	1	3% mol. **67**, 1.5 h	99%
H	Ph	H	1	18% mol. **67**, 2 d	48%
Me	H	H	1	3% mol. **67**, 2 h	93%
H	H	H	1	21% mol. **67**, 2 d	45%

Scheme 47

8.3. Diastereoselective reactions using RCM

A challenge in RCM reaction is the control of diastereoselectivity. Due to the efficiency of the metathesis catalysts, it is generally difficult to achieve directly and efficiently these objectives with simple chiral substrates.

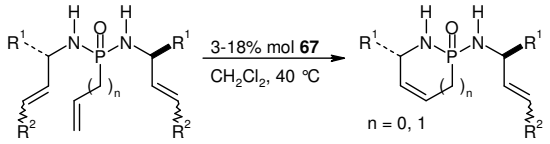
As example, desymmetrization of pseudo-C_2-symmetric phosphonic acid derivatives **126** was used in order to develop methods to obtain P-chiral phosphonates **127** or phosphonamides **129** (Scheme 48). Diastereotopic differentiation of phosphonates was achieved using the RCM reaction. Unfortunately, the diastereomeric ratio remained low (3.4:1).[69]



126 **127** (75%)
dr 3.4:1.0

Scheme 48

By contrast, it was possible to reach diastereomeric ratio up to 15:1 with phosphonamides **128**. The diastereomeric excesses for the formation of the P-stereogenic heterocycles ranged from 13% to 87%. The best selectivities were observed for the five-membered ring cyclic phosphonamides (n = 0). When the N-allyl double bond has substituents, the reaction rate was slower but a considerable increase in selectivity was observed. By contrast, six-membered heterocycle formation (n = 1) is almost unselective (Scheme 49).



128 **129**

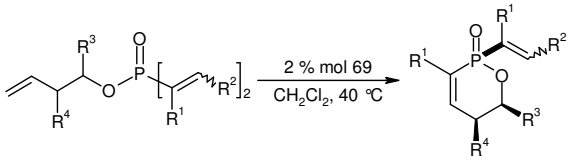
R^1	R^2	n	Conditions	Yield (%)*	*de* (%)
Me	(*Z*)-*i*-Pr	0	3% mol **67**, 3h	64	44%
i-Pr			3% mol **67**, 2.5h	80	66%
Me	(*E*)-Ph	0	6% mol **67**, 24h	69	84%
i-Pr			3% mol **67**, 8h	66	87.5%
i-Bu			6% mol **67**, 20h	63	87.5%
Me	(*E*)-*i*-Pr	0	3% mol **67**, 3h	61	59%
i-Bu	H	0	18% mol **67**, 72h	37	40%
Me	(*E*)-Ph	1	6% mol **67**, 24h	50	13%
i-Bu			6% mol **67**, 24h	51	28%

* yield are given for the major product

Scheme 49

Transposition to divinylphosphinates bearing a chiral homoallylic alcohol group **130** led to 1,2-oxaphosphin-3-enes **131** in yields ranging from 33% to nearly quantitative (Scheme 50).[70] The main factor for good stereodifferentiation is the presence of a bulky group next to the oxygen on the phosphinic ester moiety ($R^3 \neq H$). The lowest diastereomeric excesses were obtained both for unsubstituted vinylphosphinate ($R^1 = R^2 = H$) and β-susbtituted allylic esters.

As previously mentioned, β-susbtituted vinylphosphinates presented superior *de* as a consequence of a decreased reaction rate. It can also be noticed that all the substituants in position 2, 5 and 6 were occupying a relative *cis*-position.

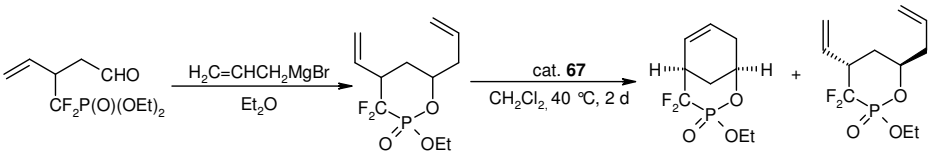


130 **131**

R^1	R^2	R^3	R^4	Yield (%)	*de* (%)
H	H	H	Me	72	20
H	H	H	Bn	78	19
H	H	H	Ph	60	13
H	*E*-Me	H	Bn	56	39
H	*E*-Me	H	Ph	61	23
H	*E*-Me	H	Me	92	50
H	H	Me	H	100	60
Me	H	Me	H	33	76
H	*E*-Me	Me	H	90	86
H	*Z*-Me	Me	H	95	75
H	*E*-Me	Bn	H	97	82

Scheme 50

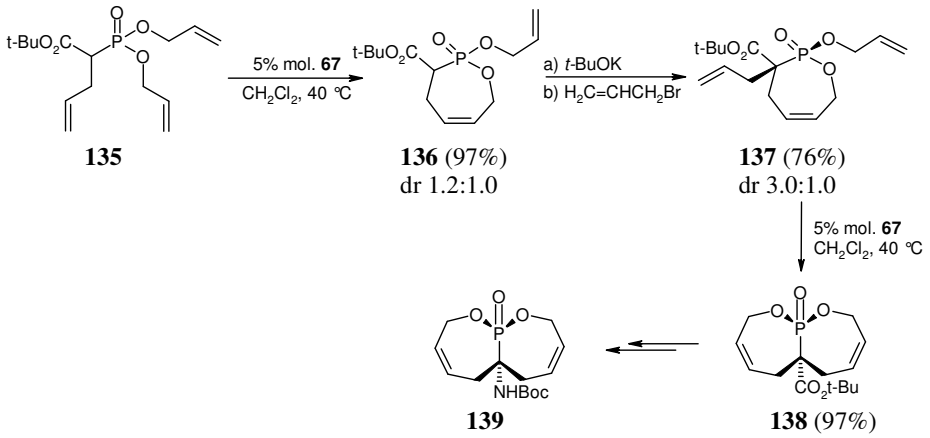
Percy *et al.* synthesized fluoro bicyclo[3,3,1]phosphonate using catalyst **69** in a two step procedure.[71] The first one allowed the formation of oxaphosphinane ring **133** by addition of allylmagnesium bromide to **132**. The control of the diastereoselectivity was performed in the second step where only the *cis*-isomer underwent the ring closing reaction **134** while the *trans*-isomer *trans*-**133** remained unreactive (Scheme 51).



132 **133** (60%) **134** (64%) *trans*-**133**

Scheme 51

Conformationaly constrained α-aminophosphonate **139** was obtained by a double RCM reaction and by Curtius rearrangement. Reaction of the unsaturated diallyl phosphonate **135** exclusively gave the seven membered ring **136** with very low diastereoselectivity (1.2:1.0). Allylation of the malonic position furnished the C-allyl derivative **137** in 76% yield and a 3:1 diastereomeric ratio.[72] RCM of the major diastereomer gave the [5.5.0]-bicyclic *tert*-butyl phosphonoacetate **138** with a *cis* junction (Scheme 52).



135 **136** (97%) dr 1.2:1.0 **137** (76%) dr 3.0:1.0

5% mol. **67** CH_2Cl_2, 40 °C

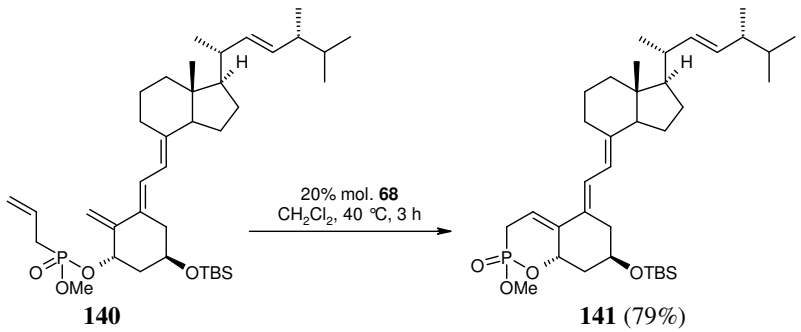
139 **138** (97%)

Scheme 52

8.4. Synthetic applications of RCM with phosphorus derivatives

8.4.1. Synthesis of functionalized 1α-hydroxyvitamin D_2 analogues

Barret *et al.* exploited the RCM reaction of phosphonate **140** to obtain C-19-functionalized 1α-hydroxyvitamin D_2 analogues **141** using catalyst **68** (Scheme 53).[73]



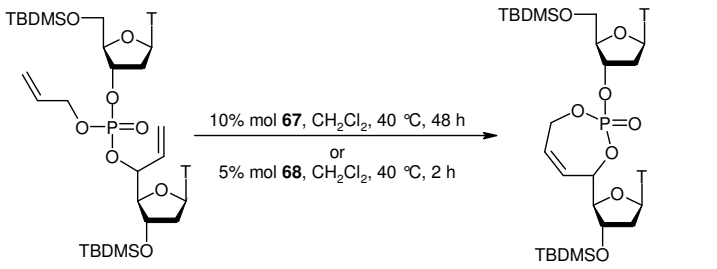
140 **141** (79%)

Scheme 53

8.4.2. Synthesis of conformationaly restricted nucleotides

Conformationaly restricted oligonucleotides have been intensively investigated for their potential therapeutic applications. RCM was employed in this field for the synthesis of medium or large ring systems through the reaction of *O*-allyl phosphates.

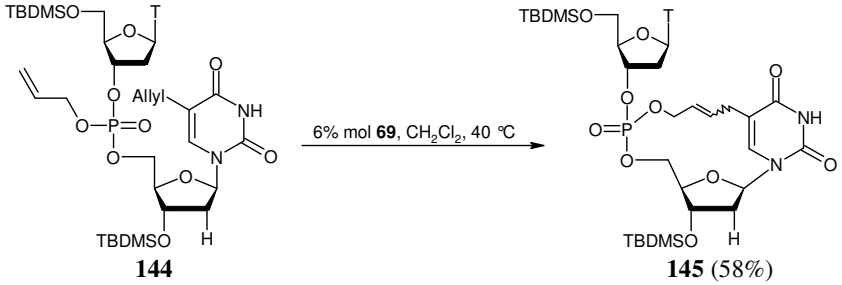
The first attempts were made to obtain seven-membered ring **143**.[74,75] The RCM reaction using Grubb's 2nd generation catalyst **69** gave the expected product **143** in 91% yield (Scheme 54).



142 **143** (65% or 91%)

Scheme 54

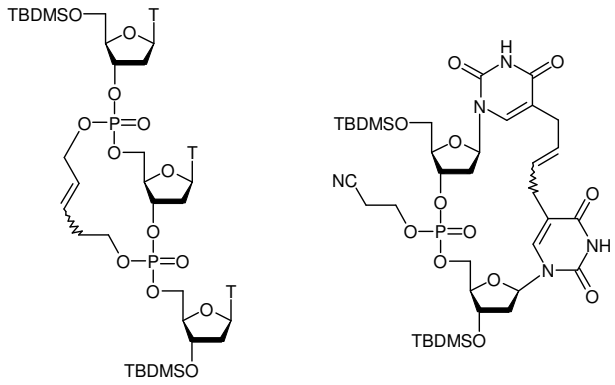
Using the previous conditions, Nielsen extended this methodology to the formation of a fourteen-membered ring **145** in 58% yield as an epimeric mixture from an *O*-allylphosphate and *C*-allylthymine precursor **144** (Scheme 55).[76] The two major products were the two phosphorus epimers with *(E)*-configuration of the but-2-ene linker with only trace amounts of the *(Z)*-isomer.



144 **145** (58%)

Scheme 55

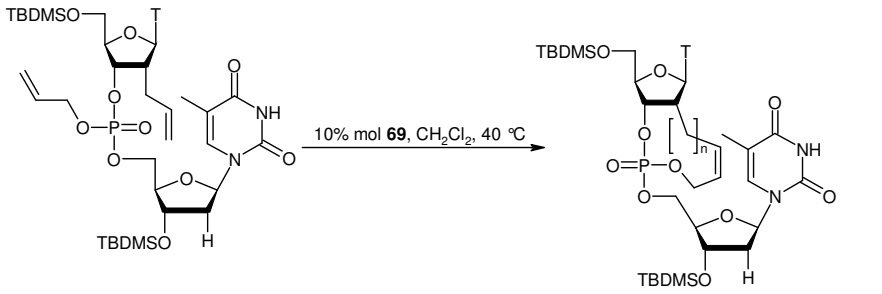
The same procedure can be applied to the synthesis of a trinucleotide **146** containing two *O*-allyl phosphate units leading to the thirteen-membered ring in 60% yield[77] or two *C*-allylthymine units in 23% yield (**147**) (Figure 3).[78]



146 **147**

Figure 3

Finally, Nielsen *et al.* recently extended their approach to the synthesis of more challenging eight and nine membered ring **149a-b** in medium to good yield as two epimers with a 62:38 or 70:30 ratio (Scheme 56).[79,80]



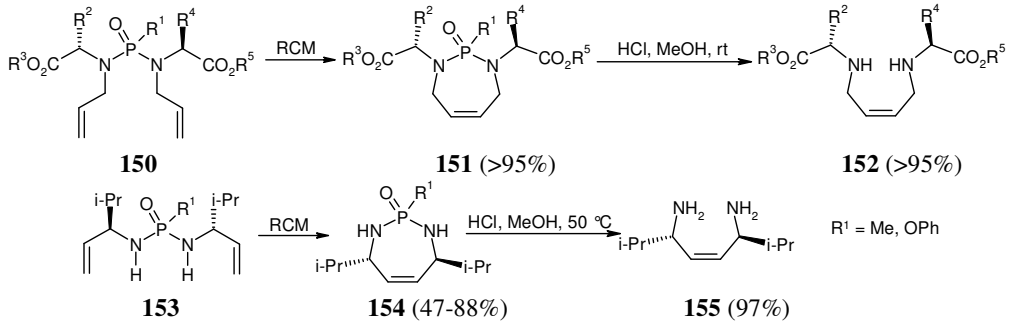
148

149a (n = 0, 26% Yield)
149b (1 = 0, 76% Yield)

Scheme 56

8.4.3. Synthesis of diamines or polyols *via* a RCM stratregy

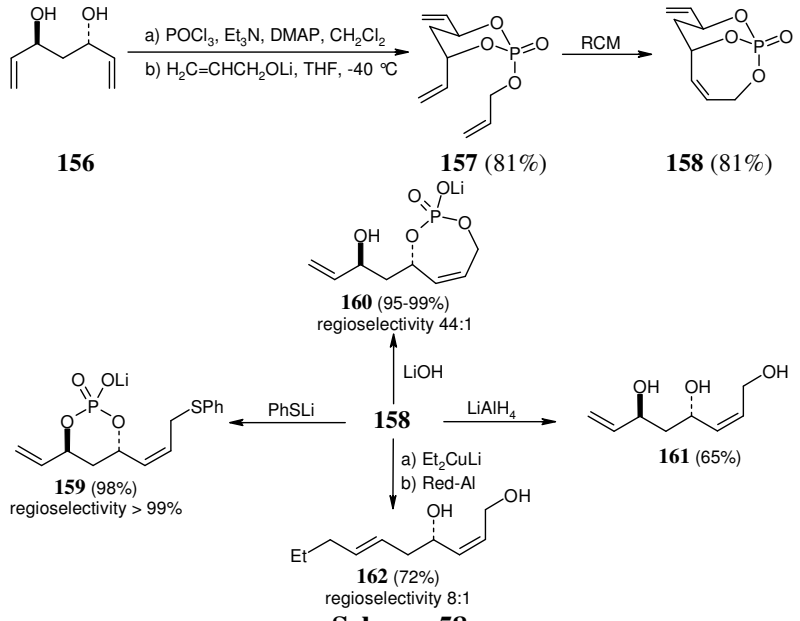
The synthesis of 1,4-diamines containing a (*Z*)-1,4-diaminobut-2-ene subunit **152** or **155** could be achieved *via* the temporary formation of a seven-membered 1,3,2-diazaphosphacycloheptene **151** or **154** by RCM strategy (Scheme 57).[81,82] Ring closing of substituted N-allylphosphonamides resulted in the exclusive formation of the (*Z*)-heterocycle generally in yields higher than 95%. Consecutively, the cleavage of the two P-N bonds in methanolic hydrochloric acid led to the expected 1,4-diamines.



150 **151** (>95%) **152** (>95%)

153 **154** (47-88%) **155** (97%)

Scheme 57



156 **157** (81%) **158** (81%)

160 (95-99%)
regioselectivity 44:1

159 (98%)
regioselectivity > 99%

161 (65%)

162 (72%)
regioselectivity 8:1

Scheme 58

RCM was also used for the desymmetrization of pseudo-C_2-tris allylic phosphate **157**.[83] Generated from phosphorus oxichloride and a C_2-symmetric-1,3-diol **156**, metathesis allowed the stereoselective

formation of the fused seven-membered ring **157** in 81% yield. In a second time, selective ring openings using various nucleophiles by S_N2 or S_N2' displacements ($LiAlH_4$, LiOH, PhSLi, Et_2CuLi) furnished dissymmetric diols **159**-**162** in good yields with a regioselectivity ranging from 8:1 to 99:1 (Scheme 58).

9. Conclusion

Phosphorus heterocycle synthesis is a fertile area and seems to hold considerable promises either in term of chemical creativity or in term of biological potential. These pioneering efforts result in the elaboration of extremely diversified and innovative structures. Not surprisingly, metathesis reaction stimulated the development of this field and appears to be a really valuable and general method.

Acknowledgments

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THE *SECURINEGA* ALKALOIDS: PURSUING A VERSATILE SYNTHETIC APPROACH

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Abstract. *The Securinega alkaloids comprise a group of around thirty tetracyclic compounds isolated mainly from some plants of the Euphorbiacea family. Although some of these alkaloids have been known for more than forty years and they exhibit a remarkable biological activity, rather limited research has been published related to their syntheses. In this review, we summarise the different published approaches directed to these targets. Our own synthetic efforts culminate with the enantioselective synthesis of (-)-norsecurinine in nine steps and 11% overall yield. The crucial reactions of our last generation strategy are a palladium-catalysed enantioselective imide alkylation, a vinylogous Mannich reaction, and a ring-closing metathesis process. This approach is general for any antipode of the final target of either securinine- or norsecurinine-type alkaloids.*

Contents

1. Introduction

1.1. Sources

Nature produces a plethora of plants, which have been used from ancient times as natural remedies against different diseases. These plants biosynthesise a series of substances, which are responsible of the therapeutic effect and thus they can be considered as potential drugs. The *Securinega* alkaloids[1] comprise a

group of compounds initially isolated from some plants of the *Securinega* (also named *Flueggea*) and *Phyllanthus* species, belonging to the Euphorbiaceae family, and later on found also in other Euphorbiaceae species, such as *Margaritaria* and *Breynia*, and in *Zygogynum pauciflorum* (Winteraceae). Due to their medicinal properties,[2] some of these plants have been widely used for years in traditional folk medicine in China and Amazonia. In particular, they have found application as diuretics[3] and antipyretics,[4] in the treatment of hepatic disorders,[5] and against skin eruptions.[6]

Securinine, the most abundant of these alkaloids, was first isolated in 1956 and its structure was fully established in the 1960's.[7] Since then, around 30 related alkaloids have been isolated and characterised. The structures of seven of them ((+)-norsecurinine,[8] (+)-nirurine,[9] bubbialine,[10] bubbialidine,[10] securinol A,[11] ent-phyllantidine,[12] and securinine[13]) were elucidated by X-ray analyses, whereas those of the remaining alkaloids (allosecurinine,[1] virosecurinine,[1] dihydrosecurinine,[1] (-)-norsecurinine,[1] dihydronorsecurinine,[1] viroallosecurinine,[1] phyllantine,[1] securinol B,[1] securinol C,[1] securitinine,[1] phyllantidine,[1] 4-methoxynorsecurinine,[14] fluggeainol,[15] fluggeaine,[15] simplexine,[16] 4-hydroxysecurinine,[17] 4-methoxytetrahydrosecurinine,[17] 4-methoxydihydronorsecurinine,[17] 4-epiphyllantine,[11] margaritarine,[11] isobubbialine,[18] epibubbialine,[18] niruroidine,[19] 14,15-epoxynorsecurinine,[20] and secu'amamine[21]) were determined by their spectroscopic data and/or by chemical correlation.

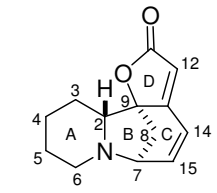
1.2. Structures

Typically, the skeleton of *Securinega* alkaloids encloses a 6-azabicyclo[3.2.1]octane system (rings B and C) fused to a 2-furanone (ring D) and either a piperidine or pyrrolidine (ring A), with the size of this last ring characterizing the securinine- and norsecurinine-type subgroups, respectively (Figures 1 and 2).[22] The members within each one of these subgroups differ in the configuration of their stereogenic centres and/or they present slight functionality alterations. The enantiomer of securinine, virosecurinine, and their epimers at C2, allosecurinine and viroallosecurinine, have all been isolated from natural sources, an unusual event in the field of natural products, but quite recurrent among this class of alkaloids. Thus, (-)-norsecurinine, the first isolated and most representative member of its subgroup,[23] and its antipode (+)-norsecurinine are both naturally occurring.

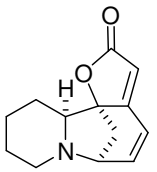
There are also several *Securinega* alkaloids that show significant modifications of the typical structural framework (Figure 3). Phyllantidine and ent-phyllantidine, which present rings A and C connected through an oxygen bridge, may be formed by an oxidation process, resulting in the insertion of an oxygen atom in the N-C7 bond of allosecurinine and viroallosecurinine, respectively. In securinol A, nirurine, bubbialine, isobubbialine, epibubbialine, bubbialidine, and niruroidine, the benzofuranone moiety (rings C and D) is connected to the nitrogen atom of the piperidine or pyrrolidine subunit through a different position, originating a 2-azabicyclo[2.2.2]octane system (isoquinuclidine nucleus). Secu'amamine, the *Securinega* alkaloid last described, includes an additional carbon atom between rings A and D, originating a 2-azabicyclo[3.3.1]nonane system.

1.3. Biological activity

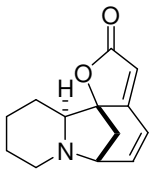
The *Securinega* alkaloids have been associated with a number of biological activities, some of which are well documented. Securinine (**1**) is an acetylcholine esterase (ACE) inhibitor,[24] a stimulant of the central nervous system,[25] and has shown antimalarial[26] and antibacterial activities.[27]



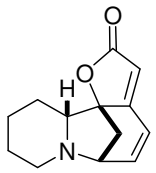
securinine
[α]=-1042 (EtOH)[1a]
-1089 (EtOH)[1b]
-1115 ($CHCl_3$)[1b]



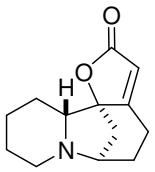
allosecurinine
(phyllochrisine, securinegine)
[α]=-1082 (EtOH)[1a]



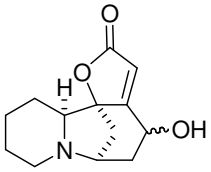
virosecurinine
[α]=+1035 (EtOH)[1a]
+1148 ($CHCl_3$)[1b]



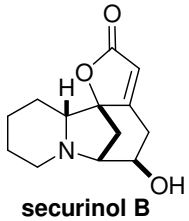
viroallosecurinine
[α]=+1085 (EtOH)[1a]
+1420 ($CHCl_3$)[12]



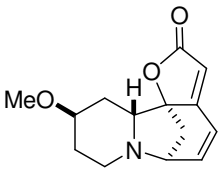
dihydrosecurinine
[α]=-81 (EtOH)[1a]



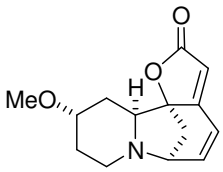
securinol C
[α]=-82 (EtOH)[1a]



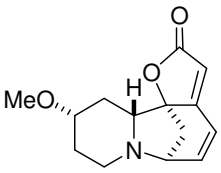
securinol B
[α]=+120 (EtOH)[1a]



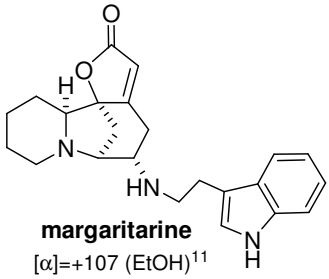
phyllantine
[α]=-898 ($CHCl_3$)[1a]
-1508 (EtOH)[11]



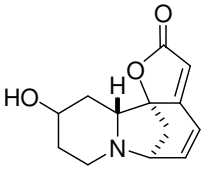
securitinine
[α]=-952 (EtOH)[1a]



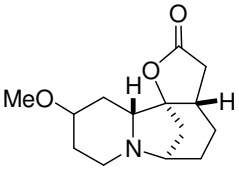
4-epiphyllantine
[α]=-753 (EtOH)[11]



margaritarine
[α]=+107 (EtOH)[11]



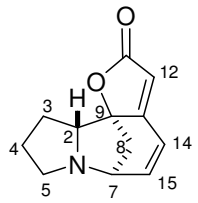
4-hydroxysecurinine



4-methoxytetrahydrosecurinine

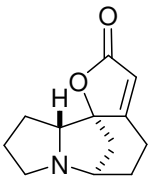
Figure 1

It has been described that several *Securinega* alkaloids are specific $GABA_A$ receptor antagonists.[28] To get information about the interaction site with the biological receptor, conformational studies of securinine in solution were performed.[29]



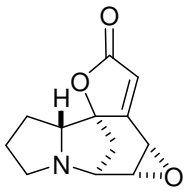
(-)-norsecurinine

[α]=-272 (EtOH)[1a]

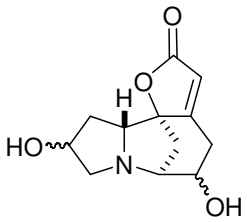


dihydronorsecurinine (virosine)

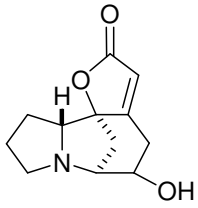
[α]=-13 (dioxane)[1a]



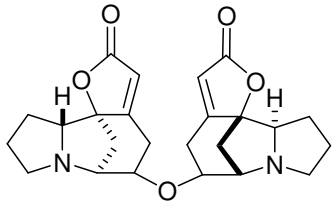
14,15-epoxynorsecurinine



simplexine

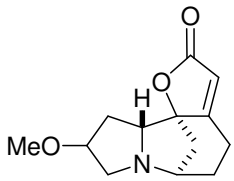


fluggeainol

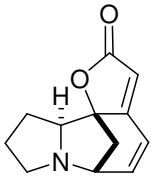


fluggeaine

[α]=+106 ($CHCl_3$)[1b]



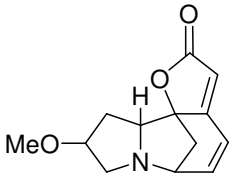
4-methoxydihydronorsecurinine



(+)-norsecurinine (ent-norsecurinine)

[α]=+213 ($CHCl_3$)[1a]

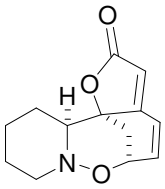
[α]=+256 (MeOH)[8]



4-methoxynorsecurinine

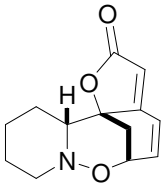
[α]=-47 (MeOH)[1b]

Figure 2



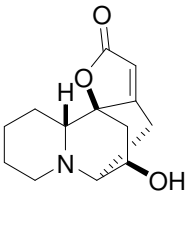
phyllantidine

[α]=-450 ($CHCl_3$)[1b]



ent-phyllantidine

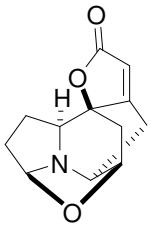
[α]=+333 ($CHCl_3$)[12]



securinol A

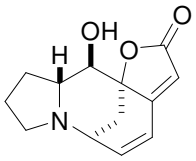
[α]=+58 ($CHCl_3$)[1a]

+57(MeOH)[11]



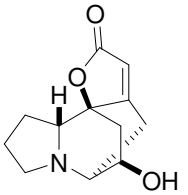
nirunine

[α]=+196 (MeOH)[1b]



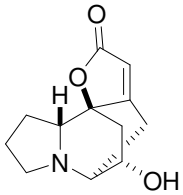
secu'amamine A

[α]=-479 ($CHCl_3$)[21]



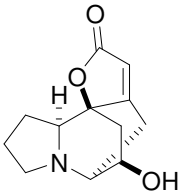
bubbialine

[α]=+129 (MeOH)[10]



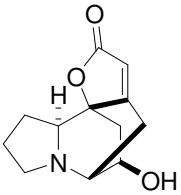
isobubbialine

[α]=+11.7 (not given)[18]



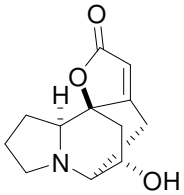
epibubbialine

[α]=-14.5 (not given)[18]



bubbialidine

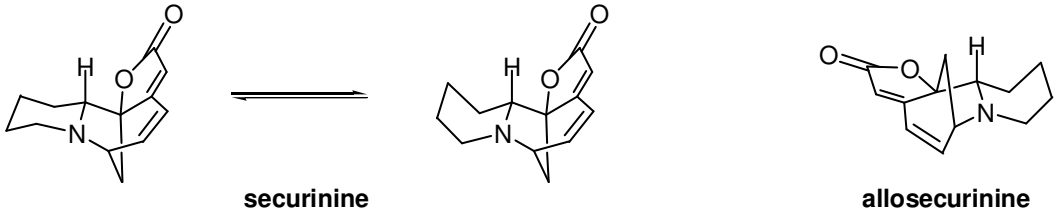
[α]=-85 (MeOH)[10]



niruroidine

Figure 3

An equilibrium involving a rigid chair conformer and a boat conformer (Scheme 1) is supported by molecular mechanics calculations and is consistent with the nmr data in $CDCl_3$ solution, recorded at different temperatures. For allosecurinine the experimental results are in better agreement with a distorted boat conformer.



Scheme 1

Some *Securinega* alkaloids act also as antitumor agents[30] and the structural requirements for significant cytotoxicity have even been established.[30a] A comparison of the cytotoxicity of virosecurinine, several of its derivatives, and viroallosecurinine indicated that an α,β- and a γ,δ-unsaturated lactone located in a strained ring system is structurally required for significant toxicity. The stereochemistry of the A/B ring juncture may also play an important role in contributing to cytotoxicity.

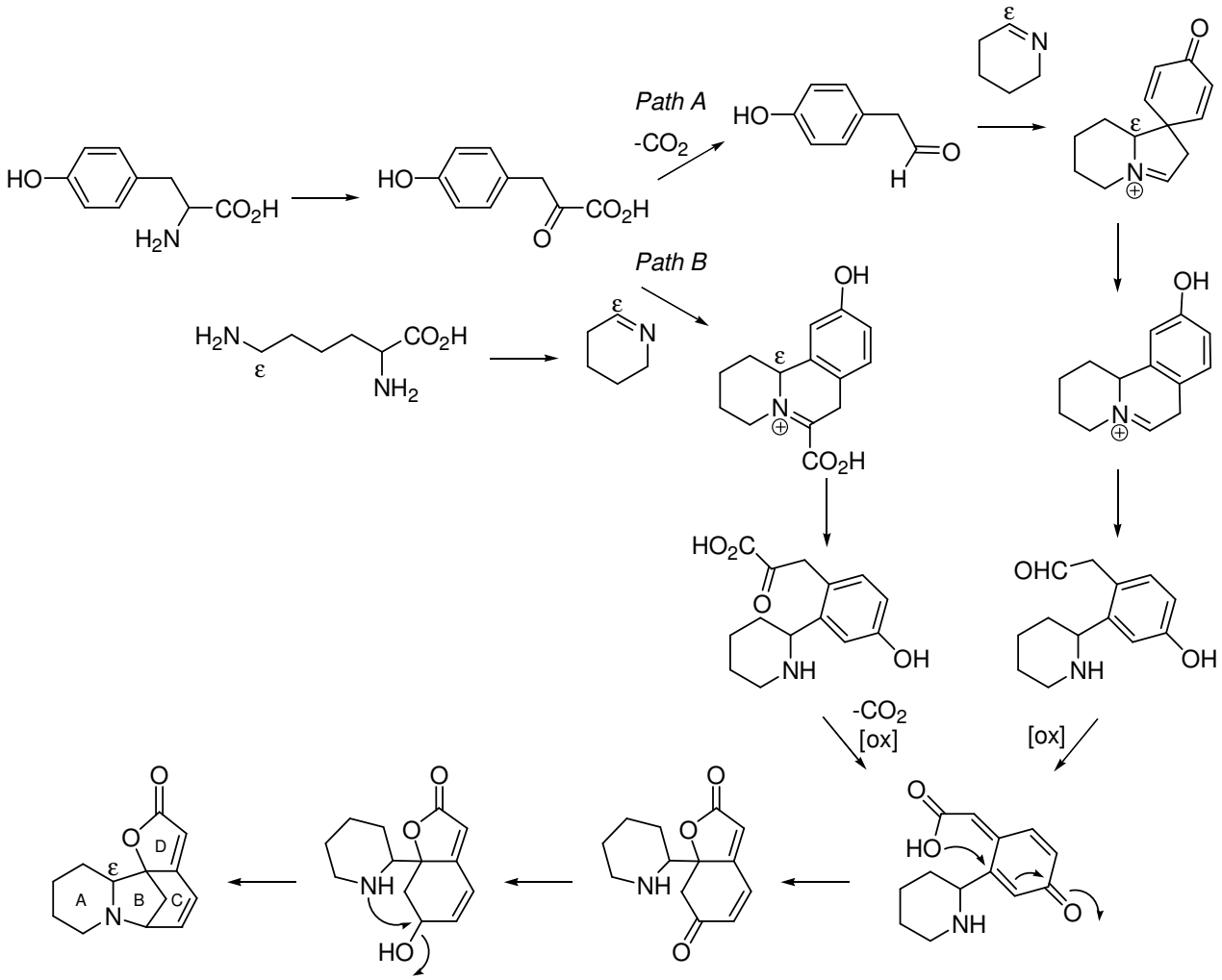
(+)-Norsecurinine inhibits spore germination of some plant pathogenic fungi.[31] Its efficacy was significantly high even at low concentrations, suggesting the possibility of its use for the control of plant diseases under field conditions.

1.4. Biosynthesis

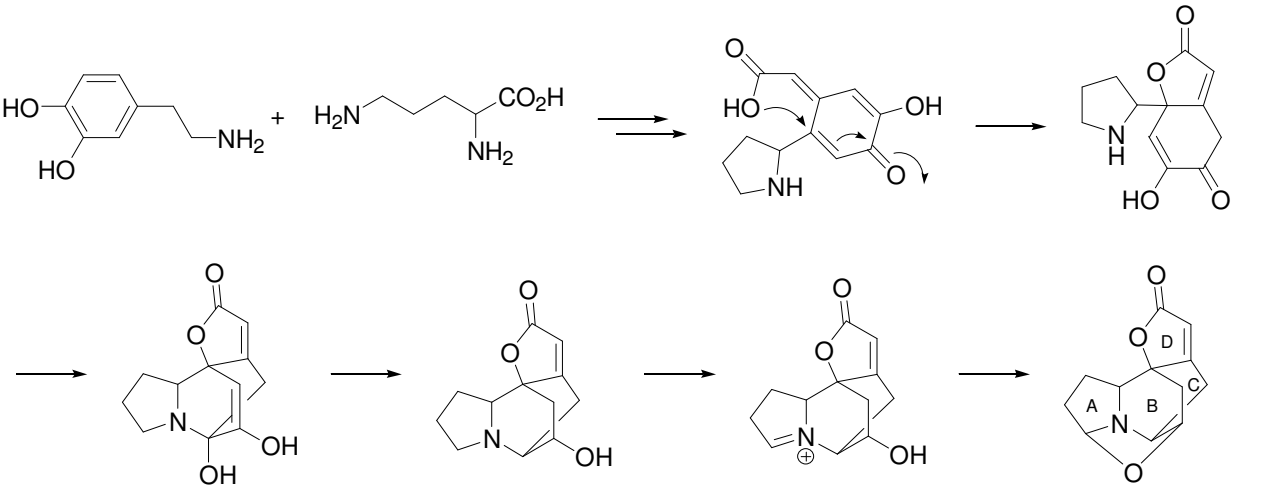
Parry proposed for securinine the biogenetic pathway shown in Scheme 2,[32] which is consistent with experiments performed with labelled precursors. According to his proposal, the piperidine fragment (ring A) is originated from lysine in non-symmetrical fashion, since the nitrogen atom in securinine is derived from the ε-amino nitrogen of lysine.[33] The six-membered carbocycle and the γ-lactone (rings C and D) derive from tyrosine *via* 4'-hydroxyphenylpyruvic acid. The experiments with labelled precursors did not allow concluding if the decarboxylation takes place before (path A) or after (path B) the condensation of the aromatic intermediate with the Δ^1-piperidine. In the last steps, an intramolecular nucleophilic substitution to generate the ring B would complete the tetracyclic skeleton. Some investigations support the hypothesis that dihydrosecurinine is derived *in vivo* by reduction of securinine. It has been speculated that the biosynthesis of norsecurinine may possibly follow a parallel pathway, with the pyrrolidine ring deriving from ornithine instead of lysine.[32,34]

Although no evidences were given, Cordell and co-workers suggested a biosynthetic route for nirunine, based on its structural similarity with the former alkaloids.[9] These authors proposed dopamine as the precursor of the benzofuranone moiety (rings C and D) and ornithine as the precursor of the pyrrolidine ring (Scheme 3).

However, the synthetic work developed by the group of Magnus[35] illustrated the easy rearrangement of the seco-nirurine skeleton into the norsecurinine skeleton, when (±)-hydroxynirurine was exposed to standard mesylation conditions (Scheme 4), an observation that may have biogenetic relevance.

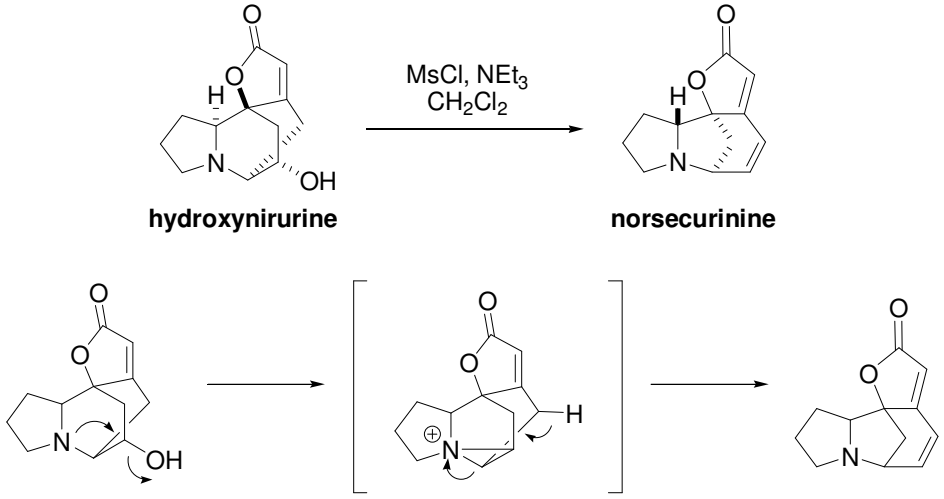


Scheme 2



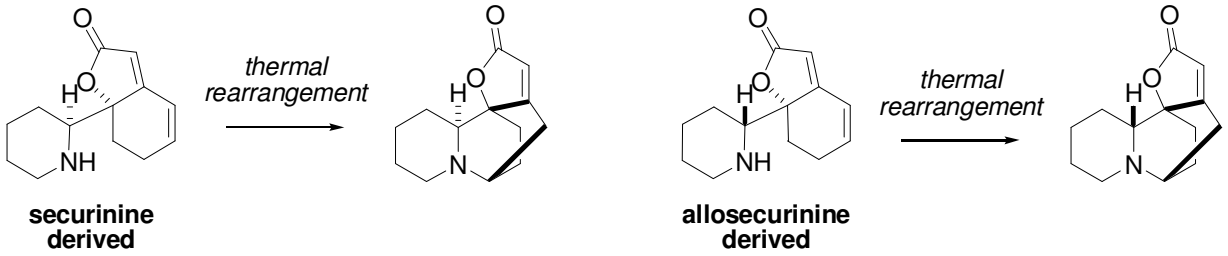
Scheme 3

Interconversions between the [2.2.2] and the [3.2.1] bridged systems have been observed for related azabicyclic compounds and the intervention of an aziridinium cation seems to be the most plausible hypothesis.[36]



Scheme 4

Previously, Horii and co-workers had also described the thermal rearrangement of the piperidino lactones in Scheme 5, obtained from securinine and allosecurinine in degradative studies, into the isoquinuclidine derivatives.[37]



Scheme 5

2. Synthesis

2.1. General remarks

Despite their attractive potential as pharmacological agents, published synthetic investigations related to the *Securinega* alkaloids are rather limited. Considering that most of the well-established procedures for the isolation of securinine and other alkaloids of its family are protected by patents, the scant amount of described synthetic work is quite intriguing. The chronogram in Figure 4 resumes all the total and formal syntheses of *Securinega* alkaloids isolated from natural sources that have appeared in the literature to date.

Racemic securinine was synthesised by Horii *et al.* few years after its isolation,[38] as a logical continuation of the structural assignment investigations performed by these chemists. They also accomplished the resolution of the racemate through the formation of the diastereomeric *d*-camphor-10-sulphonates. For the next two decades the subject of "*Securinega* alkaloids as synthetic targets" was absent

from the organic chemistry literature, and it was not until 1987 that Heathcock and von Geldern disclosed the first synthesis of racemic norsecurinine,[39] the most representative alkaloid of the second subgroup. Two additional total syntheses[40,41] and one formal synthesis[42] of (±)-securinine have been later on reported, as well as one total synthesis of (±)-norsecurinine.[35,43] In this last work, a small quantity of the oxygen bridged alkaloid (±)-nirurine was also obtained.

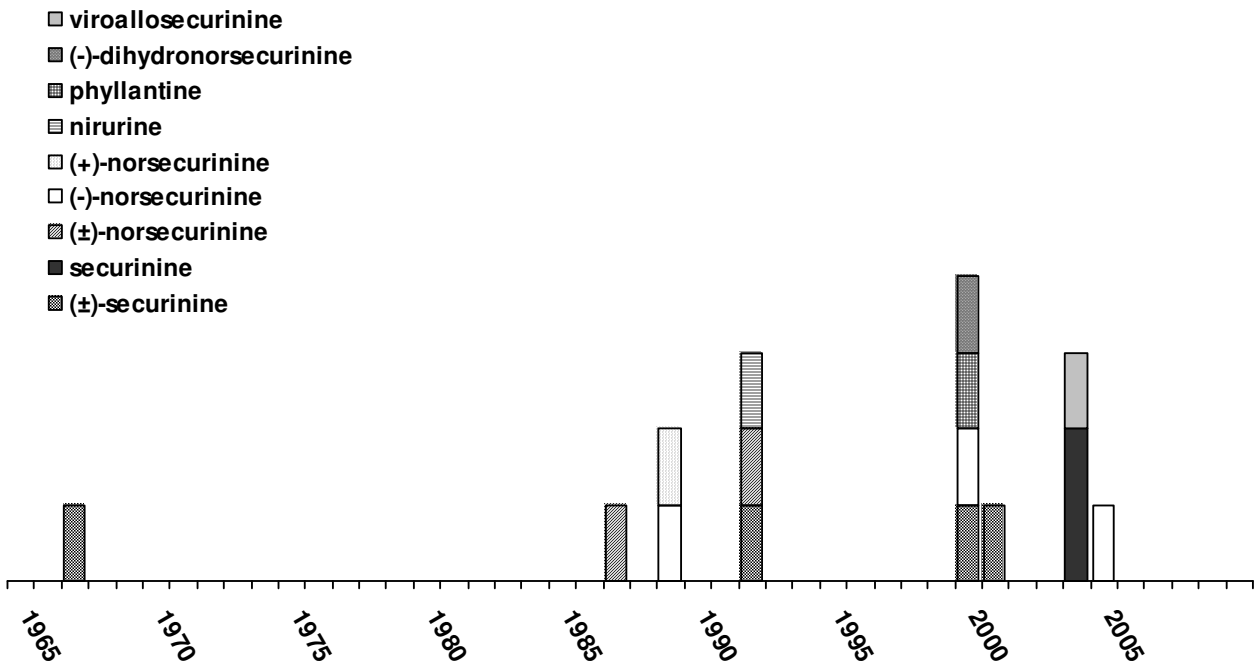


Figure 4

The first non-racemic total synthesis of a *Securinega* alkaloid was published in 1989, when Jacobi and co-workers reported the independent preparation of (+)- and (-)-norsecurinine, starting from L- and D-proline, respectively.[44] In 2000, the group of Weinreb described the second successful approach to (-)-norsecurinine,[45] together with the first preparation of (-)-dihydronorsecurinine, both alkaloids derived from a common synthetic intermediate. Simultaneously, and through an analogous sequence, the authors also reported the preparation of phyllantine (4-methoxysecurinine), the first non-racemic synthesis among the securinine subgroup. Very recently, two rather similar diastereoselective syntheses of securinine have been disclosed by the group of Honda[46] and ours,[47] both of them starting from (*R*)-pipecolinic acid. As part of the same investigations, the Japanese group has also accomplished the synthesis of (+)-viroallosecurinine[48] and we have obtained a previously unknown epimer at C2 of (-)-norsecurinine, named (-)-allonorsecurinine.[47] In parallel to these studies, we were trying to develop a general and enantioselective strategy for the synthesis of both types of *Securinega* alkaloids. Our goal was originating enantioselectivity in a catalytic process rather than deriving it from a chiral pool material, in order to make either antipode of the target alkaloid equally available. The efficiency of our enantioselective approach has been illustrated by concluding a total synthesis of (-)-norsecurinine.[49]

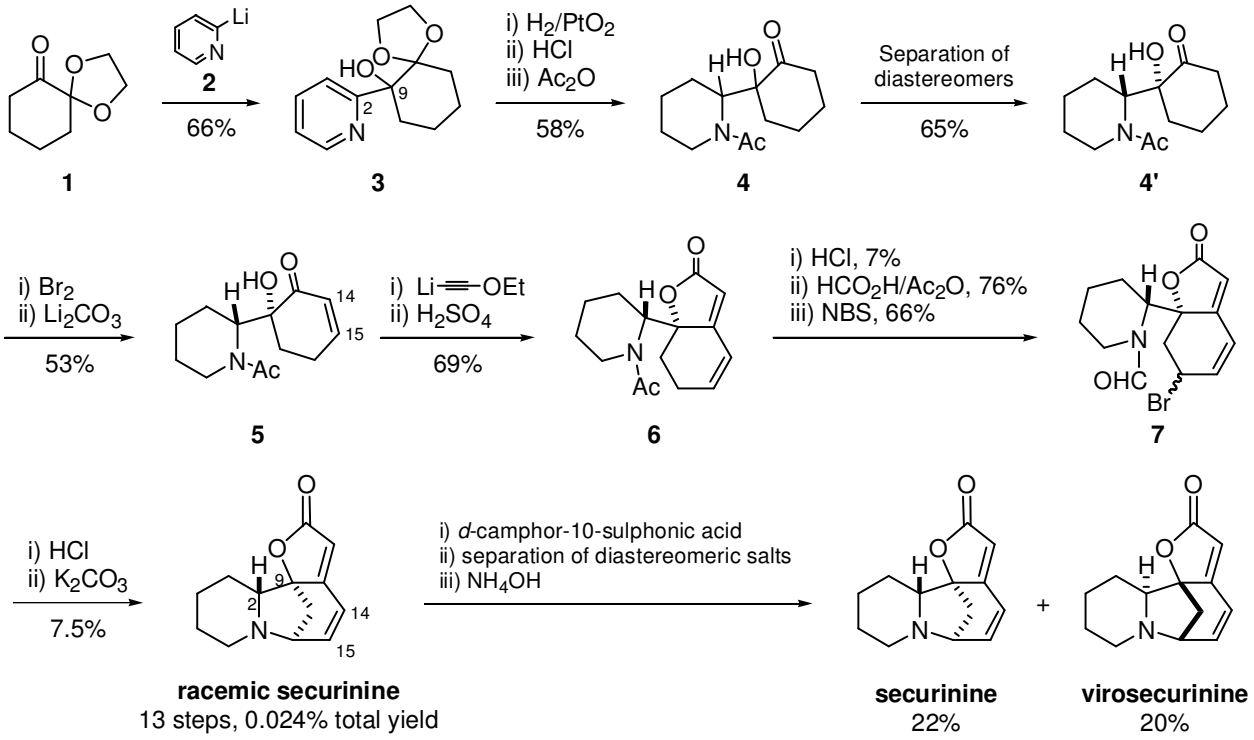
In the following sections, the synthetic approaches to *Securinega* alkaloids that have been published to date are briefly summarised. They have been classified in three categories: racemic, chiral pool and

enantioselective. Within each category, the securinine- and norsecurinine-type subgroups are examined separately. All along the discussion, the mentioned carbon atoms of synthetic intermediates are referred to with the number of the corresponding atom in the alkaloid.[22]

2.2. Syntheses of racemic alkaloids

2.2.1. (±)-Securinine

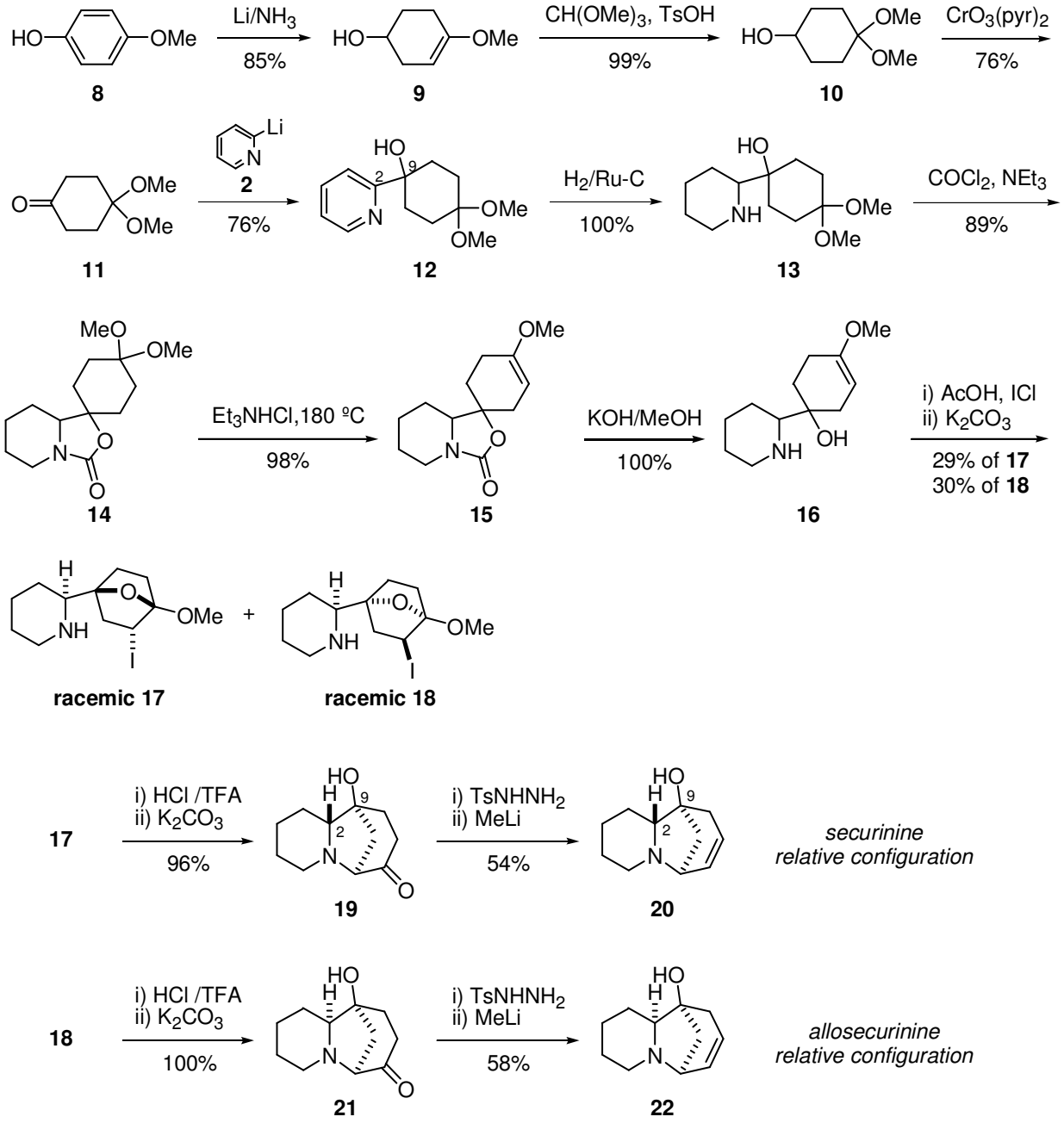
In the pioneer synthesis of securinine developed by Horii and co-workers[38] (Scheme 6), rings A and C were connected by condensation of 2-pyridyllithium, **2**, with the ethylene monoketal of 1,2-cyclohexadione, **1**, resulting in the formation of the crucial C2-C9 bond of the alkaloid.



Scheme 6

The adduct **3** was hydrogenated to furnish a diastereomeric mixture of alcohols, which were subsequently hydrolysed and *N*-acetylated to render the mixture of hydroxyketones **4**. After chromatographic separation of diastereomers, the major ketone **4'** was treated with bromine and then base to introduce the α,β-unsaturation, corresponding to the C14-C15 double bond in securinine. After extensive experimentation, the best method found for the construction of the butenolide ring D was condensation of the hydroxyketone **5** with lithium ethoxyacetylide followed by treatment with diluted sulphuric acid. To complete the tetracyclic skeleton, the *N*-acetyl derivative **6** was converted into the corresponding *N*-formyl analogue and an allylic bromination provided the appropriate intermediate for the closure of ring B. The cyclisation was accomplished by acid hydrolysis of the formyl amide **7**, followed by refluxing with potassium carbonate in chloroform. In this way, the first synthesis of racemic securinine was completed in 0.024% total yield, through a sequence involving thirteen synthetic steps. The racemic modification was resolved by selective crystallisation of the diastereomeric *d*-camphor-10-sulphonates exploiting the higher solubility of the virosecurinine salt in hot acetone.

More than twenty years later, Lessard *et al.* published an alternative preparation of the tricyclic A-B-C core of the alkaloids of the securinine subgroup (Scheme 7).[50]

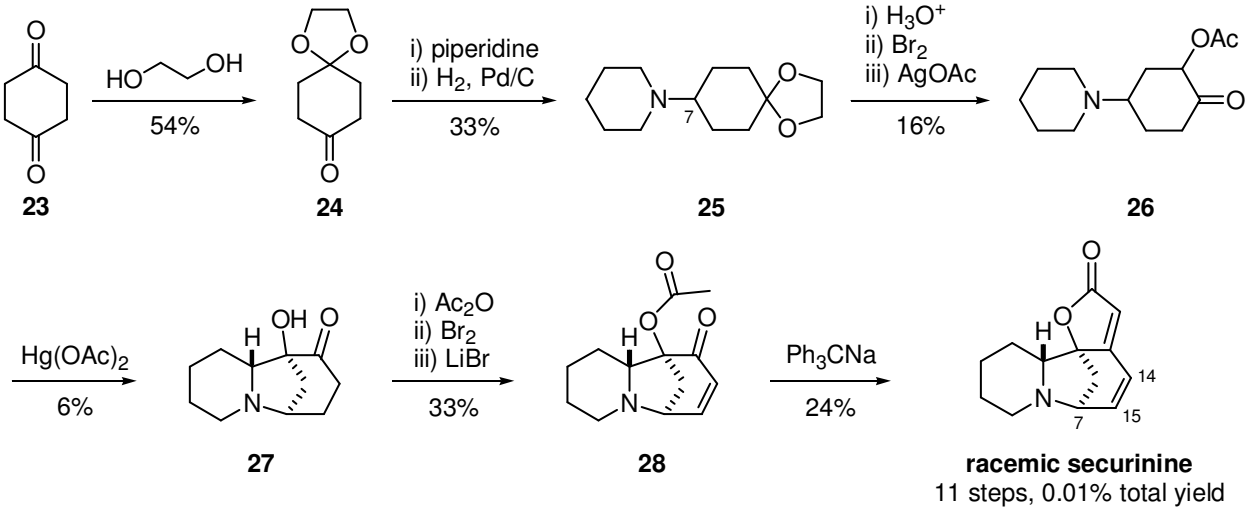


Scheme 7

As in Horii's approach, rings A and C were coupled through a condensation between 2-pyridyllithium, **2**, and a cyclohexanone, but the ketone partner **11** used in this case was derived from 1,4-cyclohexadione. Hydrogenation of the aromatic ring of the adduct **12** furnished a mixture of diastereomeric amino alcohols **13**, which was treated with phosgene and triethylamine to form the cyclic carbamates **14**. The ketal functionality in **14** was converted into the methyl enol ether by acid catalysed pyrolysis and the resulting derivative **15** was deprotected by methanolysis. The mixture of amino alcohols **16** was then converted into the corresponding amine acetates, which were treated with iodine monochloride, followed by alkaline work-

up to furnish the iodo ketals **17** and **18**. At this point, the two diastereomers were chromatographically separated and each iodoketal was processed independently. The tricyclic ketones **19** and **21**, with securinine-like and allosecurinine-like C2-C9 relative configuration respectively, were formed by hydrolysis of the corresponding iodoketal precursors. When they are in solution, these ketones decompose fairly quickly in the presence of oxygen, to give a complex mixture of polar compounds. As a further step in the potential route to the alkaloids, olefins **20** and **22** were also prepared, using the Bamford-Stevens protocol.

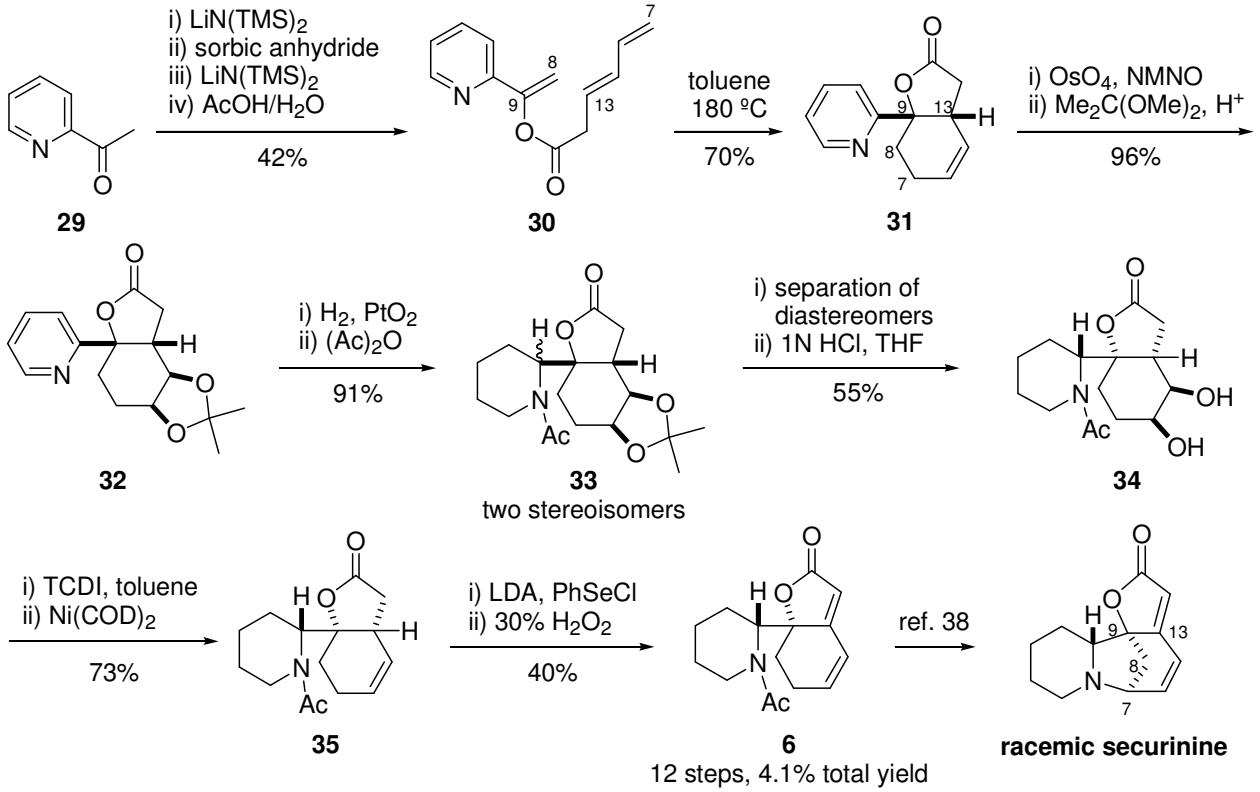
The second synthesis of racemic securinine (Scheme 8) was published by Xi and Liang three years later.[40] As in the former approaches, rings A and C were connected in the first stage of the synthesis, in this case through the early formation of the nitrogen-C7 bond. 1,4-Cyclohexadione, **23**, was converted into the corresponding ethylene monoketal **24**, which was tretated with piperidine, followed by hydrogenation of the condensation product. The resulting amino ketal **25** was hydrolysed, the free ketone was treated with bromine and the α-bromo derivative transformed into the acetoxy ketone **26**. An intriguing cyclisation catalysed by mercuric acetate provided the tricyclic derivative **27**, although in very low yield. To end the synthesis, compound **27** was acetylated, the C14-C15 double bond was generated using standard α-bromination/dehydrobromination methodology, and an intramolecular aldol-type condensation led to the formation of the remaining D-ring. The sequence involved only eleven steps, but the overall yield was around 0.01%.



Scheme 8

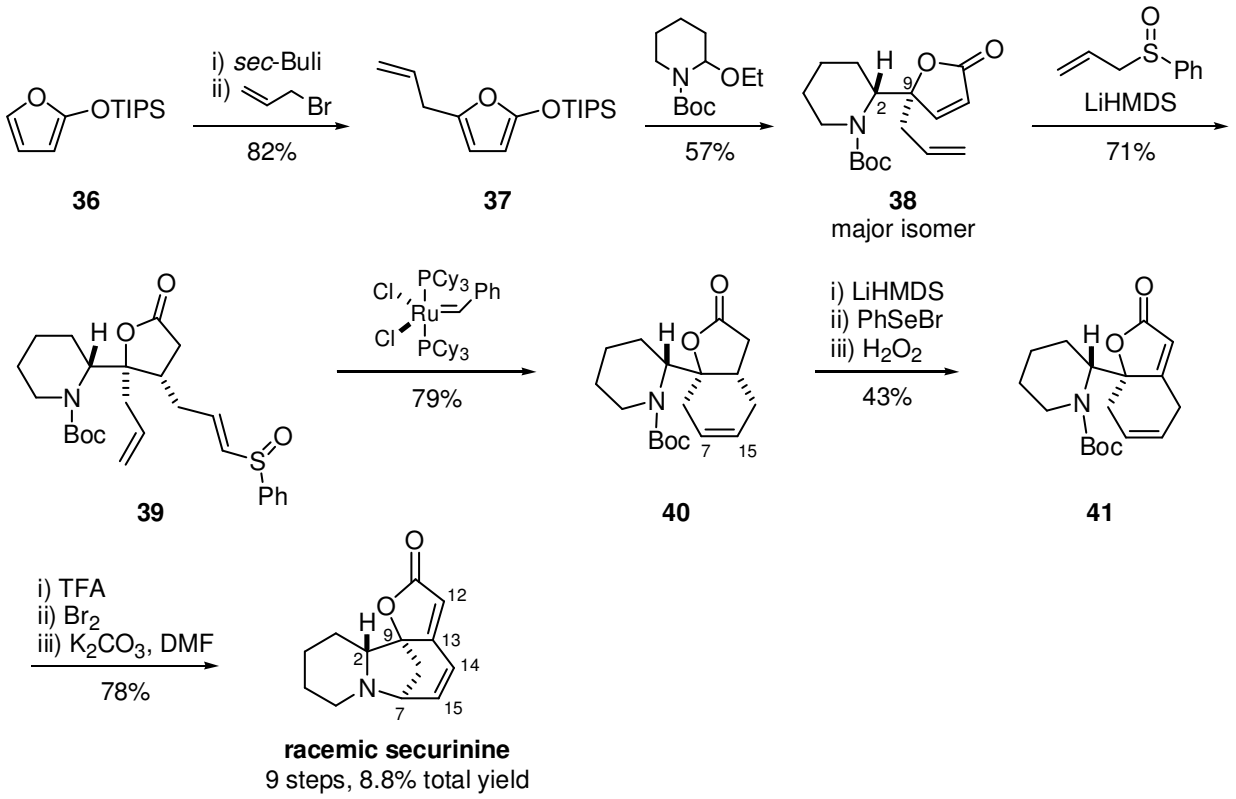
A formal total synthesis of (±)-securinine was published in 2000 by the group of Honda (Scheme 9).[42] The key step of their strategy was the intramolecular Diels-Alder reaction of the enol ester **30**, derived from 2-acetylpyridine **29**, and sorbic acid. This cycloaddition resulted in the simultaneous construction of rings C and D, through the formation of the C7-C8 and C9-C13 bonds of the alkaloid. The *cis* adduct **31**, coming from an *exo* transition state which is sterically less encumbered than the competing *endo* transition state, was mainly formed. The carbon-carbon double bond was then protected, and hydrogenation of the aromatic ring gave the piperidine derivatives which, on acetylation, furnished the corresponding acetates **33**, as a 2:3 mixture of diastereomers. The relative configuration of the major isomer was unambiguously determined by X-ray analysis of the derived diol **34**. To regenerate the C14-C15 double bond, diol **34** was converted into

the corresponding thionocarbonate and then treated with bis(1,5-cyclooctadiene)nickel(0). Finally, the C12-C13 unsaturation was introduced *via* phenylselenylation and subsequent oxidative elimination. For the twelve-step sequence from 2-acetylpyridine to the tricyclic product **6** the overall yield was 4.1%. Compound **6** was an advanced intermediate in the previous synthesis of Horii, although its conversion in racemic securinine had been achieved in very low yield.



Scheme 9

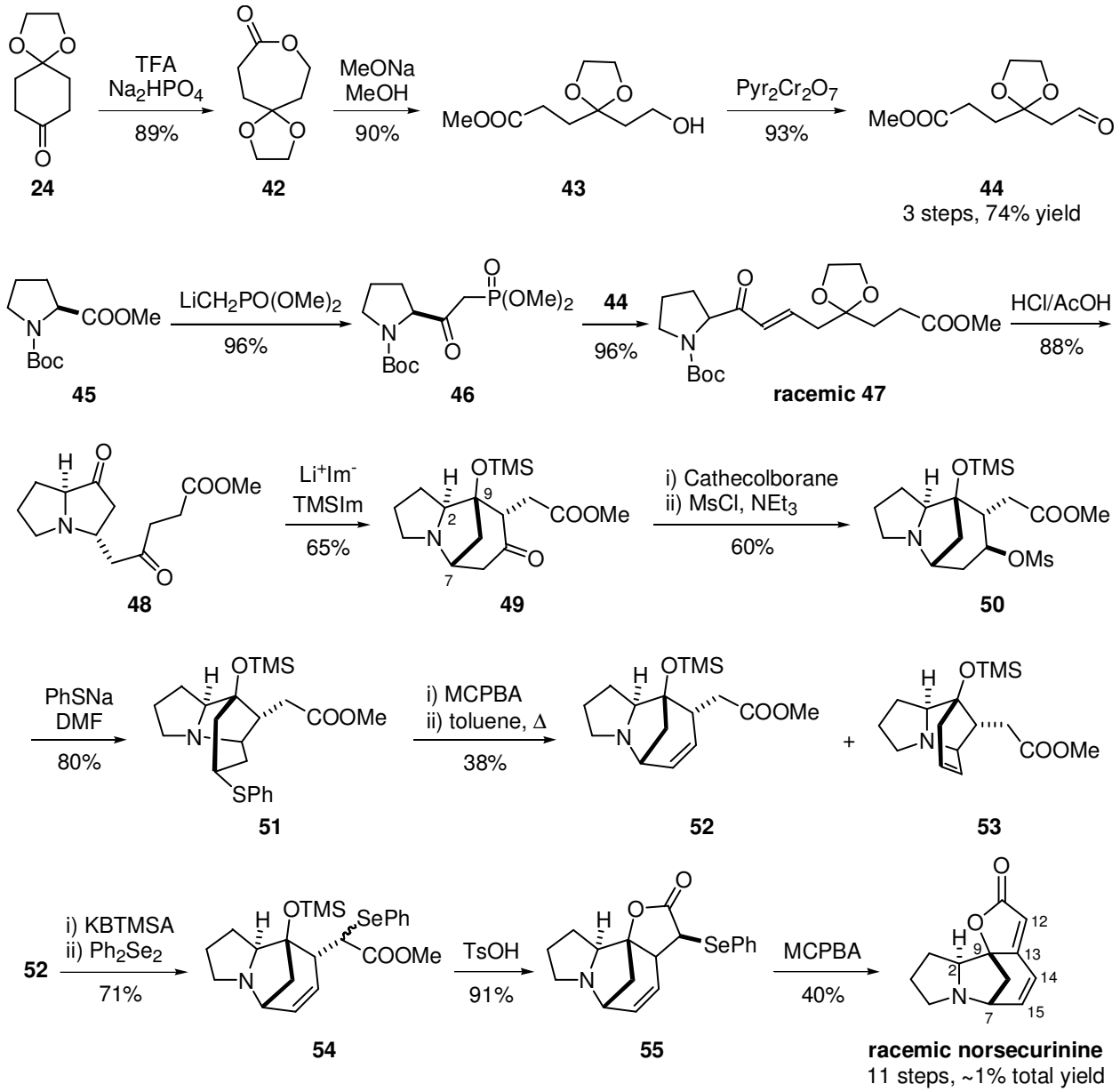
Very shortly afterwards, Liras *et al.* published an alternative method for assembling the securinine skeleton, which was illustrated with a new synthesis of the alkaloid (Scheme 10).[41] In this new approach, rings A and D were connected first through the formation of the crucial C2-C9 bond. This was achieved by means of a vinylogous Mannich reaction between an *N*-acyl iminium ion, which provided the piperidine ring, and silyloxyfurane **37**, which provided the lactone properly substituted at C9. The relative configuration of the major adduct **38** was determined from a crystal structure of the amine hydrochloride formed by removal of the *N*-Boc group with HCl in ethyl acetate. The construction of the cyclohexane C-ring was planned *via* a ring closing metathesis (RCM) reaction. The RCM precursor **39** was satisfactorily prepared by addition of **38** to lithiated phenyl allyl sulphoxide, but its conversion to the cyclohexene **40** could be accomplished in a reasonable yield only by using a full equivalent of the Grubbs reagent. Next, the C12-C13 double bond was installed, as in the previous synthesis, through α-carbonyl phenylselenylation/oxidative elimination. From diene **41**, the synthesis of (±)-securinine was completed by removal of the nitrogen-protecting group with trifluoroacetic acid, treatment of the crude trifluoroacetate salt with bromine, and base promoted HBr elimination, resulting in cyclisation to furnish ring B and concomitant formation of the C14-C15 double bond. The complete sequence consists of nine steps in 8.8% overall yield.



Scheme 10

2.2.2. (±)-Norsecurinine and (±)-nirurine

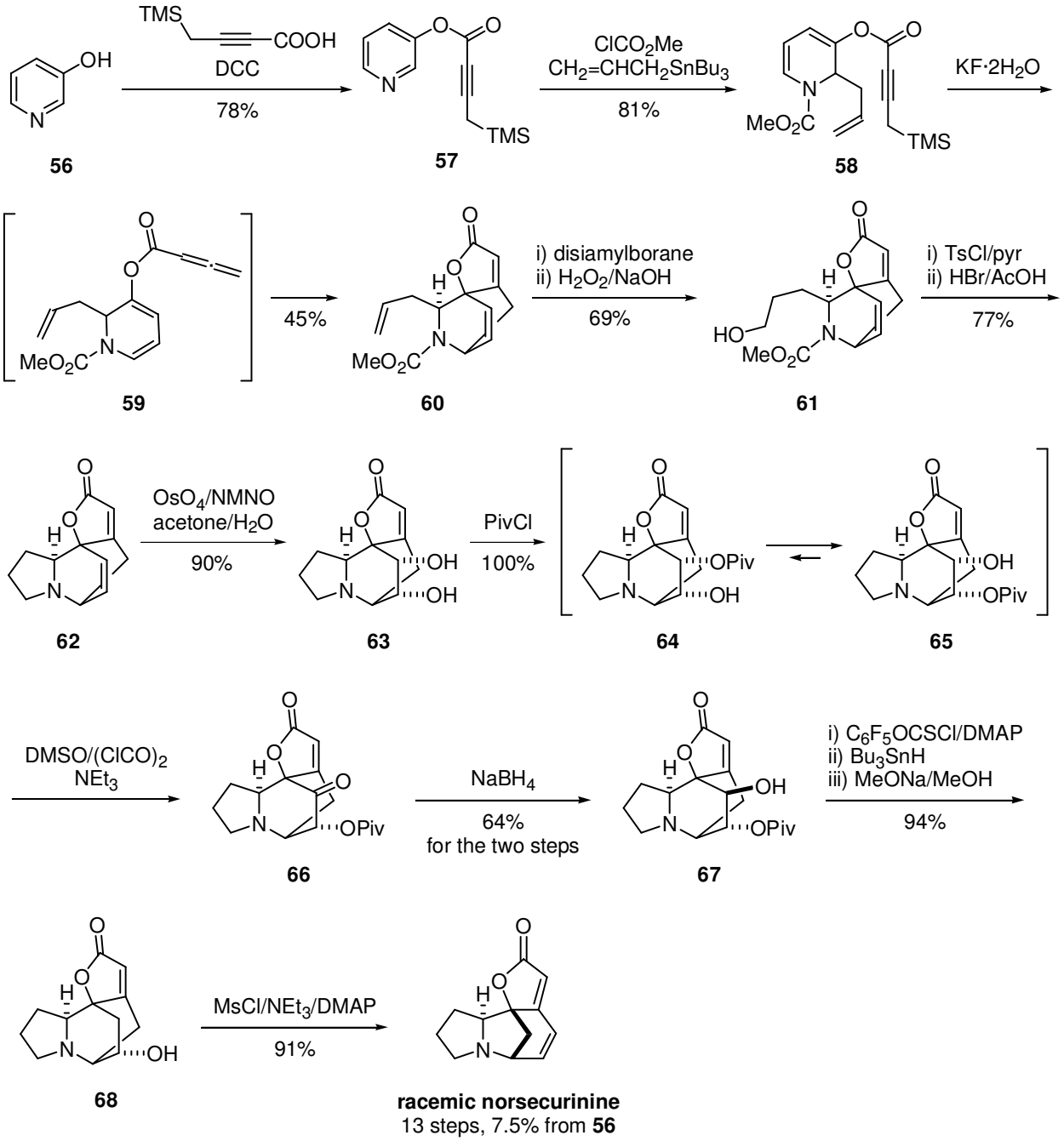
The first total synthesis of racemic norsecurinine was published by Heathcock and von Geldern in 1987.[39] In their approach (Scheme 11), L-proline furnished the pyrrolidine A-ring of the alkaloid and the remaining rings (B, C, D) were gradually incorporated, until completing the tetracyclic skeleton. The actual sequence began with the preparation of aldehyde **44** from the monoketal of 1,4-cyclohexadione **24** in a three-step protocol, consisting of a Baeyer-Villiger reaction, followed by methanolysis of the lactone, and then oxidation of the alcohol. When aldehyde **44** was condensed with the ketophosphonate **46**, derived from the *N*-Boc prolinate **45**, enone **47** was obtained in very good yield, but in racemic form. Although alternative conditions were found to obtain the enone in enantiomerically enriched form, the synthesis was continued with the racemate. Treatment of enone **47** with HCl in acetic acid furnished pyrrolizidone **48**, which reacted with lithium imidazolide and trimethylsilylimidazole to provide the tricyclic ketone **49**, with the same relative configuration C2-C7-C9 as in the target alkaloid. To generate the C14-C15 olefin, it was planned to attempt the pyrolysis of a sulphoxide derived from ketone **49**. To this end, the mesylate **50** was prepared but, when treated with thiophenoxide in DMF, it furnished the rearranged sulphide **51**. The sulphide was oxidated to the sulphoxide, which was pyrolysed by heating in toluene, providing a roughly 1:1 mixture of the tricyclic amines **52** and **53**, suggesting that the sulphoxide elimination occurs *via* ionisation of the carbon-sulphur bond, probably with the participation of an azetidinium ion, which may facilitate the skeletal rearrangements observed in these compounds.[51] From amine **52**, the synthesis of (±)-norsecurinine was concluded by α-selenylation of the ester, followed by lactonisation and oxidation-pyrolysis of the selenyl group to introduce the C12-C13 double bond. From the protected prolinate **45**, the completion of the synthesis required eleven steps and the overall yield was around 1%.



Scheme 11

In 1992, the group of Magnus reported a second synthesis of (±)-norsecurinine, together with the first synthesis of (±)-nirurine.[35,43] These investigators based their approach on the possible biogenetic relationship between both alkaloids, taking advantage of the inter-conversion between the azabicyclo[2.2.2]octane core of nirurine and the azabicyclo[3.2.1]octane core of norsecurinine. The synthesis of (±)-norsecurinine (Scheme 12) began with the condensation reaction between 3-hydroxypyridine, **56**, and 4-trimethylsilyl-2-butynoic acid to furnish the labile ester **57**, which immediately was regioselectively converted into the 2-allyl-1,2-dihydropyridine carbamate **58**. Fluoride ion induced desilylation of **58** produced the azabicyclo[2.2.2]octane **60**, presumably *via* the intermediate allenyl-diene **59**. Selective hydroboration of the terminal carbon-carbon double bond, followed by oxidative work-up, provided the primary alcohol **61**, which was converted to the tetracyclic amine **62** by tosylation, followed by treatment with hydrogen bromide in acetic acid containing cyclohexene as a bromine scavenger. The disubstituted double bond in **62** presented extremely low reactivity towards electrophilic addition and it could only be functionalised by osmylation to

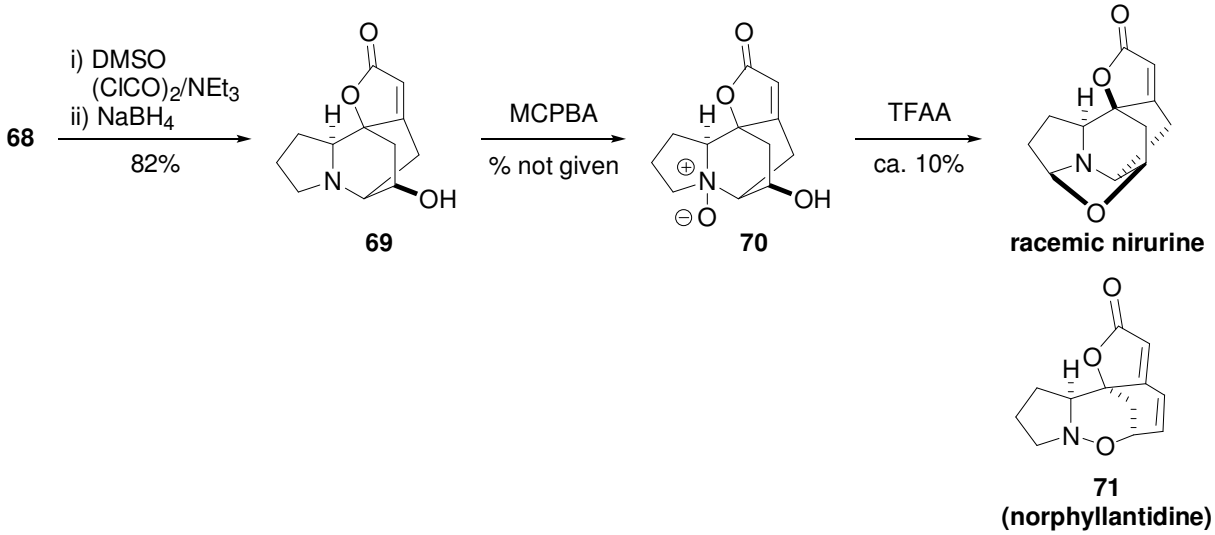
give the diol **63**. Pivaloylation of the diol furnished an equilibrium mixture of monopivaloates **64** and **65**. Under Swern oxidation conditions, this mixture of alcohols delivered essentially ketone **66**, meaning that alcohol **65** was more rapidly oxidised than its regioisomer **64**, therefore allowing re-equilibration of the mixture. Ketone **66** was reduced to alcohol **67**, which was deoxygenated using the Barton-McCombie methodology, and methanolysis of the pivaloate gave alcohol **68**. Alcohol **68** cleanly rearranged to norsecurinine on exposure to standard mesylation conditions. In this manner, the synthesis of racemic norsecurinine was completed in thirteen steps from 3-hydroxypyridine, **56**, and 7.5% total yield.



Scheme 12

For the synthesis of (±)-nirurine (Scheme 13), alcohol **68** was epimerised by oxidation to the ketone and subsequent reduction with sodium borohydride. The inverted alcohol **69** when treated with

m-chloroperbenzoic acid gave the unstable *N*-oxide **70**, which rapidly rearranged to give largely **71** and a small quantity of nirurine. It was then concluded that **69** is probably not the biogenetic precursor of nirurine.

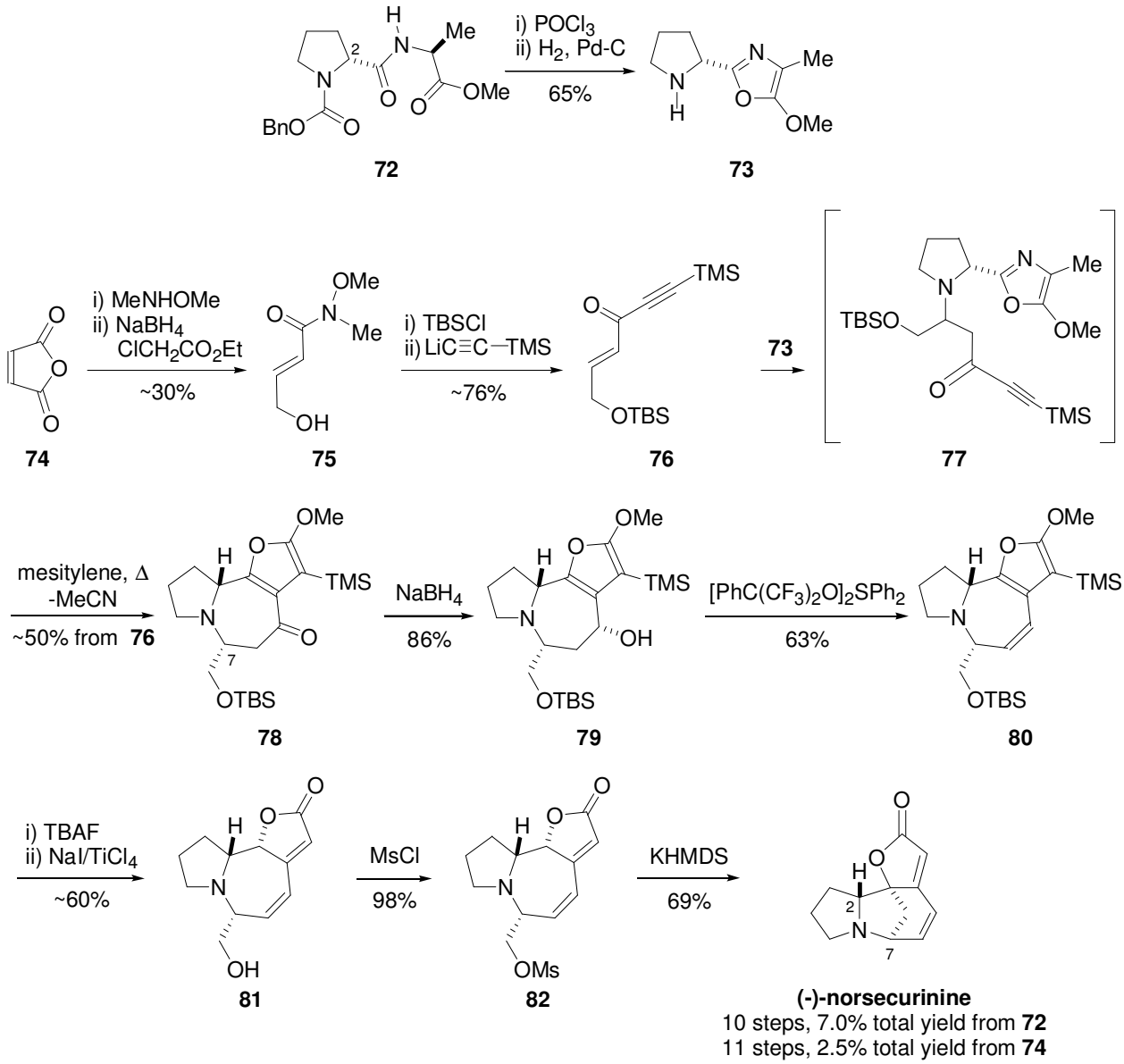


Scheme 13

2.3. Diastereoselective, enantiospecific syntheses: chiral pool approaches

2.3.1. (+)- and (-)-Norsecurinine and (-)-dihydronorsecurinine

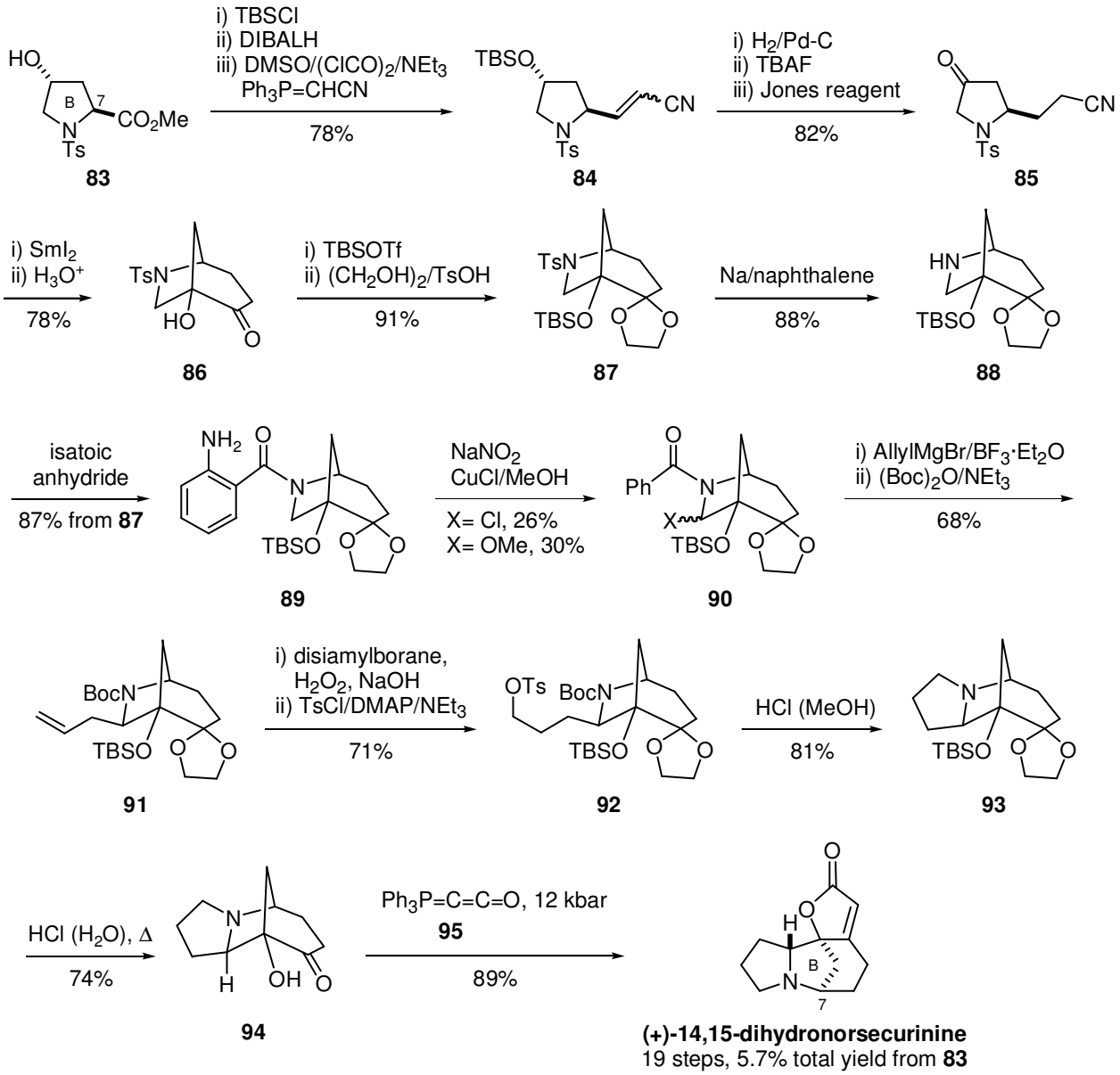
The first non-racemic approach to a *Securinega* alkaloid appeared in the literature ended up with the elegant synthesis of (+)- and (-)-norsecurinine and was unveiled by the group of Jacobi in 1989.[44] The syntheses of the dextro- and the levorotatory antipodes were accomplished starting from D- and L-proline, respectively (Scheme 14). The main step of the strategy was a tandem cycloaddition/elimination process, making use of the oxazole Diels-Alder methodology developed by the authors, with the simultaneous formation of the alkaloid D-ring and the seven-membered cycle enclosing rings B and C. The amino acid precursor furnished ring A of the alkaloid and the stereogenic centre at C2. The crucial oxazole intermediate **77** was prepared in a highly convergent fashion. The D-proline derivative **72** was converted into the oxazole pyrrolidine **73** by cyclodehydration followed by deprotection through catalytic hydrogenation. Maleic anhydride, **74**, was treated with *N,O*-dimethylhydroxylamine, and the resulting *E*-amidoacid was reduced to the alcohol **75**. Silylation, followed by condensation with lithiotrimethylsilylacetylide furnished the protected enynone **76**. Conjugate addition of the oxazole pyrrolidine **73** to the enone provided the acetylenic oxazole intermediate **77**, which without purification was converted to the furanoketone **78** by thermolysis in mesitylene. The product consisted of an approximately 2:1 mixture of **78** and its C7 epimer, although the undesired isomer could be recycled by epimerisation with Na_2CO_3 in MeOH, *via* an elimination-conjugate addition sequence proceeding through an intermediate enone. Compound **78** was converted into the olefin **80** by initial reduction with $NaBH_4$ followed by elimination with Martin's reagent. Desilylation and subsequent hydrolysis afforded the butenolide **81** as a single isomer, which was transformed into the corresponding mesylate **82**. A final transanular alkylation furnished (-)-norsecurinine, isolated as its HCl salt. Repetition of an identical sequence of reactions, but beginning with L-proline, afforded (+)-norsecurinine. The overall yield for the eleven-step sequence from maleic anhydride, **74**, was around 2.5% and for the ten-step sequence from **72** around 7%.



Scheme 14

In 2000 the group of Weinreb published a general approach to the synthesis of the *Securinega* alkaloids, which was illustrated by completing the second total synthesis of (-)-norsecurinine, along with the syntheses of (+)-14,15-dihydronorsecurinine, and (-)-phyllantine.[45] The strategy of these authors consisted of using *trans*-4-hydroxy-L-proline as a source of the alkaloid B-ring and the C7 configuration, elaborating C-ring through intramolecular pinacol-type chemistry, and then successively building up rings A and D. The enantiomerically pure ester **83** was converted *via* the α,β-unsaturated nitrile **84** to the ketonitrile **85** (Scheme 15). Exposure of **85** to samarium iodide, followed by acidic hydrolysis, provided the bicyclic hydroxyketone **86**, which was then transformed into the protected ketal silyl ether derivative **87**. The *N*-tosyl group of **87** was removed to afford the free amine, which was acylated with isatoic anhydride to render the *o*-aminobenzamide **89**. This amide was converted into the mixture of α-substituted amides **90**, precursors of the iminium cation intermediate of the subsequent allylation step. Treatment of **90** with a large excess of allylmagnesium bromide in the presence of boron trifluoride etherate afforded the allylation product, as a

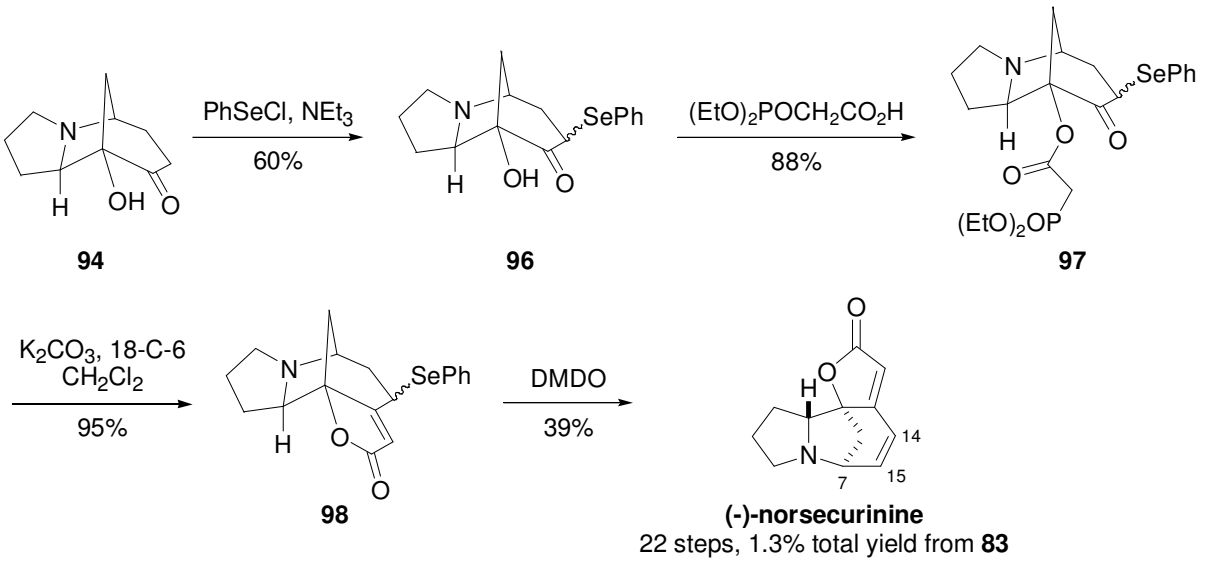
single diastereomer, and also led to removal of the benzoyl group. The amine was protected as the *N*-Boc derivative **91** that, after hydroboration of the olefin, was transformed to the tosylate **92**. Mild acidic treatment of **92** cleaved the Boc group and produced cyclisation to the tricycle **93**. The hydrolysis of the ketal and silyl ether protection required stronger acidic conditions and furnished the α-hydroxyketone **94**. After extensive experimentation, a convenient method was found to construct the butenolide ring D from **94**, by treatment with the phosphonium ylide **95** at 12 kbar. This reaction provided the alkaloid (+)-14,15-dihydronorsecurinine (virosine) in nineteen synthetic steps and 5.7% total yield from **83**.



Scheme 15

Since all attempts to directly oxidise the dihydro alkaloid to (-)-norsecurinine were ineffective, it was necessary to introduce the norsecurinine C-ring double bond at an earlier stage, a matter that turned out to be more difficult than expected. After multiple alternative trials, the sequence that completed the synthesis (Scheme 16) implied α-selenylation of ketone **94** with phenylselenyl chloride and triethylamine to deliver a

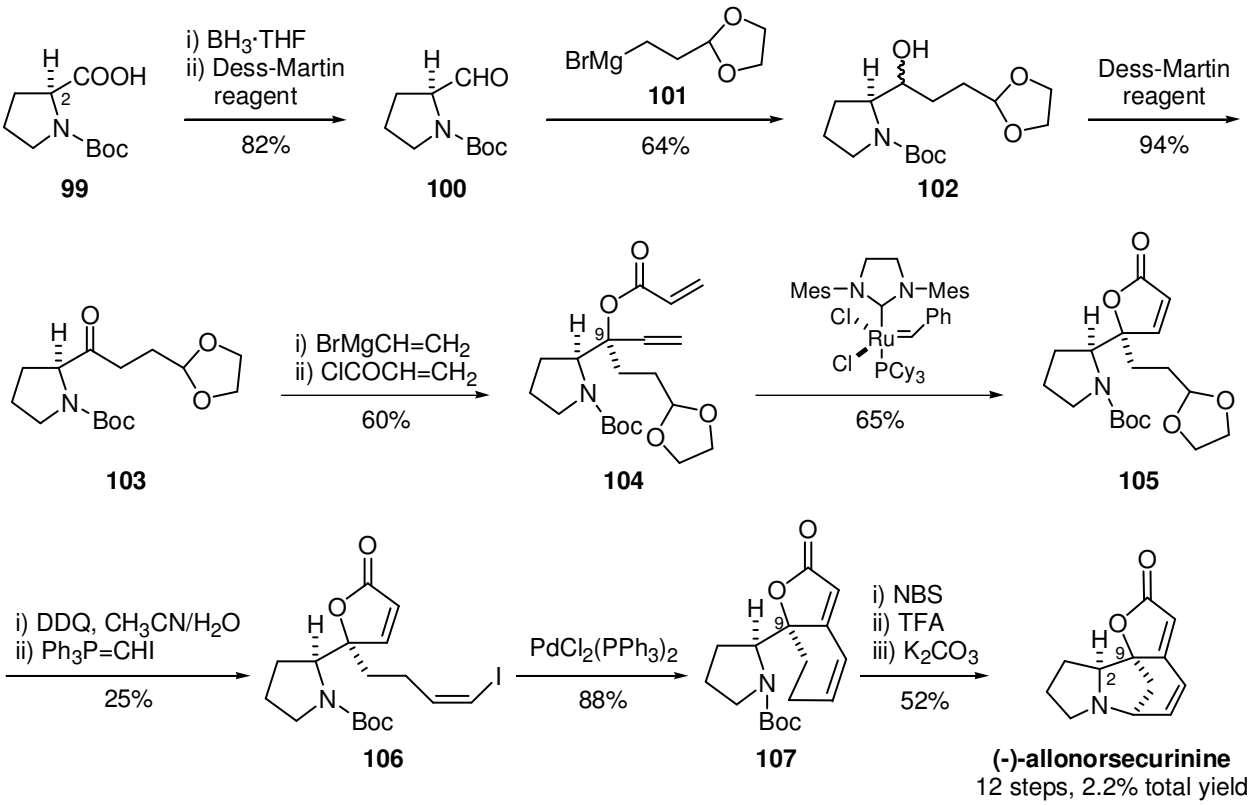
mixture of epimeric alcohols **96**, which were esterified with diethylphosphonoacetic acid to produce phosphonate **97**. An intramolecular Wadsworth-Horner-Emmons reaction of **97** afforded the butenolide **98**, completing the tetracyclic skeleton. The oxidation-elimination protocol required to generate the C14-C15 olefin could be performed in moderate yield only by treatment of **98** with dimethyldioxirane. The synthesis of (-)-norsecurinine was therefore achieved in twenty two steps from **83** and 1.3% total yield.



Scheme 16

We had been working in a project devoted to develop a general, efficient entry to both types of *Securinega* alkaloids. In 2004, a publication of Honda *et al.* reporting the first chiral synthesis of securinine,[46] which was closely related to one of our own approaches, prompted us to disclose part of our results in the field.[47] Both Honda's and our syntheses make use of a RCM as one of the crucial steps, to generate the alkaloid D-ring, while a chiral pool amino acid derivative provides ring A and the stereogenic centre C2. As part of this work, we accomplished the total synthesis of a previously unknown alkaloid, epimer of (-)-norsecurinine at C2, that we named (-)-allonorsecurinine, by analogy to allosecurinine (Scheme 17). As in Heathcock synthesis of racemic norsecurinine, we started with an L-proline derivative. Reduction of the *N*-Boc proline, **99**, followed by Dess-Martin oxidation provided the commercially available aldehyde **100**. Its reaction with the Grignard reagent **101** furnished a mixture of diasteromeric alcohols **102**, which was submitted without separation to Dess-Martin oxidation yielding ketone **103**. The required olefin moieties for the RCM reaction were incorporated by sequential treatment of **103** with vinylmagnesium bromide and acryloyl chloride in a one-pot procedure. This reaction afforded a 6:1 mixture of diastereomeric acrylates. The major isomer **104** was isolated and converted into the butenolide **105**, in the presence of a catalytic amount of the Grubbs reagent. The hydrolysis of the dioxolane system was attempted under a variety of conditions, but it could only be realised by treatment with dichlorodicyanoquinone. Then, the resulting aldehyde was transformed into the *Z*-iodoolefin **106**. Closing of ring C was accomplished by reaction with dichlorobis(triphenylphosphine)palladium(II) in the presence of sodium carbonate. NOESY experiments performed with compound **107** unveil its *S* configuration at C9, opposite to that of (-)-norsecurinine. Allylic bromination of **107**, removal of the carbamate group, and treatment of the resulting

crude material with potassium carbonate afforded (-)-allonorsecurinine {[α] -441 (EtOH)}. Like norsecurinine, allonorsecurinine and most intermediates involved in the sequence are relatively unstable compounds. The sequence consisted of twelve steps with 2.2% overall yield.



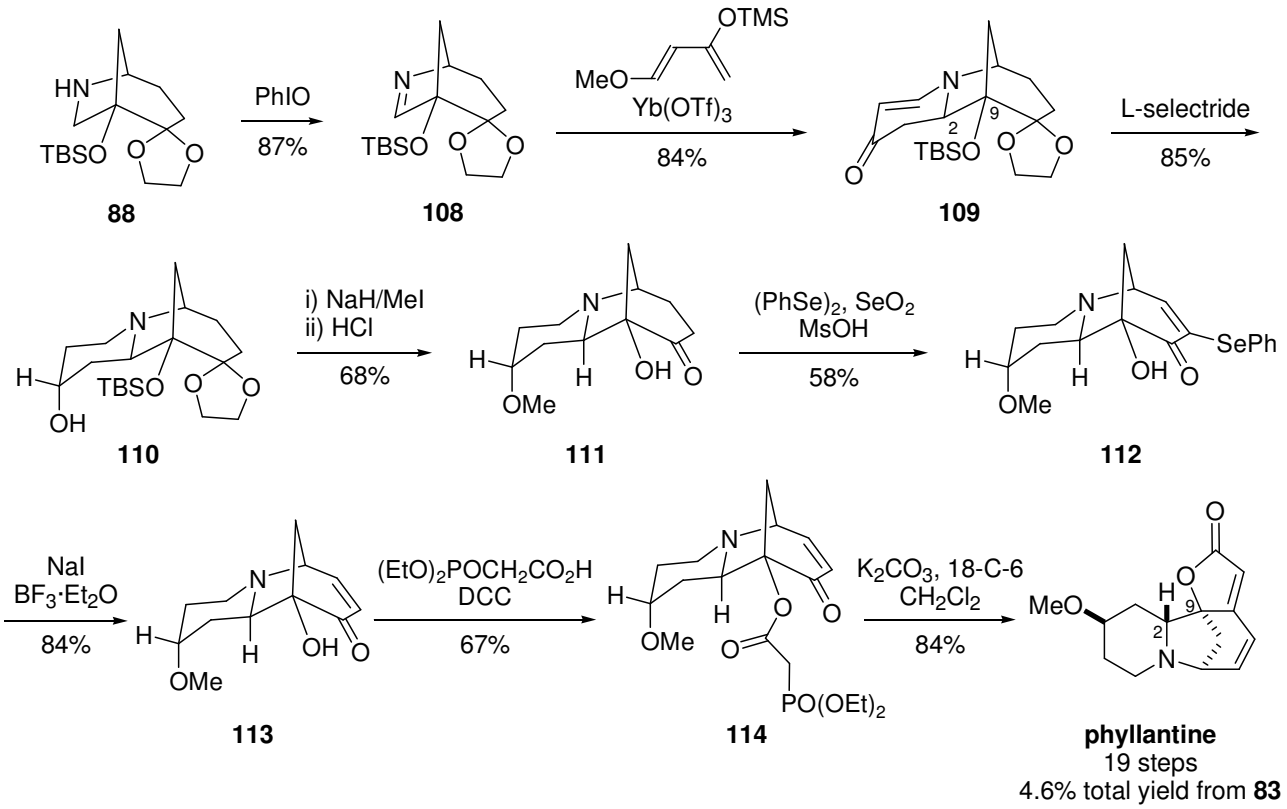
Scheme 17

2.3.2. Phyllantine, securinine and viroallosecurinine

Among the securinine subgroup, phyllantine was the first alkaloid synthesised in non-racemic form. Its preparation was accomplished as part of the work developed by the group of Weinreb[45] (Scheme 18). Amine **88**, an intermediate in the synthesis of (-)-norsecurinine, was oxidised with iodosobenzene to imine **108**. The alkaloid A-ring was constructed by cycloaddition of **108** to Danishefsky's diene in the presence of ytterbium triflate. This reaction afforded the tricyclic amine **109**, with the correct C2 configuration of phyllantine. Reduction of **109** with L-selectride furnished stereoselectively the axial alcohol **110**. *O*-Methylation of alcohol **110** gave the corresponding methyl ether, which upon acid hydrolysis led to the tricyclic α-hydroxyketone **111**. As in the norsecurinine synthesis, the formation of the butenolide ring D was quite problematic. The α-phenylselenoenone **112** was unexpectedly obtained when ketone **111** was treated with diphenyldiselenide, selenium dioxide, and methanesulphonic acid. Selenoenone **112** could be converted to the stable tricyclic enone **113** using sodium iodide in the presence of boron trifluoride etherate. Annulation of the D-ring was finally accomplished through Wadsworth-Horner-Emmons methodology. The synthesis of phyllantine was in this way completed in nineteen steps from hydroxyprolinate **83** and 4.6% total yield.

In 2003, Wanner *et al.* described the asymmetric preparation of two compounds with the tricyclic A-B-D core and C2-C9 configuration of virosecurinine and allosecurinine (Scheme 19).[52] Enantiopure (*S*)-2-

anisylpiperidine, **119**, was used as the pivotal precursor. This compound provided the alkaloid A-ring and the C2 sterocentre, while rings B and D were sequentially formed.

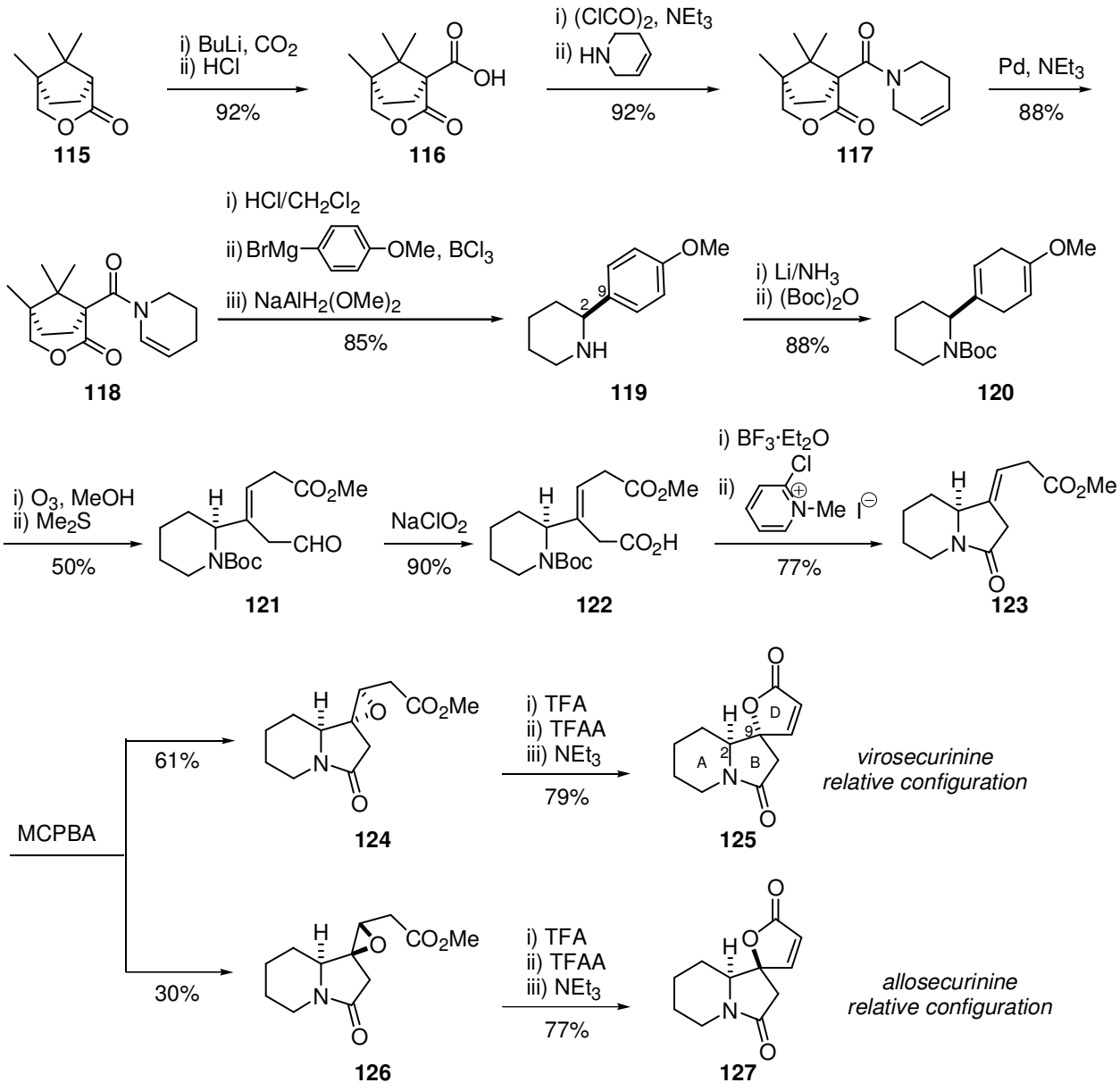


Scheme 18

Piperidine **119** was obtained by an asymmetric electrophilic α-amidoalkylation reaction employing the chiral enamide **118**, which in turn was prepared in four steps from lactone **115**, derived from camphoric acid. Next, compound **119** was subjected to a Birch reduction, providing a cyclohexadienylpiperidine, which was protected with a Boc group to furnish carbamate **120**. Ozonolysis of **120** delivered the aldehyde **121**. To convert **121** to the bicyclic lactam **123**, the aldehyde was subjected to an oxidation reaction with sodium chlorite, in the presence of 2-methyl-2-butene as chlorine-scavenger, that provided the carboxylic acid **122**. Deprotection with boron trifluoride etherate led to the γ-amino acid, which was treated without further purification with Mukaiyama's reagent to promote cyclisation, affording lactam **123**. The bicyclic lactam was subjected to an epoxidation reaction with *m*-chloroperbenzoic acid, which resulted in the formation of the two oxiranes **124** and **126**. The epimers were separated and each one converted to the corresponding tricyclic lactone **125** or **127**, using standard methodology.

The first diastereoselective synthesis of enantiopure securinine was published in 2004 by the group of Honda (Scheme 20).[46] (+)-Pipecolinic acid, **128**, was used as starting material, providing securinine A-ring and the C2 stereocentre. The key step of the sequence was a tandem RCM of a dienyne system with simultaneous formation of rings C and D. The enantiopure thioester **130** was prepared from pipecolinic acid and then treated with (*Z*)-3-hexenylmagnesium bromide to give ketone **131**. The reaction of **131** with trimethylsilylacetylide and cerium(III) chloride furnished the tertiary alcohol **132**, as the sole product. The observed steric course of the process was rationalised by assuming that the addition of the lithium reagent to

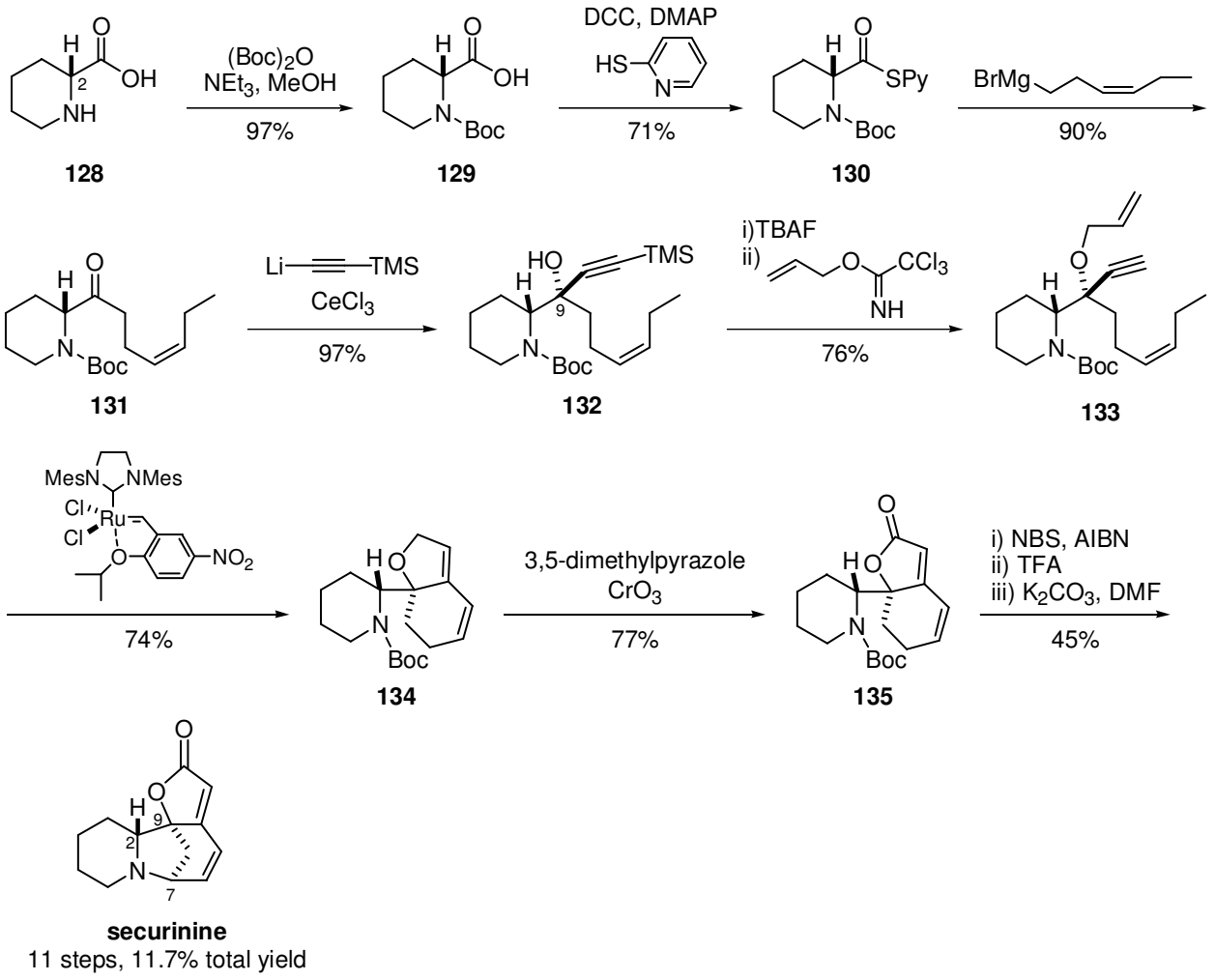
132 proceeded *via* the Felkin-Ahn model. Desilylation of **132** and treatment with allyl trichloroacetimidate gave allyl ether **133**, which upon RCM conditions produced the tricyclic diene **134**. To accomplish the total synthesis of securinine, diene **134** was oxidised at the allylic position with chromium trioxide and 3,4-dimethylpyrazole to provide lactone **135**. The final steps involved allylic bromination, followed by removal of the *N*-protecting group, and subsequent cyclisation of the resulting amino bromide induced by potassium carbonate. This first synthesis of (-)-securinine was completed in eleven steps and 11.7% overall yield.



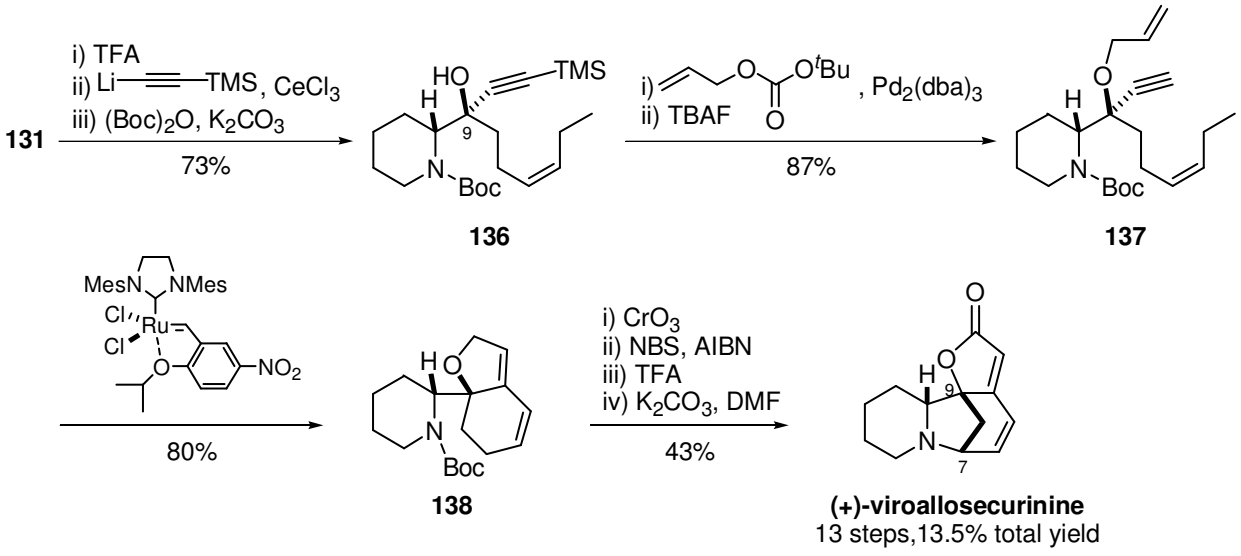
Scheme 19

As part of the same work, the alkaloid viroallosecurinine was also synthesised (Scheme 21).[46,48] Since securinine and viroallosecurinine have opposite configurations at C7 and C9, the synthesis of viroallosecurnine required the introduction of the alkyne moiety to ketone **131** with the opposite stereoselectivity to the securinine sequence. The requisite stereoselectivity was achieved by employing the

free amine instead of the carbamate, likely favouring a chelation transition state for the addition of the lithium reagent.



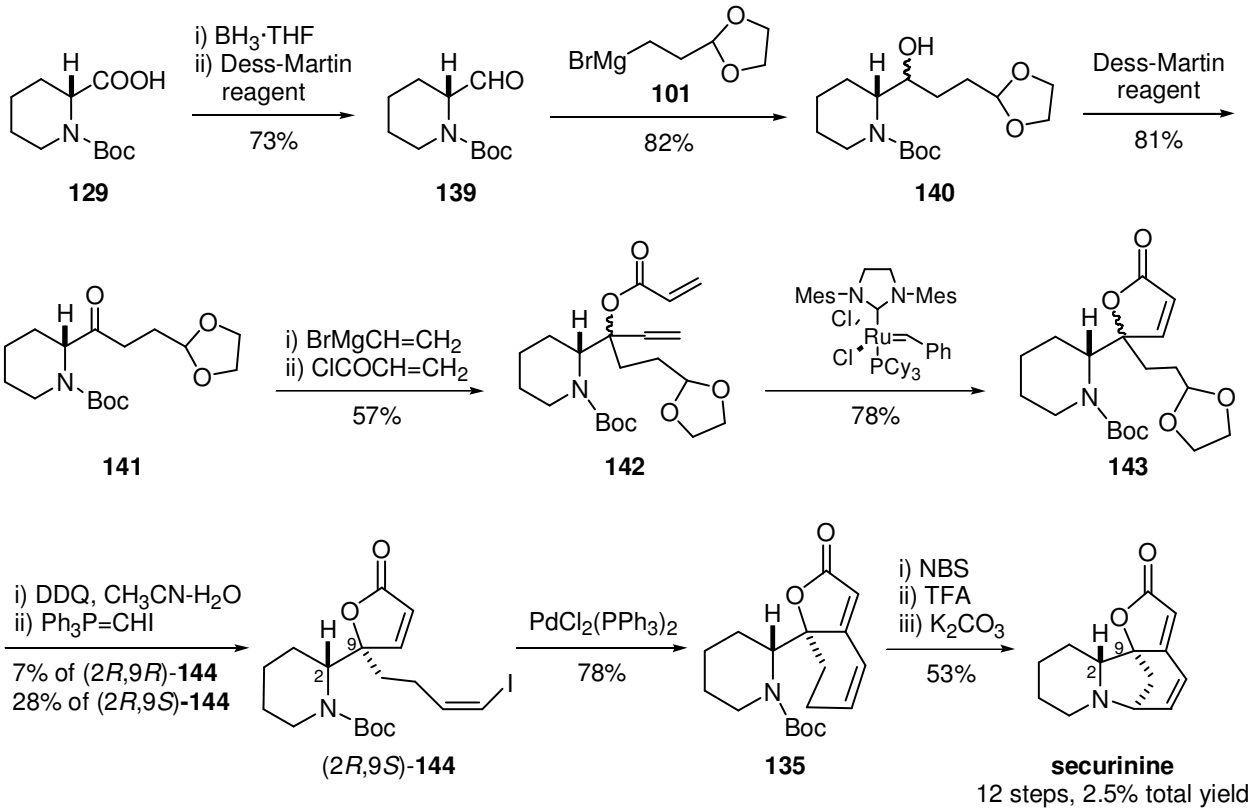
Scheme 20



Scheme 21

Thus, the carbamate **131** was deprotected and the resulting amino ketone treated with the lithium acetylide to furnish mainly the expected tertiary alcohol, which was converted to its *N*-Boc derivative **136**. In this case, the *O*-allylation was more conveniently performed by reaction of **136** with allyl *tert*-butyl carbonate and triphenylposphine in the presence of a palladium catalyst. After removal of the trimethylsilyl group, the resulting dienyne **137** was subjected to the tandem RCM process to give the tricyclic derivative **138**. Its conversion to viroallosecurinine was performed in identical fashion as for the transformation of **134** to securinine. The synthesis of viroallosecurinine from (+)-pipecolinic acid comprised thirteen steps with 13.5% total yield.

As it was already indicated, Honda's syntheses of securinine and viroallosecurinine were closely related to one of our approaches to *Securinega* alkaloids. For our chiral pool synthesis of securinine[47] (Scheme 22), we started from the known aldehyde **139**. Its reaction with the Grignard reagent **101** provided a mixture of diastereomeric alcohols **140**, which was oxidised to ketone **141**.



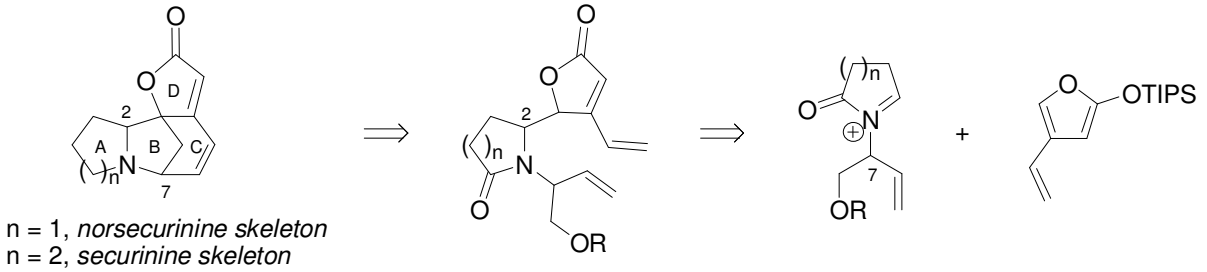
Scheme 22

Sequential treatment of this ketone with vinylmagnesium bromide and acryloyl chloride afforded an inseparable mixture of diastereomeric acrylates **142** in a 6:1 ratio. When subjected to the RCM reaction, **142** provided the mixture of butenolides **143**. Treatment with dichlorodicyanoquinone followed by Wittig reaction gave rise to a mixture of (*Z*)-iodoolefins **144**, from which each stereoisomer could be separated. When the major isomer was subjected to the Heck reaction, the tricyclic compound **135** was isolated. The relative configuration of **135** indicates that the addition of the Grignard reagent occurred mainly at the *re* face of the piperidinyl ketone **141**, in strong contrast with the facial selectivity observed in the analogous addition to the pyrrolidinyl ketone **103** (Scheme 17). The stereochemical outcome of the addition is consistent with

the Felkin-Ahn model for **141**, where the attack to the *si* face is clearly hindered by the protecting carbamate group. Conversely, for ketone **103** the attack to the *si* face is less sterically demanding. The last steps were accomplished performing essentially the same protocol used by Honda *et al.* The total synthesis of the target alkaloid was accomplished in twelve steps and 2.5% total yield.

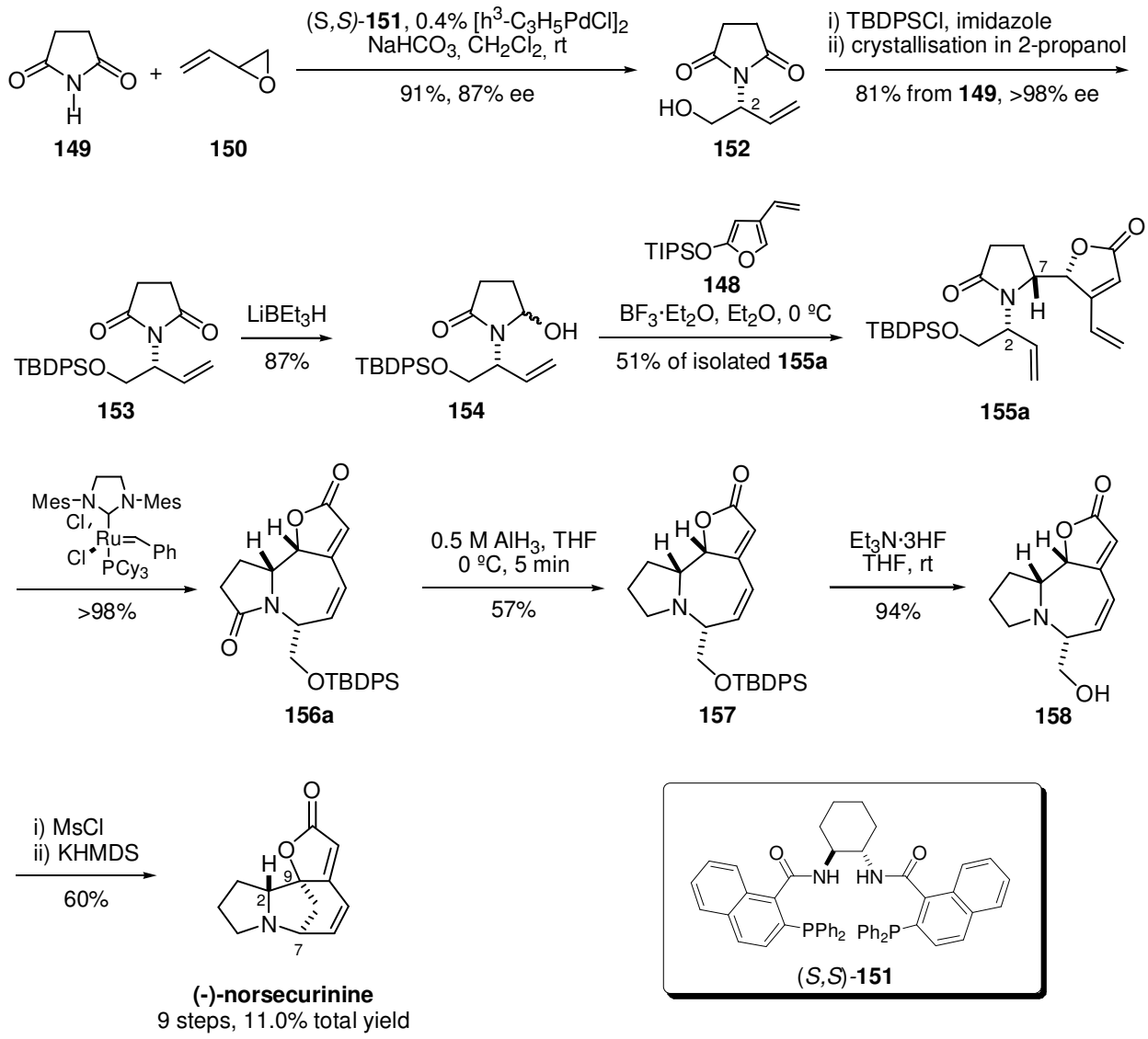
2.4. The enantioselective approach. (-)-Norsecurinine

Simultaneously to these investigations, we were also trying to develop an enantioselective approach to the *Securinega* alkaloids.[49] Scheme 23 shows our retrosynthetic analysis, where key steps are a vinylogous Mannich reaction between an iminum cation **147** and silyloxyfuran **148**, which would, respectively, provide rings A and D of the alkaloid, and a RCM reaction, which would furnish the seven membered cycle embracing rings B and C. The stereogenic centre of **147** should afford the configuration at C7 in the alkaloid, while the diastereoselectivity of its addition to **148** would determine the relative configuration at C2. Therefore, we needed to prepare a suitable precursor of **147** in enantiopure form.



Scheme 23

Trost *et al.* had described the conversion of racemic butadiene monoepoxide, **150**, into a single enantiomeric product through a palladium-catalysed asymmetric allylic alkylation of phthalimide in the presence of some chiral phosphine ligands.[53] The reaction between succinimide, **149**, and epoxide **150** under similar conditions (Scheme 24) furnished the alkylated product **152** in 91% yield and 87% ee. We tentatively assigned the *R* configuration to the major enantiomer, by analogy to the phthalimide analogue obtained in the presence of the same ligand. Alcohol **152** was converted into the corresponding *tert*-butyldiphenylsilyl ether **153**, which upon crystallisation in 2-propanol afforded a highly enantiomerically enriched material (>98% ee) in 81% yield from succinimide. Reduction of **153** with lithium triethylborohydride delivered a mixture of the epimeric aminals **154**. Triisopropylsilyloxyfuran **148** was prepared in 97% yield from 4-vinyl-2(5*H*)-furanone.[54] The vinylogous Mannich reaction[55] was accomplished by treatment of **154** with 1.2 equivalents of **148** in ether at 0 ºC, in the presence of $BF_3{\cdot}Et_2O$, furnishing a mixture of diastereomeric products **155a-d** (Figure 5). The relative configuration of **155a-d** was established by performing a RCM experiment with the crude reaction material containing the mixture of all the isomers. The dienes **156a-d** were separated and their configuration was determined with the help of nOe experiments. The major diastereomer **156a** presented the same relative configuration at C2 and C7 as norsecurinine. All attempts to separate the isomers of the vinylogous Mannich adducts **155** by chromatography led to complex mixtures of decomposition products, but, on standing at room temperature overnight, the major isomer **155a** crystallised and could be separated from the mixture by filtration in 51% yield. When the RCM reaction was applied to the crystallised isomer **155a**, the expected diene **156a** was isolated in nearly quantitative yield.



Scheme 24

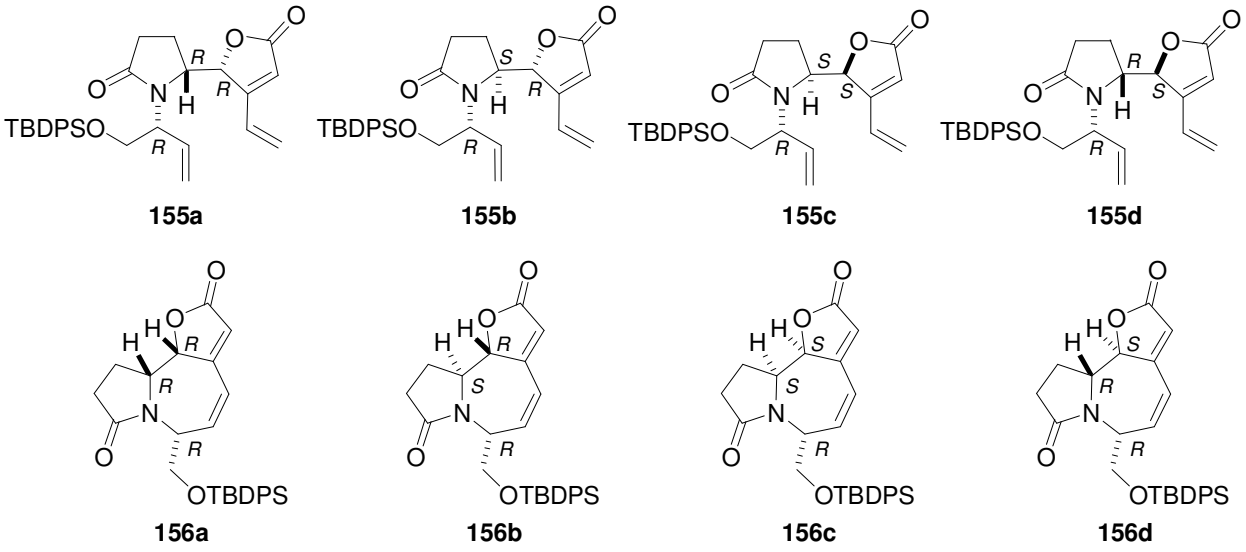
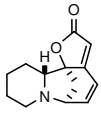
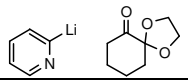
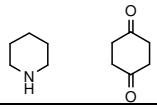
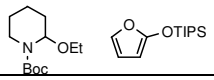
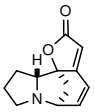
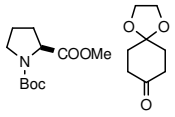
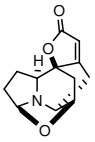
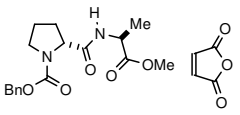
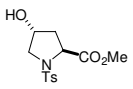
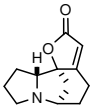
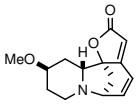
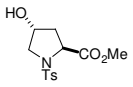
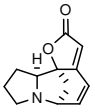
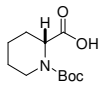
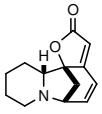


Figure 5

Table 1. Summary of the published syntheses of *Securinega* alkaloids

Alkaloid	Ref.	Year	Starting Materials	Linear/Convergent (Steps)	Yield
Racemic Syntheses					
 **(±)-securinine**	38	1967		Linear (13)	0.024%
	40	1992		Linear (11)	0.01%
	42	2000		Linear (12)	4.1%
	41	2001		Linear (9)	8.8%
 **(±)-norsecurinine**	39	1987	 **45** **24**	Convergent (11 from **45**) (13 from **24**)	~1% ~1%
	35, 43	1992		Linear (13)	7.5%
 **(±)-nirurine**	35, 43	1992		Linear (16)	not given
Chiral Pool Syntheses					
(+)-norsecurinine and (-)-norsecurinine	44	1989	 **72** (or enantiomer) **74**	Convergent (10 from **72**) (11 from **74**)	7.0% 2.5%
(-)-norsecurinine	45	2000		Linear (22)	1.3%
 **(+)-14,15-dihydronorsecurinine**	45	2000		Linear (19)	5.7%
 **phyllanthine**	45	2000		Linear (19)	4.6%
 **(-)-allonorsecurinine**	47	2004		Linear (12)	2.2%
securinine	46	2004		Linear (11)	11.7%
	47	2004		Linear (12)	2.5%
 **viroallosecurinine**	46	2004		Linear (13)	13.5%
Enantioselective Synthesis					
(-)-norsecurinine	49	2005		Linear (9)	11.0%

The two transformations required to conclude the synthesis of (-)-norsecurinine were reducing the lactam to amine and connecting the stereogenic centres C7 and C9 through the one-carbon bridge to complete the tetracyclic skeleton. The reduction of lactam **156a** was more difficult than expected. Its conversion to the corresponding thiolactam, followed by treatment with Raney nickel or other reducing agents, ended up with decomposition products, but direct reduction with freshly prepared aluminum hydride[56] allowed the isolation of **157** in fairly good yield. The free alcohol **158** was obtained by reaction of **157** with an excess of $Et_3N{\cdot}3HF$ in THF. Alcohol **158** was the penultimate intermediate in the Jacobi's synthesis of (-)-norsecurinine,[44] but an optical rotation value was not given. Therefore, to assess the absolute configuration of our synthetic material we completed the synthesis of the alkaloid according to Jacobi's protocol. The yields were satisfactorily reproduced and we obtained the levorotatory enantiomer of norsecurinine. In this way, we completed the enantioselective synthesis of (-)-norsecurinine in nine steps and 11% total yield. The three crucial steps of this synthesis (enantioselective allylic alkylation of succinimide, vinylogous Mannich reaction, and RCM) were performed in a synthetically useful scale (more than 500 mg). Since the enantioselectivity was originated by the phosphine ligand (*S*,*S*)-**151**, the antipode of which is equally available, the same route gives access to (+)-norsecurinine.

3. Conclusion

A summary of the total and formal syntheses discussed above is presented in Table 1. Considering that some of these alkaloids have been known for more than forty years and in view of their attractive potential as pharmacological agents, the number of successful approaches is obviously very scarce and, in most cases, the synthetic sequences are developed in too small scale to provide enough material for biological assays. One of the main difficulties associated to the synthesis of these alkaloids is likely their low stability, particularly within the norsecurinine subgroup. This lack of stability is often extensive to some of their putative synthetic precursors, making the *Securinega* alkaloids very elusive targets. Although securinine can be obtained from natural sources in a substantial amount, the other members of the family are not so available. Some of the previous syntheses are elegant academic illustrations of novel synthetic strategies. We hope that our enantioselective approach will contribute to the progress of the field, where is still a long way to run.

Acknowledgments

The investigations of our group included in this chapter are based on the doctoral dissertations of Laia Elias, Marta Ballbé, Elena García-García and David González-Gálvez. Prof. Josep Font, Prof. Pedro de March, and Dr. Ramón Alibés collaborated in the development of this research. We acknowledge financial support from DGES (BQU2001-2600) and CIRIT (2001SGR00178). Grants from *Generalitat de Catalunya* to Elena García-García (DGR) and Pau Bayón (AUR) and from *Ministerio de Educación y Ciencia* to Marta Ballbé, David González-Gálvez, and Félix Busqué (*Programa Ramón y Cajal*) are gratefully thanked.

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ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED 1(3*H*)-ISOBENZOFURANONE DERIVATIVES

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Abstract. *This account described the enantioselective synthesis of chiral 3-substituted 1(3H)-isobenzofuranones and 3,3-disubstituted 1-isobenzofuranones using either a chiral protecting group or a chiral reagent.*

Contents

1. Introduction

Natural products have been and continue to be a leading source of molecules for drug discovery. Different important classes of natural products known for their various biological activities involve a benzoannelated butyrolactone (1(3*H*)-isobenzofuranone, phthalides) as a synthon. Of particular importance, in a wide range of medicinal properties, has been the discovery of 3-substituted phthalide derivatives (Figure 1) such as 3-butylphthalide (**1**),[1] Isopestacin (**2**),[2] Fuscinarin (**3**),[3] Spirolaxine (**4**),[4] Cytosporone E (**5**),[5] Monascodilone (**6**),[6] isoochracinic acid (**7**),[7] Herbaric acid (**8**),[8] (-)-Alcyopterosin (**9**),[9] Cryphonectric acid (**10**),[10] Rubiginone H (**11**),[11] (-)-Hydrastine (**12**),[12] Vermistatin (**13**)[13] and (-)-Typhaphthalide (**14**).[14]

Diverse enantioselective approaches have been successful in providing these types of chiral 3-substituted phthalides. For the sake of clarity, the following account has been arranged to describe the major chemical syntheses with examples being chosen from work published over the last 30 years.

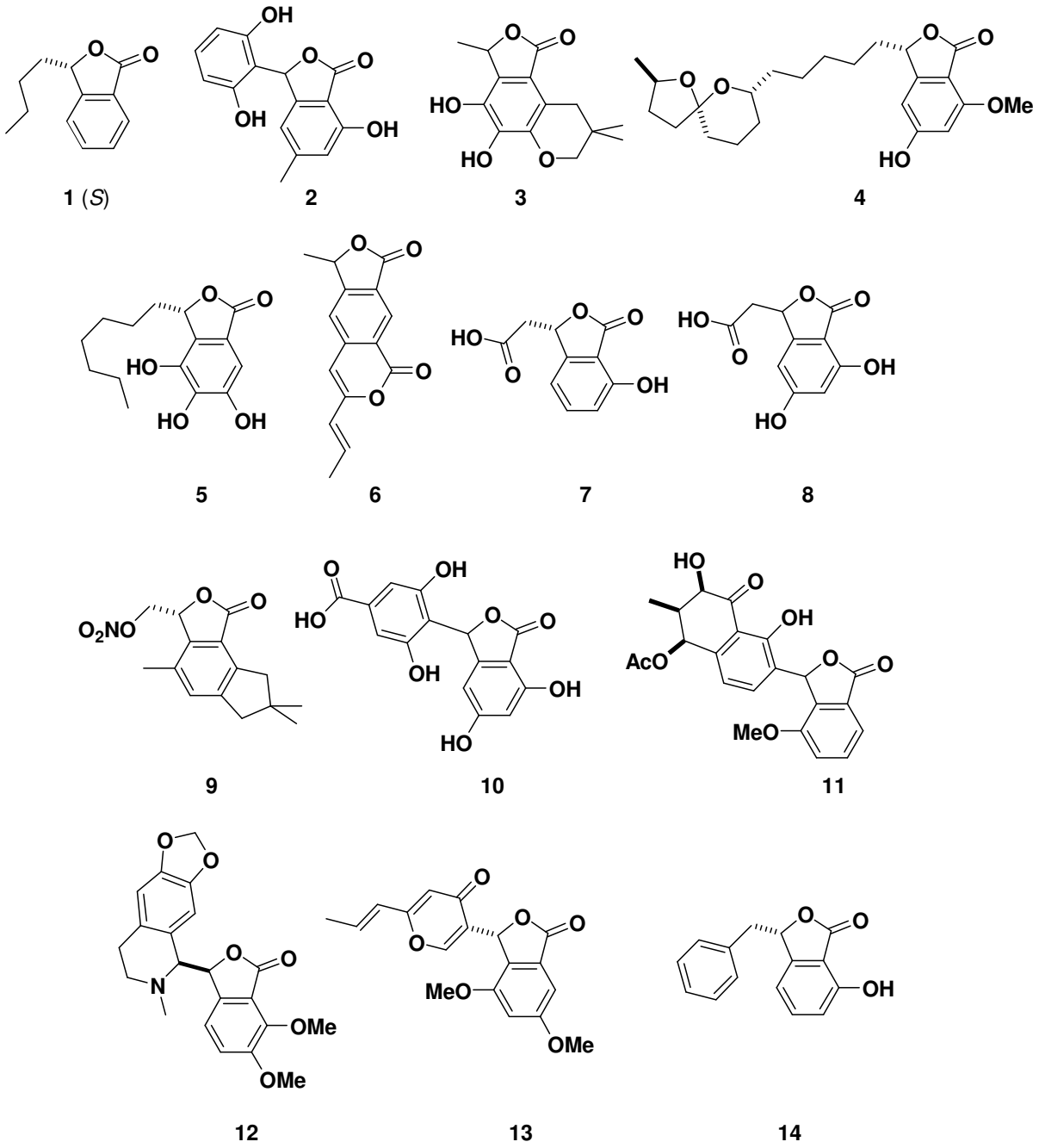
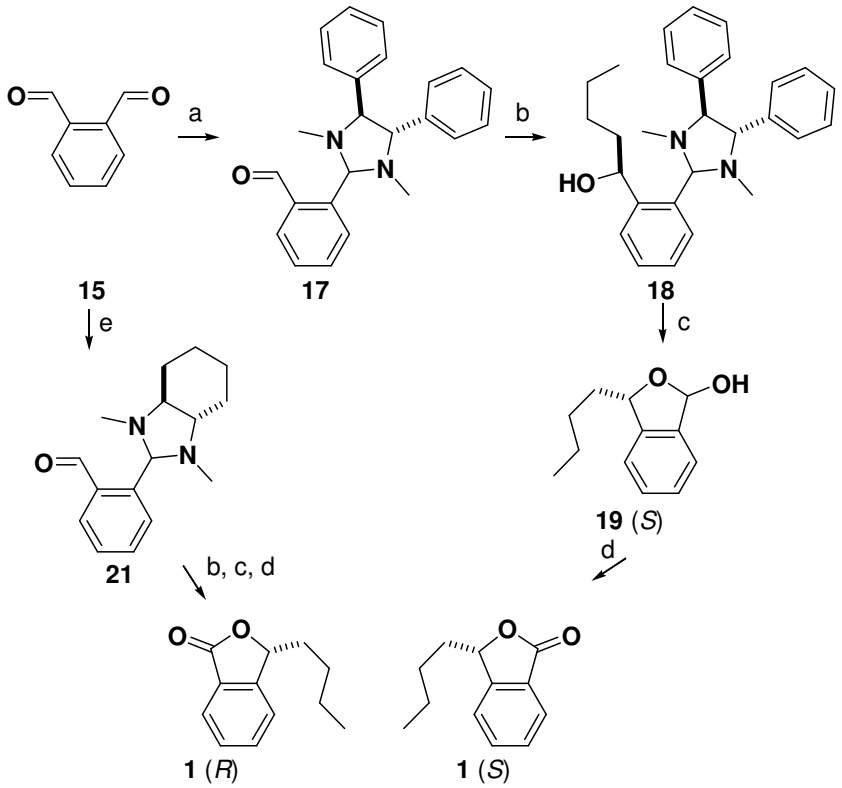


Figure 1

2. Enantioselective synthesis of 3-substituted 1(*3H*)-isobenzofuranones using a chiral protecting group

2.1. Organometallic attack on an aldehyde bearing a chiral protecting group

Alexakis *et al.* reported a selective route to the 3-substituted phthalides *via* organometallic attack on an aldehyde bearing a chiral imidazolidine group.[15] Starting from *o*-phthalic dialdehyde (**15**), treatment with chiral 1,2-bis-*N*-methylamino-1,2-diphenyl ethane (**16**) in the presence of molecular sieves 4 Å in diethyl ether afforded the aldehyde **17** having a chiral 1,2-diamine with a C_2 axis of symmetry. The aldehyde **17** was reacted with lithium dibutyl cuprate to give the corresponding alcohol **18** (de 100%). Hydrolysis of the aldehyde protection on compound **18** gave the corresponding lactol **19** (*S*) after simultaneous cyclisation. The lactol **19** (*S*) was subsequently oxidized using Ag_2O to the (*S*)-lactone **1** (*S*) (Scheme 1).



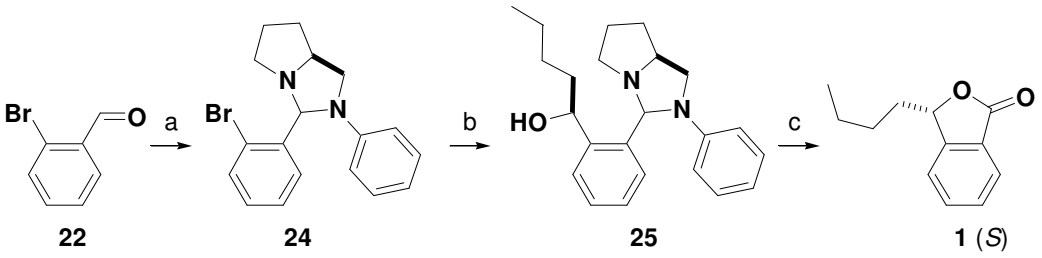
(a) **16**, Et_2O, molecular sieves 4Å; (b) Bu_2CuLi, Et_2O; (c) H_3O^+; (d) Ag_2O, MeOH, H_2O; (e) **20**, Et_2O, molecular sieves 4Å.

Scheme 1

It is notable that the use of butylmanganese bromide instead lithium dibutyl cuprate (Scheme 1) gave the opposite enantiomer almost exclusively (ee 99%). Application of this strategy using chiral 1,2-bis-*N*-methylamino cyclohexane (**20**) as protecting group in presence of lithium dibutyl cuprate furnished the corresponding (*R*)-lactone **1** (*R*) (ee 90%) *via* intermediate **21** (Scheme 1).

2.2. Chiral aryllithium attack on an aldehyde and ketone

Asami and Mukaiyama reported a selective route to the 3-substituted phthalides *via* chiral aryllithium attack on an aldehyde.[16] Starting from 2-bromobenzaldehyde (**22**), treatment with (*S*)-2-(anilinomethyl)pyrrolidine (**23**) in refluxing benzene afforded the aminal **24** (Scheme 2). Classical metal exchange by treatment with n-butyllithium in hexane and subsequent reaction with pentanal gave the corresponding alcohol **25** (ee 87%) having the *S* configuration. Application of the procedure described above enabled the target corresponding lactone **1** (*S*) to be obtained.



(a) **23**, C_6H_6; (b) 1. *n*-BuLi, Et_2O; 2. C_4H_9CHO; (c) 1. HCl 2%, Et_2O; 2. Ag_2O, MeOH, H_2O.

Scheme 2

The authors proposed a mechanism for the reaction where the key step involved an intramolecular coordination of the chiral aminal function to the lithium metal. Thus, starting from the rigid tricyclic five membered ring structure, the approach of the aldehyde would be from the less hindered front side (Figure 2).

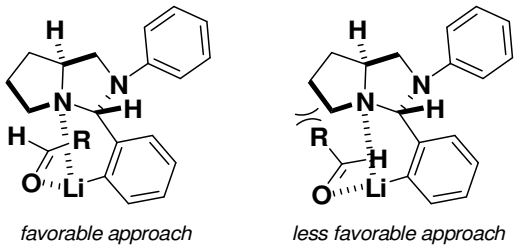
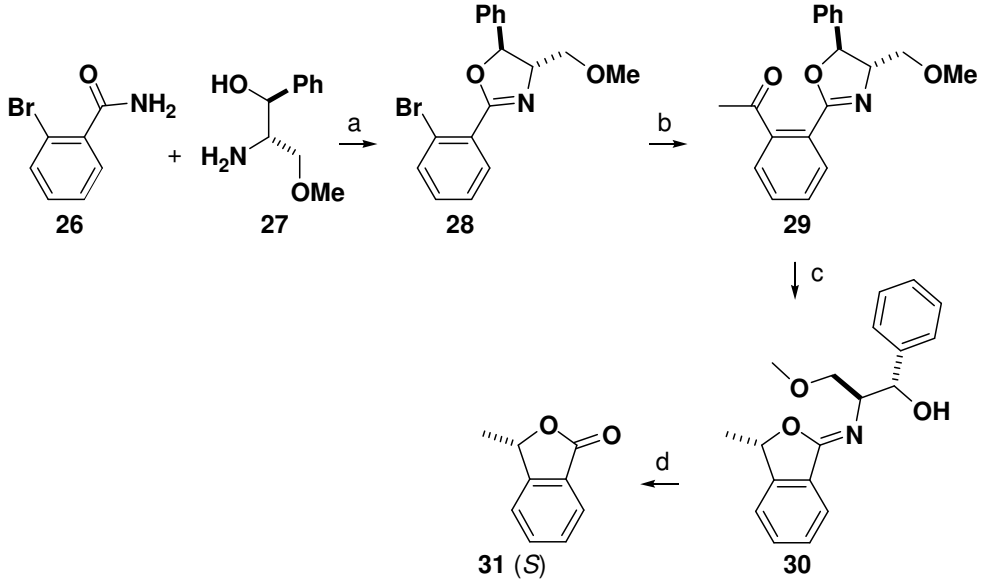


Figure 2

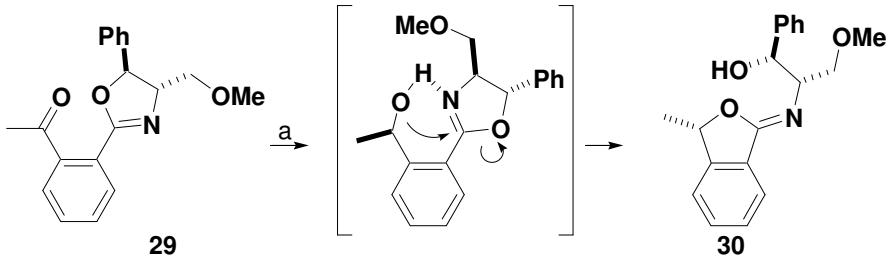
Application of the method developed by Asami and Mukaiyama[16] was reported by Meyers et *al.*.[17] Starting from *o*-bromobenzamide (**26**), Meerwein methodology[18] followed by treatment with chiral (1*S*,2*S*)-2-amino-3-methoxy-1-phenylpropan-1-ol (**27**) gave the optically pure bromophenyloxazoline **28** in 82% yield (Scheme 3). Halogen metal exchange was performed with *n*-butyllithium followed by addition of various electrophiles (de 0-32%). Due to the lack of stereoselectivity with the chiral aromatic derivative **28**, Meyers *et al.* described the synthesis of 3-substituted 1(*3H*)-isobenzofuranone by hydride reduction of *o*-acyl aryoxazolines.[17] Starting from compound **28**, treatment with *n*-butyllithium in THF followed by addition of acetic anhydride as an electrophile led to the corresponding ketone **29** in 50% yield. Treatment of **29** with tri-*sec*-butyl borohydride (L-Selectride) in THF provided the *S* epimer **30** (de 44%). Subsequent hydrolysis with saturated aqueous oxalic acid in THF furnished the phthalide **31** (*S*) with an ee comparable to the diastereomeric ratio.



(a) Et_3OBF_4, $C_2H_4Cl_2$; (b) *n*-BuLi, THF then Ac_2O; (c) L-Selectride, THF; (d) oxalic acid, THF.

Scheme 3

The rearrangement seen in the conversion of **29** to **30** *via* the corresponding alcohol is likely to be due to a facile tautomerism as in the mechanism depicted in Scheme 4.



(a) L-Selectride, THF.

Scheme 4

The predominance of the *S*-enantiomer **30** was consistent with the approach of the reducing agent wherein the hydride was delivered from the *re* face of the carbonyl group. The authors proposed that topside entry was probably precluded by the presence of the phenyl group which inhibits approach of the Grignard reagent (Figure 3).[17]

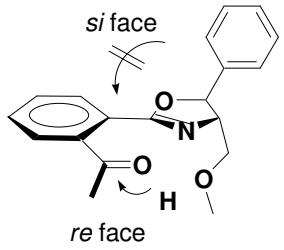


Figure 3

This strategy proved successful for the preparation of compounds **32** (*S*) (ee 70%) and **33** (*S*) (ee 48%) (Figure 4).

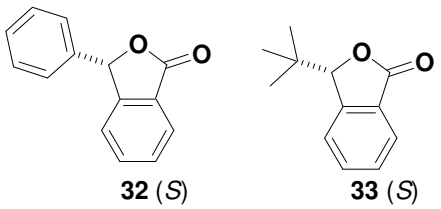
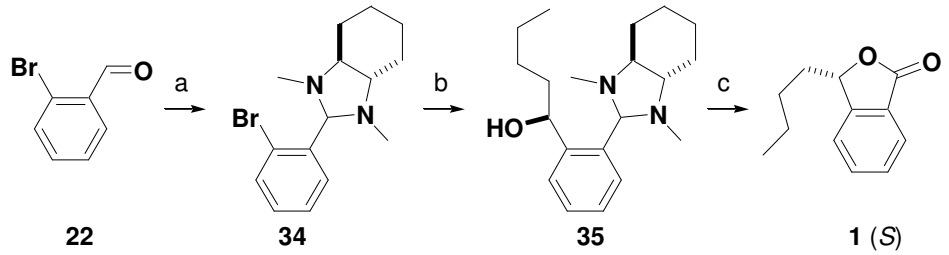


Figure 4



(a) **20**, Et_2O, molecular sieves 4Å; (b) *n*-BuLi, THF then C_4H_9CHO, LiBr; (c) H_3O^+; (d) Ag_2O, MeOH, H_2O.

Scheme 5

Alexakis *et al.* reported a selective route to the 3-substituted phthalides using another chiral protected group.[19] Successive selective protection of the aromatic compound **22** with the chiral diamine **20** and

halogen metal exchange using *n*-butyllithium followed by addition of pentanal with an excess of lithium salt furnished the corresponding alcohol **35** in 80% yield having the *S* carbon atom with an absolute configuration. Classical treatment of **35** gave the corresponding (*S*)-lactone **1** (*S*) (Scheme 5).

The authors explained that an intramolecular coordination of the lithium atom by one of the nitrogen atoms of the aminal could explain the selectivity. Due to steric interaction the metallic derivative added, on to the *si* face of the aldehyde rather than on to the *re* face affording the *S* configuration (Figure 5).

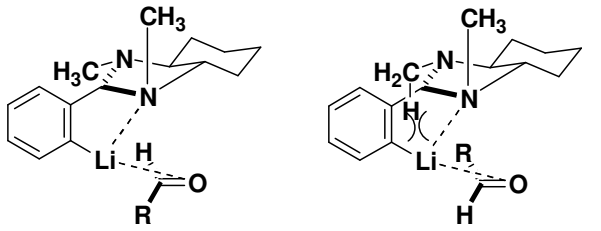
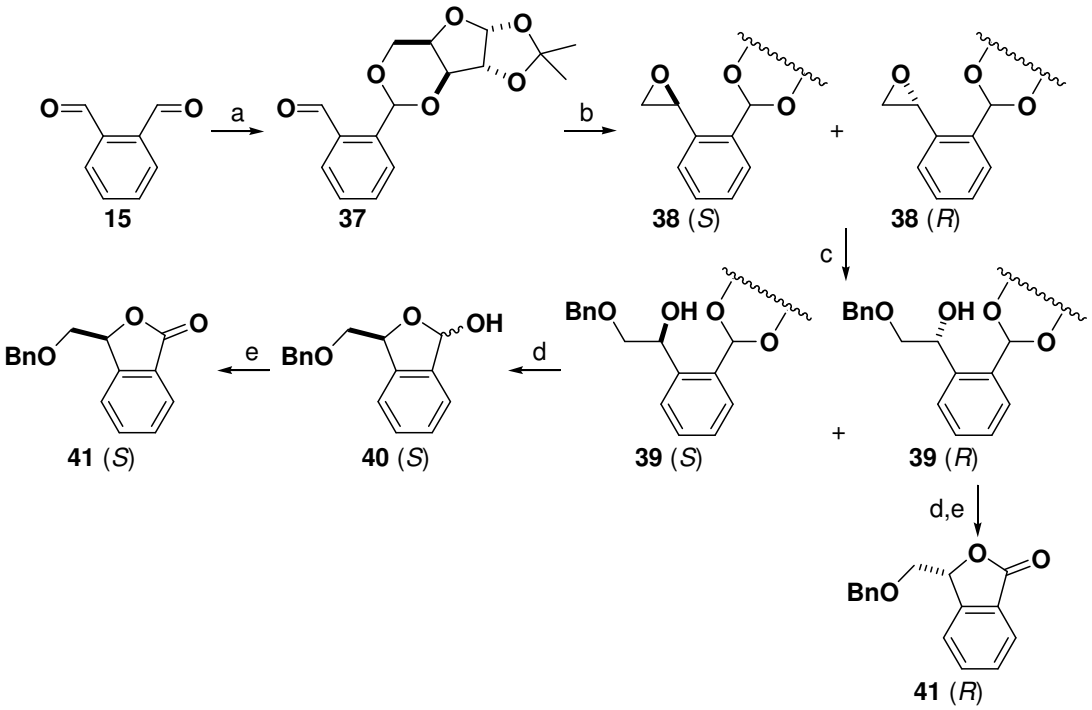


Figure 5

Application of this strategy using different homochiral protecting groups such as (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol, (1*S*,2*S*)-1,2-diphenylmethoxy-1,2-ethanediol, 1,2-bis-*N*-methylamino-1,2-diphenylethane failed to improve the selectivity and the yield.

2.3. Corey and Wittig homologations of an aldehyde bearing a chiral protecting group

A selective route to the 3-hydroxymethyl phthalide derivatives was effected by Len *et al.*.[20] Selective protection of dialdehyde **15** with 1,2-*O*-isopropylidene-α-D-xylofuranose (**36**) in presence of PTSA in THF formed the benzylidene derivative **37** (de 100%) in 50% yield (Scheme 6).[21]

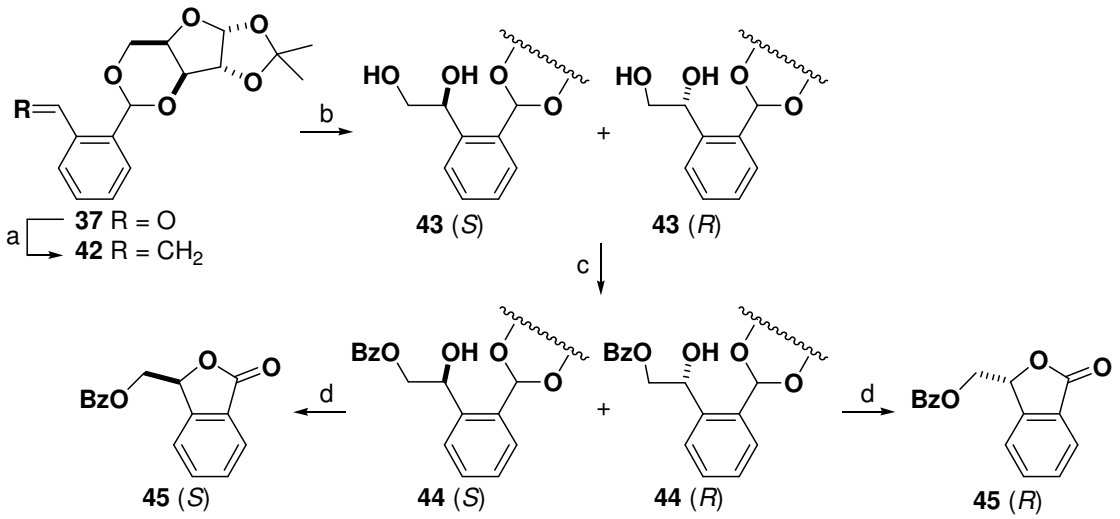


(a) **36**, PTSA, THF; (b) $Me_3SO^+I^-$, NaH, DMSO; (c) NaH, BnOH, DMF; (d) Ac_2O, H_2O; (e) $NaIO_4$, $RuCl_3$, acetonitrile, ethyl acetate, H_2O.

Scheme 6

Introduction of one carbon atom was achieved by conversion of the aldehyde **37** into the oxirane **38** using the Corey method.[22] This oxidation step afforded a mixture of two stereoisomers **38** (*S*) and **38** (*R*) (ratio 1:1) which were easily converted to the separable benzylated diols **39** (*S*) and **39** (*R*) by treatment with the sodium salt of benzyl alcohol. Starting from **39** (*S*), removal of the respective chiral protecting groups and spontaneous cyclisation furnished the corresponding lactol **40** (*S*). Classical oxidation of compound **40** (*S*) with $RuCl_3$-$NaIO_4$[23] afforded the corresponding lactone **41** (*S*) in 50% yield. Compound **39** (*R*) gave the enantiomer **41** (*R*) in a similar yield.

Starting from the chiral benzaldehyde **37**, homologation *via* a classical Wittig reaction afforded the styrene derivative **42**, which was converted into the corresponding diols **43** (*R*) and **43** (*S*) (ratio 1:1) using OsO_4 in 70% yield (Scheme 7).[24] Compounds **43** (*R*) and **43** (*S*) were easily converted into the benzoylated diols **44** (*R*) and **44** (*S*) by treatment with benzol chloride in presence of triethylamine and toluene. After chromatography the alcohols **44** (*S*) and **44** (*S*) were converted into the corresponding lactones **45** (*S*) and **45** (*R*) respectively as described above.[20] Thus it is notable that the presence of a chiral protecting group such as the D-xylose derivative did not produced any selectivity in the oxidation steps *via* Corey epoxidation and dihydroxylation (Schemes 5 and 6). It is likely that the chiral influence is too remote to exercise any stereocontrol.



(a) $BrMePh_3P$, *n*-BuLi, THF; (b) OsO_4, *t*-BuOH, NMO, pyridine, H_2O; (c) BzCl, $N(C_2H_5)_3$, toluene; (d) 1. AcOH, H_2O; 2. $NaIO_4$, $RuCl_3$, acetonitrile, ethyl acetate, H_2O.

Scheme 7

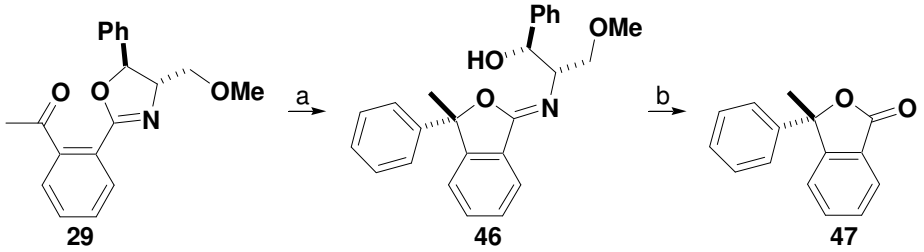
3. Enantioselective synthesis of 3,3-disubstituted 1-isobenzofuranones using a chiral protecting group

Meyers *et al.* reported a selective route to the 3,3-disubstituted phthalides *via* chiral aryllithium attack on a ketone followed by organometallic addition.[17] The ketone **29** reacted with PhMgBr as Grignard reagent in diethyl ether, to afford the imino lactone **46** in 97% yield (de 80%). Hydrolysis of **46** using oxalic acid in a mixture of THF and water gave the phthalide derivative **47** having the *S* carbon atom (Scheme 8).

Application of this strategy was successful in obtaining the 3,3-disubstituted phthalides **48-51** (Figure 6).

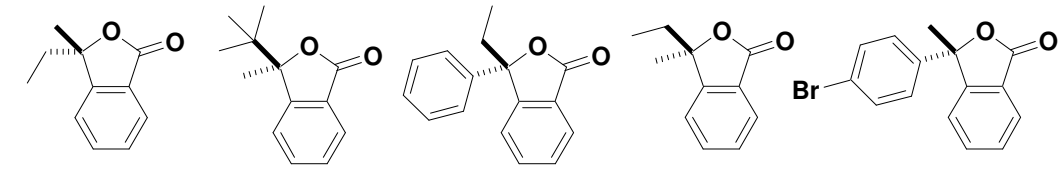
Introduction of *t*-butyl group *via* its Grignard reagent gave, unexpectedly, the *R*-configuration which may have been due to the reactivity of *t*-BuMgCl with carbonyls *via* electron transfer, as has been shown

previously.[25] It is notable that reversing the order of the alkyl introduction also reverses the absolute configurations, as exemplified with compounds **29** and **52** (Scheme 9).



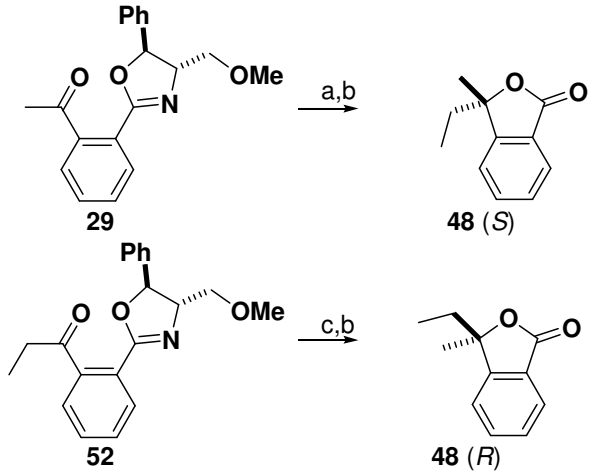
(a) PhMgBr, THF; (b) oxalic acid, THF, H_2O.

Scheme 8



48 (*S*) (*S*, ee 46%) **49** (*R*, ee 66%) **50** (S, ee 66%) **48** (*R)* (*R*, ee 64%) **51** (*S*, ee 74%)

Figure 6



(a) EtMgBr, THF; (b) oxalic acid, THF, H_2O; (c) MeMgBr, THF.

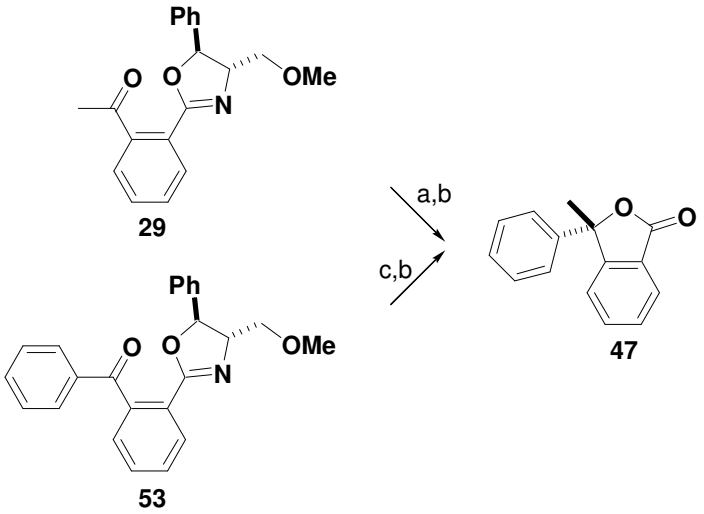
Scheme 9

On the other hand, no change of absolute configuration was observed for either phenyl or methyl Grignard reagents (Scheme 10). This is undoubtedly due to a change in conformation during the approach. The 2-substituted benzophenones **53**, which possess an electron withdrawing substituent such as an aryl group, prefer the carbonyl group to be coplanar with the unsubstituted ring (Scheme 10). This explanation is in agreement with the approach of the alkyl group from the *si* face to give the *S* configuration (Figure 7).

4. Enantioselective synthesis of a 3-substituted 1(*3H*)-isobenzofuranones

4.1. Organometallic attack on an aldehyde in presence of a chiral amino alcohol

Various research groups have described the synthesis of phthalide derivatives by enantioselective addition of dialkylzinc to benzaldehyde derivatives using a β-amino alcohol as a catalyst. Using *N*,*N*-dibutylnorephedrine (DBNE) as a chiral catalyst, Soai *et al.* reported the synthesis of 3-alkylphthalide.[26]



(a) PhMgBr, THF; (b) oxalic acid, THF, H_2O; (c) MeMgBr, THF.

Scheme 10

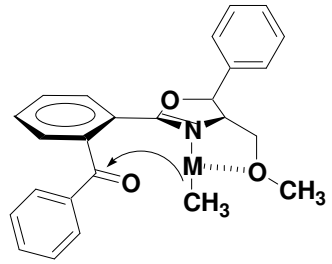
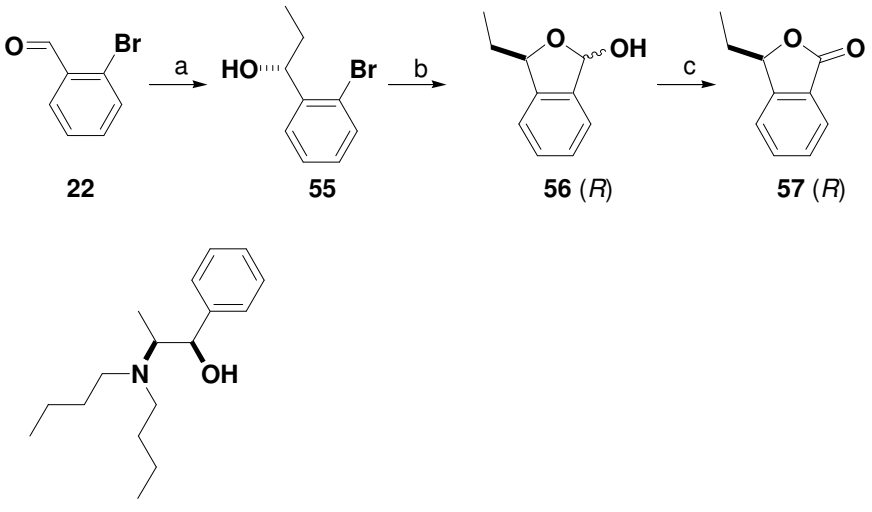


Figure 7

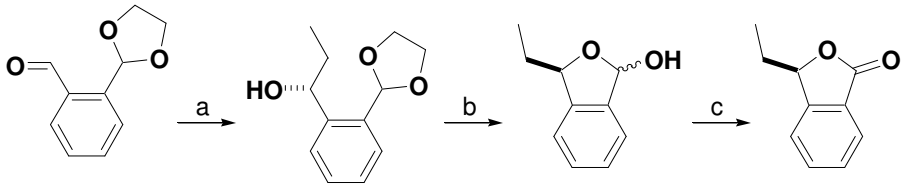
The aromatic derivative **22** was treated with Et_2Zn in the presence of (1*R*,2*S*)-DBNE **54** in hexane to give (*R*)-1-(2-bromophenyl)propanol (**55**) (ee 90%) in 94% yield. Classical *o*-formylation by treatment of *n*-butyllithium and subsequent reaction with *N*,*N*-dimethylformamide afforded the corresponding lactol **56** (*R*) in 82% yield. Subsequent, oxidation of **56** (*R*) with silver oxide gave the optically active target (*R*)-lactone **57** (*R*).



(a) $Zn(C_2H_5)_2$, **54**, hexane; (b) *n*-BuLi then DMF; (c) Ag_2O, MeOH, H_2O.

Scheme 11

In accordance with the above method, treatment of the aldehyde **22** with *n*-Bu_2Zn in presence of **54** and its enantiomer followed by *o*-formylation and oxidation furnished the (*R*)-3-butylphthalide (**1** (*R*)) (ee 86%) and (*S*)-3-butylphthalide (**1** (*S*)) (ee non determined) respectively. Soai *et al.* noted that the use of the acetal **58** and the chiral reagent **54** furnished the target phthalide **57** (*R*) in lower enantiomerical excess (76% *vs* 90%) (Scheme 12).[26]

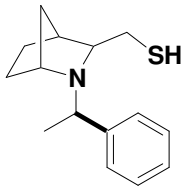


58 **59** **56** (*R*) **57** (*R*)

(a) $Zn(C_2H_5)_2$, **54**, hexane; (b) H_3O^+; (c) Ag_2O, MeOH, H_2O.

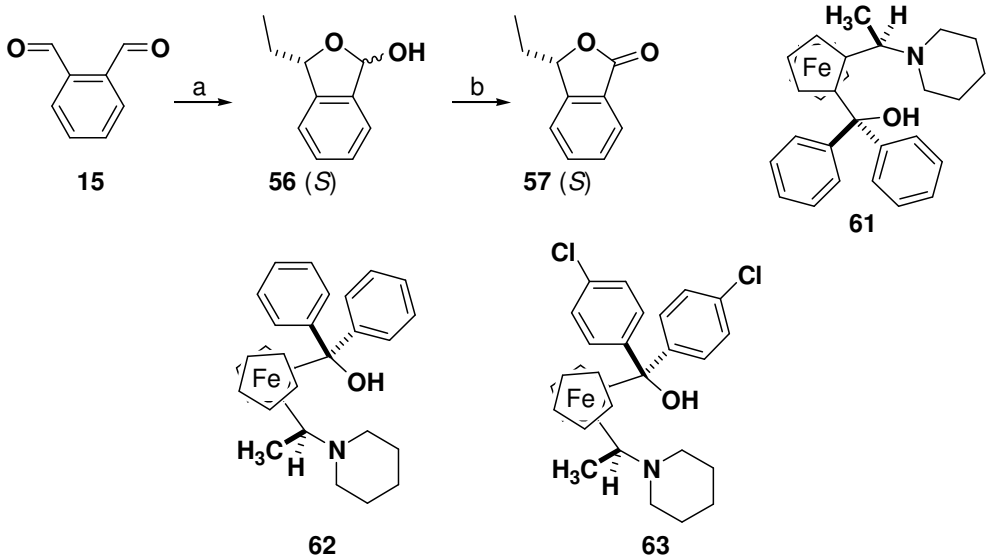
Scheme 12

The synthesis of **57** (*R*) (ee > 99%) was reported by Hongo *et al.*[27] (Scheme 13) according to the method initially developed by Soai *et al.*,[26] using (1*R*,3*S*,4*S*)-2[(*R*)-1-phenylethyl]-2-azabicyclo[2,2,1]-heptane-3-exo-methanethiol (**60**) as a chiral catalyst.



60

Figure 8



15 **56** (*S*) **57** (*S*) **61** **62** **63**

(a) $Zn(C_2H_5)_2$, **61**, hexane; (b) *n*-BuLi then DMF; (c) Ag_2O, MeOH, H_2O.

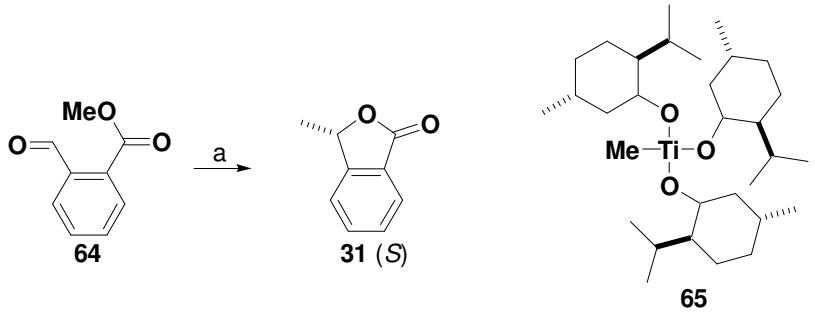
Scheme 13

A similar strategy was reported by Butsugan *et al.*[28] starting from the dialdehyde **15** and a chiral 1,2-disubstituted ferrocenylaminoalcohols as catalyst. The unprotected dialdehyde **15** was reacted with

diethylzinc in the presence of (-)-DFPE **61** and hexane at room temperature to afford the corresponding lactol **56** (*S*) (ee 88%) having the (3*S*) carbon atom absolute configuration. The lactol **56** (*S*) was oxidized with silver oxide to the optically active lactone **57** (*S*) in 80% yield without racemization (Scheme 13).

The enantiomeric (*R*)-lactone **57** (*R*) was obtained in similar enantiomerical excess using the enantiomer (+)-DFPE **62** (5%). The authors reported that the use of 10% of **62** as catalyst afforded a better enantiomeric excess (95% *vs* 88%) and the use of 10% of (*S*,*R*)-bis(4-chlorophenyl)carbinol (**63**) gave the highest enantiomeric excess (ee 98%) of the target (*R*)-lactone **57** (*R*).

Seebach *et al.* described the synthesis of the lactone **31** (*S*) with poor enantiomerical excess using a chiral organotitanium reagent.[29] Enantioselective addition of the chiral menthol derivative **65** to methyl *o*-formylbenzoate (**64**) resulted in high functional-group selectivity to afford the target lactone **31** (*S*) (ee 25%) (Scheme 14).

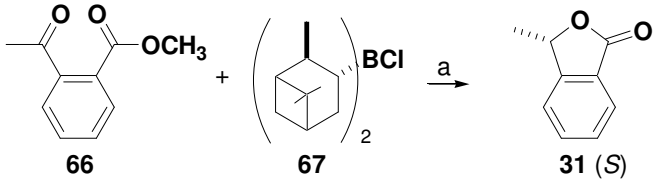


(a) **65**, Et_2O.

Scheme 14

4.2. Organometallic attack on a ketone in presence of a chiral organoborane

Brown *et al.* reported the synthesis of (*S*)-3-alkylphthalide *via* asymmetric reduction.[30] Treatment of (-)-B-chlorodiisopinocampheylborane (Ipc_2BCl, **67**) with methyl *o*-acetylbenzoate (**66**) in diethyl ether followed gave the corresponding (*S*)-lactone **31** (*S*) (ee 97%) by intermolecular asymmetric reduction (Scheme 15).



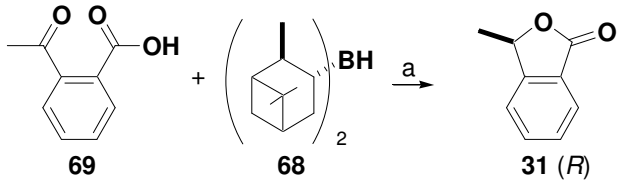
(a) 1. diethylether; 2. diethanolamine.

Scheme 15

The corresponding lactones **57** (*S*) (ee 98%) (Scheme 13) and **1** (*S*) (ee 99%) (Scheme 1) were obtained by application of the aforementioned methodology starting from methyl *o*-propionylbenzoate and methyl *o*-valerylbenzoate respectively.

The preparation of the corresponding enantiomers having the *R* absolute configuration was reported by Brown *et al.*[30] using (-)-B-diisopinocampheylborane (Ipc_2BH, **68**) and *o*-acetylbenzoic acid (**69**) in THF (Scheme 16). Intramolecular asymmetric reduction of the carboxylic acid **69** in presence of the catalyst **68** furnished the corresponding (*R*)-lactone **31** (*R*) (ee 80%) (Scheme 16). Application of this procedure starting

from *o*-propionylbenzoic acid and *o*-valerylbenzoic acid afforded the phthalides **57** (*R*) (ee 68%) (Scheme 12) and **1** (*R*) (ee 67%) (Scheme 1) respectively.



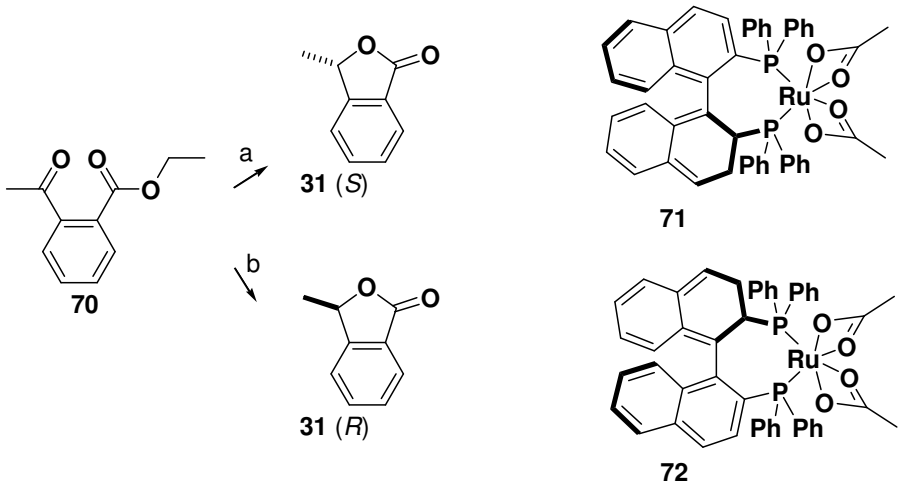
69 **68** **31** (*R*)

(a) diethylether; (b) diethanolamine

Scheme 16

4.3. Homogeneous hydrogenation of a ketone in presence of a chiral phosphine

Noyori *et al.* described the stereoselective synthesis of phthalide derivatives by asymmetric transfer hydrogenation using ruthenium catalyst.[31,32] The hydrogenation of ethyl *o*-acetylbenzoate (**70**) in ethanol in presence of the (*S*)-BINAP-Ru catalyst **71** afforded the (*S*)-lactone **31** (*S*) (ee 97%) directly. The use of the (*R*)-BINAP-Ru catalyst **72**, afforded the (*R*)-phthalide **31** (*R*) in a similar yield (ee 92%) (Scheme 17).



70

(a) **71**, H_2, 100 atm; (b) **72**, H_2, 100 atm.

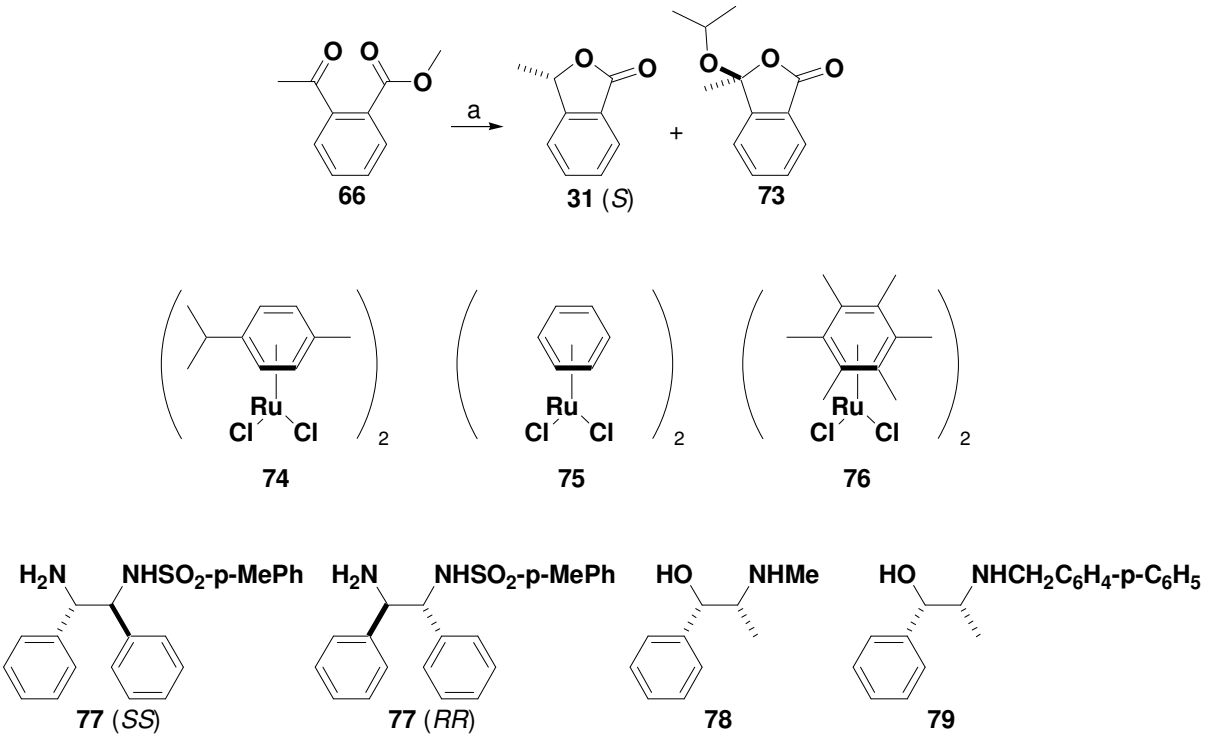
Scheme 17

4.4. Catalytic asymmetric transfer hydrogenation of a ketone in presence of a chiral aminoalcohol

Ruthenium-catalyzed asymmetric transfer hydrogenation of 2-propanol to a ketone was reported using a combination of a chlororuthenium(II)arene complex with a chiral ligand such as β-amino alcohol in the presence of a base.[33] Treatment of the ketoester **66** with $[RuCl_2(\eta^6\text{-p-cymene})]_2$ (**74**) as catalyst and (*S*,*S*)-TsDPEN **77** (*SS*) as ligand in a solution of 2-PrOK in 2-propanol provided the target (*S*)-phthalide **31** (*S*) (30% yield, ee 97%) and 3-(2-propoxy)-3-methylphthalide (**73**) (62% yield), which was obtained by lactonization of the hemiacetal of **66** (Scheme 18).[34] Carpentier *et al.* reported that use of the enantiomer **77** (*RR*) with $[(benzene)RuCl_2]_2$ (**75**) as Ru catalyst, furnished the corresponding (*R*)-phthalide **31** (*R*) (ee 91%).[35] The catalytic combination of the bulky arene **76** with either the amino alcohols **78** and **79** afforded the (*S*)-phthalide **31** (*S*) (ee 82% and 84% respectively).

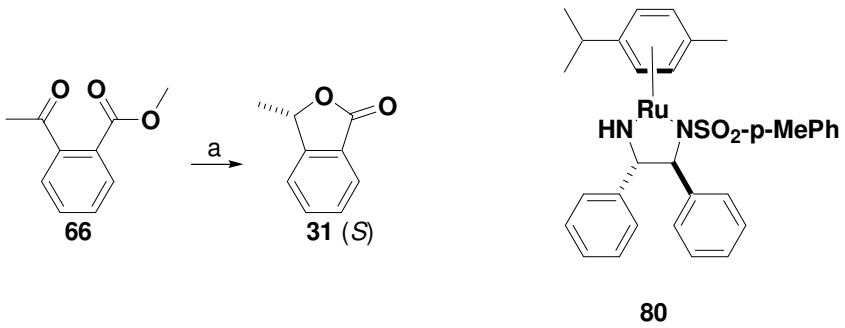
This reaction was carried out using the preformed true catalyst **80** (reaction between **74** and **77** (*SS*)) without any added 2-PrOK to give the phthalide **31** (*S*) (ee 97%) without the presence of the 2-propoxy

derivative **73** being detected in the reaction mixture (Scheme 19).[34] This result showed that an excess of the base necessary for the generation of the active catalyst favoured the formation of the side-product **73**.



(a) **74, 77** (*SS*), 2-PrOK, *i*-PrOH.

Scheme 18



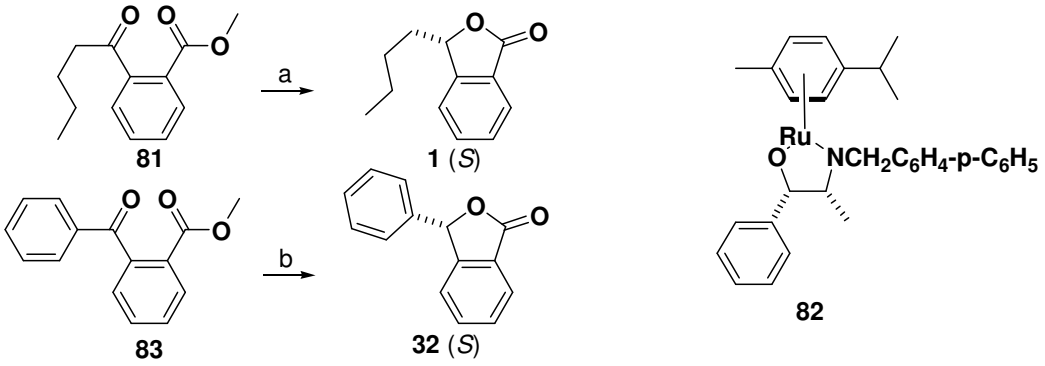
(a) **80**, *i*-PrOH.

Scheme 19

The Ru catalyst **82** formed *in situ* or preformed (reaction between **74** and **79**) was used to convert **66** into the target phthalide **31** (*S*) but with poorer enantioselectivity (83% *vs* 97%). Application of this procedure to **81**, using catalyst **80** and **83** using catalyst **82**, permitted the preparation of the (*S*)-lactones **1** (*S*) (ee 92%) and **32** (*S*) (ee 10%) respectively (Scheme 20).[34]

4.5. Metallation of a 1,3-dihydroisobenzofuran derivative in presence of a chiral lithium amide

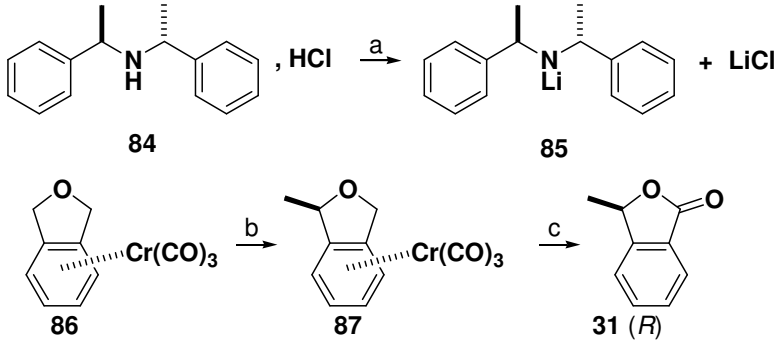
Simpkins *et al.* reported the regioselective and enantioselective synthesis of (*R*)-3-methylphthalide using a chiral base and tricarbonyl(η^6-arene)chromium complex.[36] Treatment of 1,3-dihydroisobenzofuran (**86**), with the chiral lithium amide **85** in the presence of LiCl and THF followed by the addition of methyl iodide as electrophile afforded the 1-methyl-1,3-dihydroisobenzofuran analogue **87** in 75% yield (ee 79%).



(a) **80**, *i*-PrOH ; (b) **82**, *i*-PrOH.

Scheme 20

Oxidation of the methylated compound **87** with RuO_4,[37] generated *in situ* according to the Sharpless protocol,[23] gave the corresponding lactone **31** (*R*) in 59% yield (Scheme 21). It is notable that the authors demonstrated that conducting the chiral base reactions in the presence of LiCl resulted in a dramatic acceleration of the metallation.

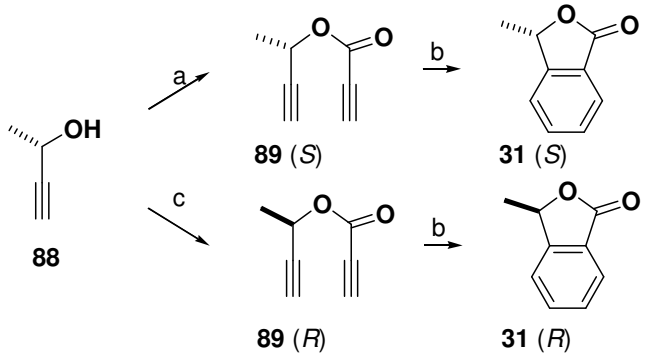


(a) BuLi, THF; (b) **85**, LiCl, THF then CH_3I; (c) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN

Scheme 21

4.6. Crossed alkyne cyclotrimerisation *via* rhodium(I)

Witulski and Zimmerman reported a route to the phthalide derivatives which involved the key step of rhodium (I) catalyzed crossed alkyne cyclotrimerisation.[38]



(a) propionic acid, DCC, DMPA; (b) HCCH, $RhCl(PPh_3)_3$; (c) DEAD, PPh_3.

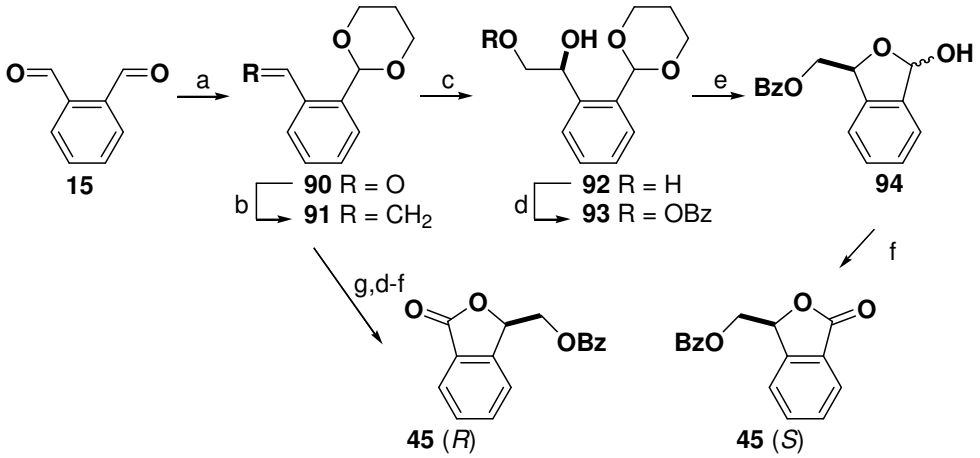
Scheme 22

The chiral starting material **88** was reacted with propionic acid in the presence of dicyclohexylcarbodiimide (DCC) to give the corresponding diyne ester **89** (*S*) in 42% yield with complete

retention of configuration. The electron deficient diyne ester **89** (*S*) underwent crossed alkyne cyclotrimerisation with acetylene, mediated by a Wilkinson catalyst to give the phthalide **31** (*S*) in 68% yield (Scheme 22). Alternatively, **88** and propionic acid were coupled to form the ester **89** (*R*) by a Mitsunobu reaction in 46% yield.

4.7. Wittig homologation from an aldehyde *via* asymmetric dihydroxylation

An enantioselective route to the 3-hydroxymethyl phthalide derivatives was devised by Len *et al.*.[39] Selective protection of dialdehyde **15** with propan-1,3-diol in presence of PTSA in toluene followed by successive Wittig homologation and asymmetric dihydroxylation using the commercial Sharpless reagent AD-mix α, furnished the corresponding diol **92** (ee 98%). Selective benzoylation of the primary hydroxyl group of the diol **92** gave the ester **93** which was cyclised to afford the corresponding 1,3-dihydrobenzo[*c*]furan derivative **94**. Classical oxidation of **94** with $RuCl_3$-$NaIO_4$[23,37] afforded the corresponding lactone **45** (*S*) in 50% yield (Scheme 23). Using the same strategy, treatment of alkene **91** with AD-mix β gave the enantiomer **45** (*R*) (ee 98%).



(a) propan-1,3-diol, PTSA, toluene; (b) $BrMePh_3P$, *n*-BuLi, THF; (c) AD-mix α, *t*-BuOH, H_2O; (d) BzCl, $N(C_2H_5)_3$, toluene; (e) AcOH, H_2O; (f) $NaIO_4$, $RuCl_3$, acetonitrile, ethyl acetate, H_2O; (g) AD-mix β, *t*-BuOH, H_2O.

Scheme 23

5. Conclusion

To date the majority of chemical synthesis work in this field has been targeted at 3-substituted 1(*3H*)-isobenzofuranones and 3,3-disubstituted 1-isobenzofuranones. Most of the strategies have permitted the syntheses of the target phthalides possessing one asymmetric carbon atom starting from achiral aromatic substrate. There is only one example of synthesis of the aromatic ring after creation of the stereocenter and the ester function.[38] In all of the other cases the achiral aromatic substrate reacted either with chiral protecting group followed by achiral reagent and deprotection[15-17,19-21,24] or with chiral reagent, solvent or catalyst.[26-36,38,39]

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SYNTHESIS OF NITROBENZAZOLES. PART I

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Abstract. *This review is devoted to the synthesis of C- and N-nitrated benzazoles. The literature data concerning the preparation of nitrobenzazoles for over thirty years are summarized and critically discussed. Part 1 deals with the nitration methods of all the known benzazoles and also the preparation methods of nitroindazoles and nitrobenzimidazoles via heterocyclization.*

Contents

1. Introduction

The nitro derivatives of azoles, in particular, nitrobenzazoles have found wide applications in various branches of medicine, technology, and agriculture. For a long time they were used as radiosensitizers, anesthetics, anticancer medications, dyes, plasticizers, ionic liquids, pesticides, herbicides and plant growth regulators.[1] The nitro derivatives of benzazoles are convenient synthons and intermediates in organic synthesis.[1]

The syntheses of five-membered ring systems with more than one nitrogen atom (pyrazole, imidazole, oxazole, thiazole, triazoles and tetrazole) have been described earlier.[2] The NMR spectroscopy[3] and mass spectrometry[4] data on five-membered nitroazoles and their annelated cycles were completely reviewed and critically discussed.

In the monograph[5] on nitroazoles only the *C*-nitro derivatives of *N*- and *N,O*-containing five-membered heterocycles were considered, whereas the nitrobenzazole derivatives remained unheeded. Some representatives of nitrobenzazoles are described in reviews.[6] The aim of the present review was to fill this gap. The enormous amount of literature related to this topic made it necessary to exclude a series of references to earlier investigations and patents cited in the above-mentioned reviews and monographs and

also in more recent publications.

Some pioneering papers dealing with the synthesis on nitrated benzazoles have been included in the present review.

2. Nitration of benzazoles

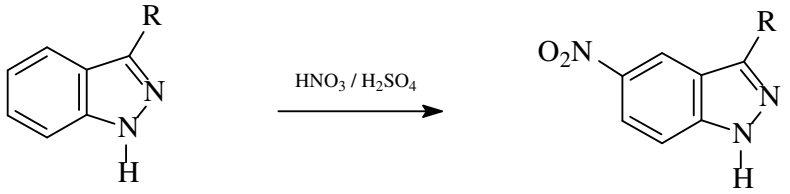
The most widespread and convenient method for the preparation of nitrobenzazoles is the reaction of nitration. Electrophilic substitution of azoles is a complex reaction in which the experimental conditions can modify the product orientation. The ability of azoles to electrophilic substitution is determined by the activity of reagents, the basicity of substrates and the acidity of medium. This caused some uncertainty in interpreting the results and complicated comparison of the reactivity of various azoles among them. The situation has changed after Katritzky and Johnson[7] had reported the criteria allowing, with a sufficient degree of reliance, the establishment in what form (base or conjugative acid) the compound reacts. The information on the mechanism of nitration of azoles is basically borrowed from the extensive literature on the nitration of aromatic and heteroaromatic compounds,[8] therefore it is no sense to discuss this point in the review.

The existence of an annelated benzene ring in the benzazole molecule influences much its ability for electrophilic substitution. All benzazoles are more easily nitrated than their five-membered analogs, and the nitro group is generally introduced into the arylene fragment of the molecule.

2.1. Indazoles

Unsubstituted indazole is nitrated into the position 5 by a mixture of sulfuric and nitric acids or just by nitric acid (Scheme 1).[9]

The presence of substituents mainly affects the direction of the process and not its rate. 1-Phenylindazole with 86% nitric acid gives a tetranitro derivative, which has one nitro group in the position 5, the second nitro group is in the *para*-position of the phenyl ring, the position of the other two being not determined reasonably well.[10] If the nitration is performed by potassium nitrate in sulfuric acid, 1-(4-nitrophenyl)-5-nitroindazole is formed. Both the electron-donating and electron-withdrawing substituents at the indazole cycle C-3 atom direct the coming nitro group to the position 5 in the nitration by nitric acid or by the mixture of sulfuric and nitric acids (Scheme 1).[10-16]

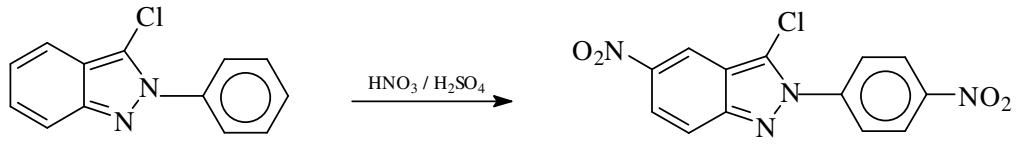


R = H, CH_3, CH_2COOH, Cl, COOH, $COOCH_3$, CN

Scheme 1

As mentioned in a patent,[17] the nitration of 3-trifluoromethylindazole results in a mixture of 5-nitro- and 7-nitro isomers. If the mixture of nitric and sulfuric acids is used as a nitrating agent, the formation of 3-methyl-7-nitroindazole as a by-product is observed.[11] Nitration of 3-chloro-2-phenylindazole with a

mixture of fuming nitric acid and concentrated sulfuric acid at 0 °C gives 3-chloro-5-nitro-2-(4-nitrophenyl)indazole in yield 73% (Scheme 2).[18]

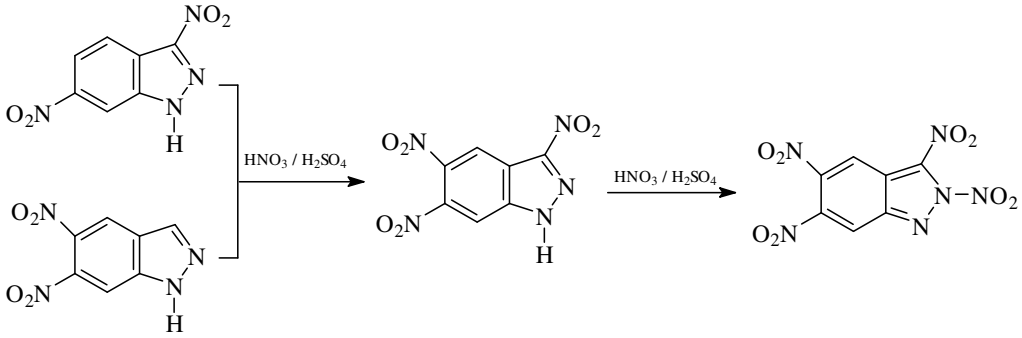


Scheme 2

The nitration of 2-phenylindazole at 0 °C with sulfuric-nitric acid mixture leads to 5-nitro-2-phenylindazole and 7-nitro-2-phenylindazole. These compounds have been identified using NMR spectroscopy.[19] In spite of the fact that the indazole positions 5 and 7 are most reactive with respect to electrophilic substitution[20] it is difficult to know beforehand a competition between the aromatic positions of the indazole ring (C-4, C-5, C-6, C-7) and the *N*-phenyl ring.

Electron-donating substituents in the indazole cycle positions 5 and 7 direct the coming nitro group to the position 4,[21-23] and 6-acetylaminoindazole is nitrated to the position 7.[22] Under further nitration of mononitroindazoles the site of introduction of the second nitro group depends on both the position of the already present one and reaction conditions. For example, 5-nitroindazole is nitrated by the sulfuric-nitric acid mixture into 5,7-dinitro derivative,[24] whereas in 6-nitroindazole the second nitro group enters into the position 5.[21,24] After the nitration 7-nitroindazole affords 5,7-dinitro derivative.[25]

The information about indazoles containing three or more nitro groups is rather scarce.[26,27] Tetranitroindazole has been first assigned a wrong structure,[26] but then it has been established to be 2,3,5,6-tetranitroindazole (Scheme 3).[27]



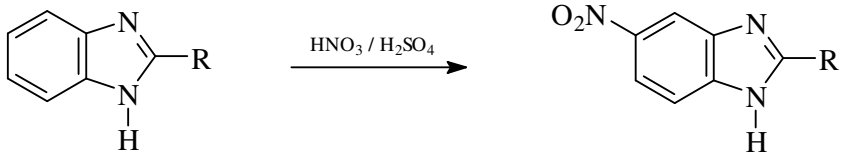
Scheme 3

The formation of *N*-nitroazoles under the effect of sulfuric-nitric mixture is a rather seldom phenomenon,[15,27] since the *N*-NO_2-bond is unstable in acids. The most convenient way to *N*-nitroindazoles is nitration by acetyl nitrate.[15,27-37] 2-Nitroindazoles, the products of nitration with nitric acid in acetic anhydride, are easily rearranged to 3-nitro derivatives that makes these isomers fairly accessible.[28] This method has been modified by Pozharskii[38] with a main goal to increase the yield of the reaction product. So 3-nitroindazole has been obtained without the intermediate 2-nitroindazole.

Kinetics and mechanism of nitration of indazoles with acetyl nitrate have not been specially investigated. In the sulfuric-nitric mixture the indazoles are nitrated in the cation-form.[39]

2.2. Benzimidazoles

Benzimidazole is nitrated to the position 5(6).[40-44] The same orientation is observed in the nitration of different 2-substituted benzimidazoles (Scheme 4).[45-67]

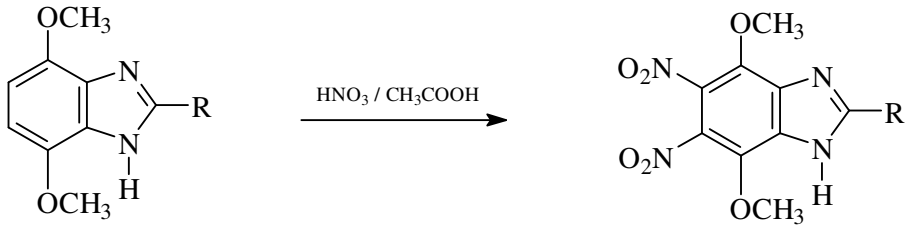


R = H, Alk, Ar, Hal

Scheme 4

In a boiling mixture of nitric (*d* 1.50) and concentrated sulfuric acids 2-chlorobenzimidazole gives 2-chloro-5,6-dinitrobenzimidazole in a 75–80% yield.[67] In analogous conditions, benzimidazole and 2-alkyl substituted benzimidazoles are also transformed into 5,6-dinitro derivatives; however, in this case simultaneous formation of 4,6-dinitro isomers, which can be separated by fractional crystallization, has been fixed.[48,68] 5(6)-Nitro-2-heterylbenzimidazoles (thiazolyl-4-, furyl-4-, and pyrrolyl-4-) having antihelminthic activity were obtained by nitration with sulfuric-nitric mixture on cooling.[69]

2-Trifluoromethyl- and 2-amino-4,7-dimetoxybenzimidazoles are nitrated to 5,6-dinitro derivatives already at 0 °C (Scheme 5).[70]



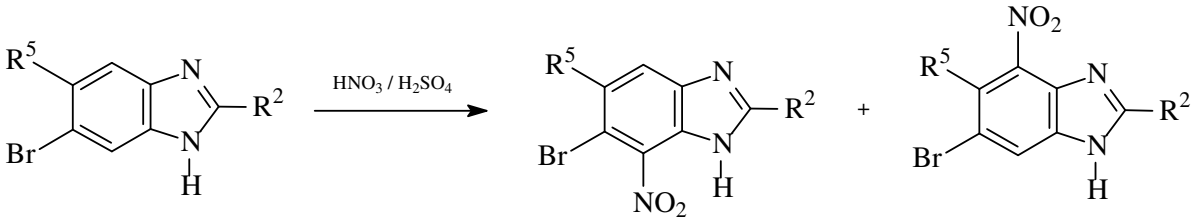
R = NH_2, CF_3

Scheme 5

The nitration of 5-nitrobenzimidazole under severe conditions gives two isomeric 5,6-dinitro- and 4,6(5,7)-dinitrobenzimidazoles. The structures of these products are identified only spectroscopically in the solution. The solid state structure of the major isomer 5,6-dinitrobenzimidazole has been determined crystallographically.[71]

The nitration of 5-substituted benzimidazoles affords both mono- and dinitro derivatives. The two nitro groups occupy exclusively the positions 4 and 6 to form 5-substituted 4,6-dinitrobenzimidazoles.[72-75] It is interesting to note if in the nitration of 5-hydroxybenzimidazole the nitro group enters into the 4 position,[74] whereas in the nitration of 5-chloro-, 5-ethyl- and 5-ethoxybenzimidazole[73] and also 5-chloro- and 5-methyl-2-alkylbenzimidazoles[76,77] it will occupy the 6 position. These data indicate that under the influence of electronic effects of the substituent in the position 5, the reactivity of C-4 and C-6 atoms of the benzimidazole ring is slightly equalized. That is why among the products of mononitration of 5-substituted benzimidazoles one can find 5-substituted 6-nitrobenzimidazoles,[49,75-80] 5-substituted 4-nitrobenzimidazoles[74,75] and a mixture of these isomers.[54,75,81,82]

The nitration of 2-alkyl-5(6)-chloro(or methyl)-6(5)-halobenzimidazoles with excess nitric acid (~ 3 equivalents) in sulfuric acid leads to a mixture of 4-nitro- and 7-nitrobenzimidazoles except for 2-methyl-5,6-dibromobenzimidazole as shown in Scheme 6.[76] It is natural that 2-methyl-5,6-dibromo-benzimidazole in the nitration under the same conditions gives 4-(7)-nitro-2-methyl-5,6-dibromobenzimidazole (in good yield).

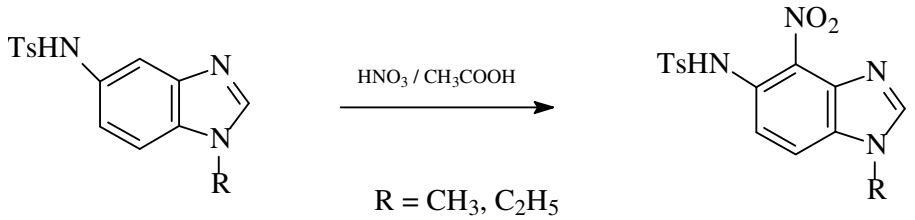


R^2 = Alk, R^5 = Hal, Me

Scheme 6

A preparation of 2,5(6)-dimethyl-4(7)-nitrobenzimidazole by nitration of 2,5(6)-dimethyl derivative has been reported in a patent,[83] but there is no supporting evidence for the correctness of the assigned structures.

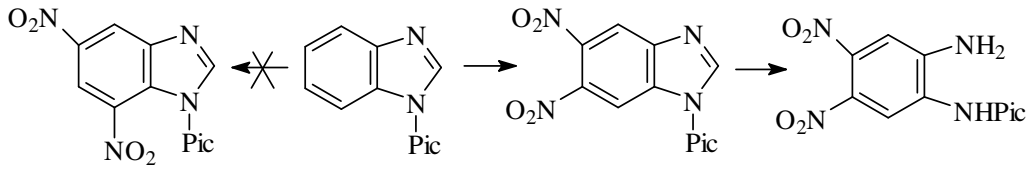
On nitration of 1-substituted benzimidazoles 5- and 6-nitro isomers[84-91] are formed. At the same time the nitration of 1-alkyl-5-tosylaminobenzimidazole with nitric acid in a solution of acetic acid leads to the formation of one isomer, the nitro group being involved into the position 4 (Scheme 7).[92]



R = CH_3, C_2H_5

Scheme 7

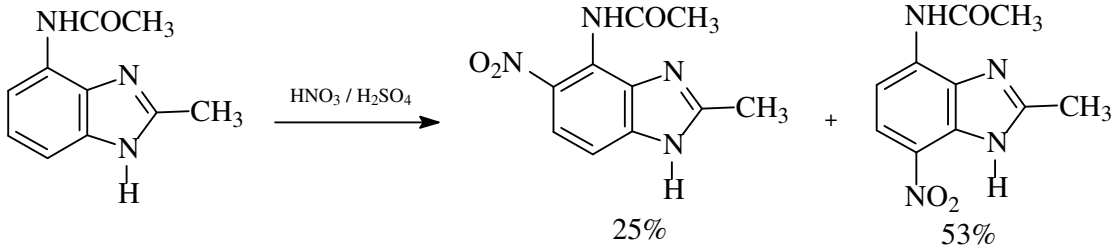
The nitration of 1-picrylbenzimidazole with 100% nitric acid and 96% sulfuric acid gave, instead of the expected 5,7-dinitro derivative, the hydrolytically unstable 5,6-dinitro-1-picrylbenzimidazole which opens to the corresponding amine as shown in Scheme 8.[93]



Scheme 8

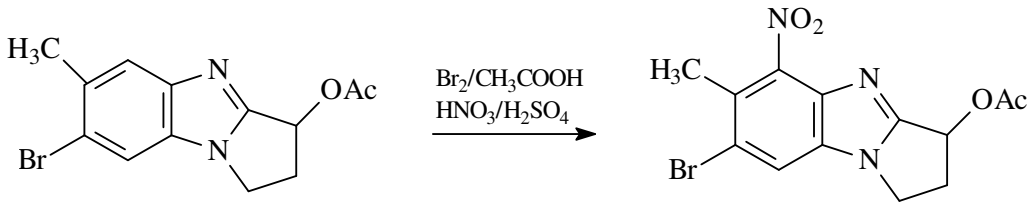
On nitration of 2-methyl-4(7)-acetylaminobenzimidazole two isomeric nitro products were obtained; the amount of 2-methyl-4(7)-acetylamino-7(4)-nitro isomer being twice as large (Scheme 9).[94]

Prevailing formation of the 7-nitro derivative was observed in the nitration of 4-fluoro-[5] and 4-*t*-butylbenzimidazole.[96,97] When the benzimidazole ring has its 4 and 6 positions substituted, the nitration proceeds across the C-4 or C-7 atom.[98-101]



Scheme 9

In a medium of bromine in acetic acid and sulfuric-nitric mixture the benzimidazole derivatives are nitrated only to position 4.[102] In this case the bromine is introduced into the position 5 (or 6) (Scheme 10).



Scheme 10

Mechanism of the nitration of benzimidazoles has not been studied much, but there are weighty arguments to conclude that they are nitrated as conjugated acids.[51,103] Kinetic studies of the nitration of benzimidazole and some its 2-substituted derivatives have confirmed that the protonated form is involved in the process.[104] Recent results of quantum-chemical studies of the nitration of benzazoles indicate the importance of the protonated benzimidazolium cations in the nitration process.[43]

It has been noted that in the nitration of 2-phenylbenzimidazole, the rate of nitration into the benzimidazole 5 position is about 3 orders of magnitude higher than that of the phenyl ring.[51]

Benzimidazolone-2 and benzimidazolthione-2 derivatives are more prone to nitration[105,106] and in this case the nitro group enters into the position 5(6). It should be noted, that depending on the reaction conditions, it is possible to obtain benzimidazolone dinitro, trinitro or tetranitro derivatives.[103,107] 5-Nitrobenzimidazolone-2 is nitrated with concentrated nitric acid on heating (80-90 °C) only to the position 6 to give 5,6-dinitrobenzimidazolone-2.[108]

In the reaction of nitronium tetrafluoroborate with 1-aminobenzimidazole the nitro group enters only into the side-chain with the formation of *N*-nitroimides.[109] In some cases the nitration of benzimidazoles with acetylnitrate leads to 1-nitrobenzimidazoles.[110]

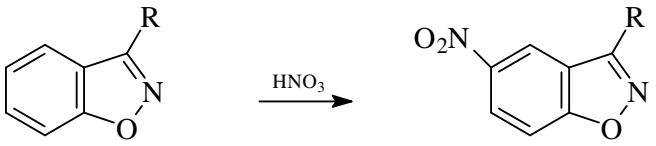
Some examples of the nitration of different derivatives of benzimidazole have been reported.[110-114]

2.3. Benzisoxazoles, benzoxazoles, benzoxadiazoles

1,2-Benzisoxazole and its 3-substituted derivatives are nitrated into the position 5 (Scheme 11).[115-125]

The nature of substituent in the arylene fragment significantly influences the nitration direction. For example, 3,5-dialkyl-1,2-benzisoxazoles are nitrated into the position 4 (the data about the formation of 3,5-dimethyl-7-nitro-1,2-benzisoxazole presented in[115] turned out to be wrong,[119] whereas 3-alkyl-5-nitro derivatives occupy the position 7.[119] The nitration of 7-methoxy-2-phenylbenzisoxazole affords 7-methoxy-2-phenyl-4-nitro derivative.[126]

The mechanism of the nitration of benzisoxazoles in sulfuric-nitric acid mixture was been studied with 3-methyl-1,2-benzisoxazole.[121] It has been found that at a sulfuric acid concentration of about 80-90% the substrate reacts as a free base, and at a higher concentration the conjugated acid undergoes nitration. It is worth mentioning that in 1,2-benzisoxazole and its 3-methyl derivative the higher electron density is concentrated on the C-7 atom and in the case of charge-controlled reactions the nitration would lead to 7-nitro isomers. Since 5-nitro derivatives are formed, the process of nitration seems to be of orbital-controlled character.[121]

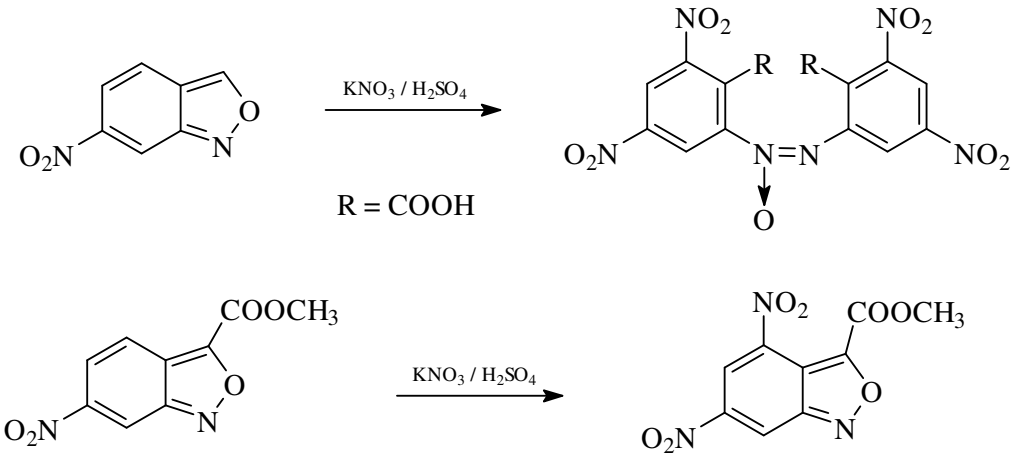


R = H, Alk, COOR'

Scheme 11

The nitration of 2,1-benzisoxazoles (anthranils) and their thioanalogs is poorly understood. Unsubstituted anthranil and its 3-methyl and 3-chloro derivatives are nitrated, generally, on the C-5 atom (in the first two cases, along with the main product small amounts of 7-nitro isomer were obtained).[127,128] When heated, 6-chloro-2,1-benzoxazole (6-chloranthranil) forms only 7-nitro derivative.[129] The nature of substituent significantly influences the site of the nitro group introduction. For example, on heating 5-chloroanthranil forms 5-chloro-4-nitroanthranil, but its 3-phenyl derivative is nitrated into the position 7 (along with the nitro group entering into the phenyl-ring).[130]

It was impossible to introduce the second nitro group into 6-nitroanthranil because of the heterocycle ring opening as shown in Scheme 12, however, 3-carbomethoxy-6-nitro-2,1-benzisoxazole is more easily nitrated to 4,6-dinitro derivative.[130]

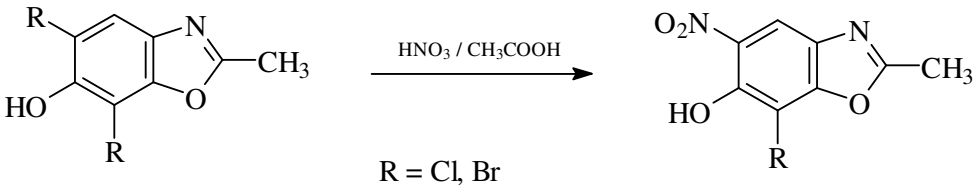


Scheme 12

In benzoxazoles and their 2-substituted derivatives the nitro group is presumably introduced into the position 6.[131-135] In the nitration of 2-methylbenzoxazole a mixture of 80% of 6-nitro- and 20% of 5-nitro

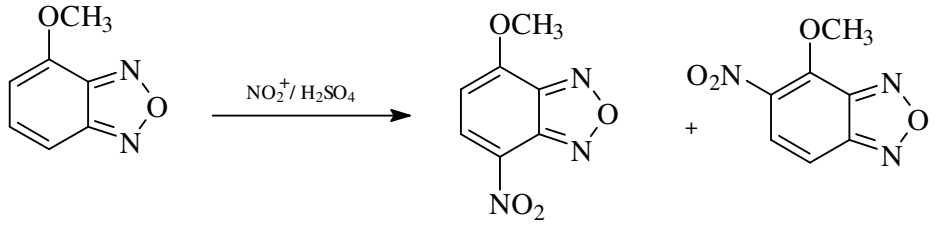
isomer was isolated. 2-Phenylbenzoxazole is first nitrated to the position 6.[136,137] The nitration of benzoxazolones-2 and benzoxazolthiones-2 proceeds in an analogous way.[138-141]

The reaction of cooled nitric acid with benzoxazole results in the formation of a mixture of 2-hydroxy-4-nitro- and 2-hydroxy-5-nitroformylanilines. On heating the same reaction gives a mixture of 5- and 6-nitrobenzoxazoles, the latter being prevailing.[131] Here a question arises whether the formation of nitrohydroxyformylaniline results from the hydrolysis of the nitrobenzoxazole formed or it is due to the nitration of hydroxyformylaniline (the product of benzoxazole hydrolysis). The authors have shown the nitration to precede the hydrolysis.[131] If the position 6 in benzoxazole is occupied, the nitration goes into the position 5.[142] In the same work an example of nitrolysis (substituting nitration, *ipso*-nitration) of 2-methyl-5,7-dihalogeno-6-hydroxybenzoxazoles is given (Scheme 13).



Scheme 13

Substituted benzoxazoles are also nitrated with sulfuric-nitric mixture into the 6 position, if it is vacant.[143,144] In earlier publications it has been stated that benzofurazans (2,1,3-benzoxadiazoles) are nitrated exclusively to the 4(7) position.[145-147] If the 4 and 7 positions are occupied, as in 4,7-dichloro-2,1,3-benzoxadiazoles, for example, the nitration is impossible. At the same time, 4,6-dichloro-7-nitrobenzofurazan was obtained in good yield from 4,6-dichlorobenzofurazan.[148] Later it has been shown, that in the presence of strong electron-donating substituents in position (like OCH_3), along with nitration to the position 7 the addition of the nitro group to the C-5 atom takes place (Scheme 14).[149]

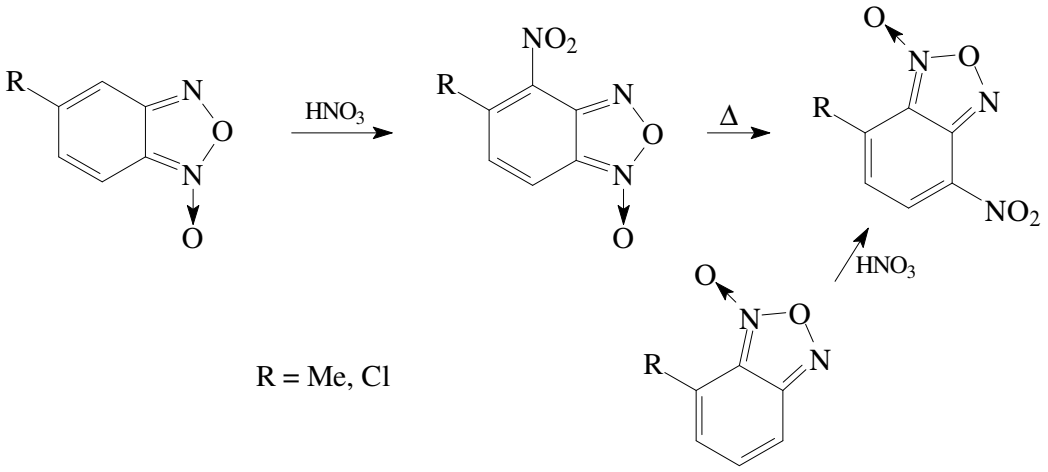


Scheme 14

As expected, strong electron-deficient substituents in the position 5 orient the incoming nitro group exclusively to the position 7.[150,151] Some examples of obtaining dinitrobenzofurazans by nitration are described in references.[152-154]

The benzofuroxan benzene ring is subjected to electrophylic substitution, in particular, nitration reaction. If the nitro group is introduced into the position neighboring to the heterocycle, the nitro compound formed undergoes the so-called Boulton-Katritzky rearrangement.[155-161]

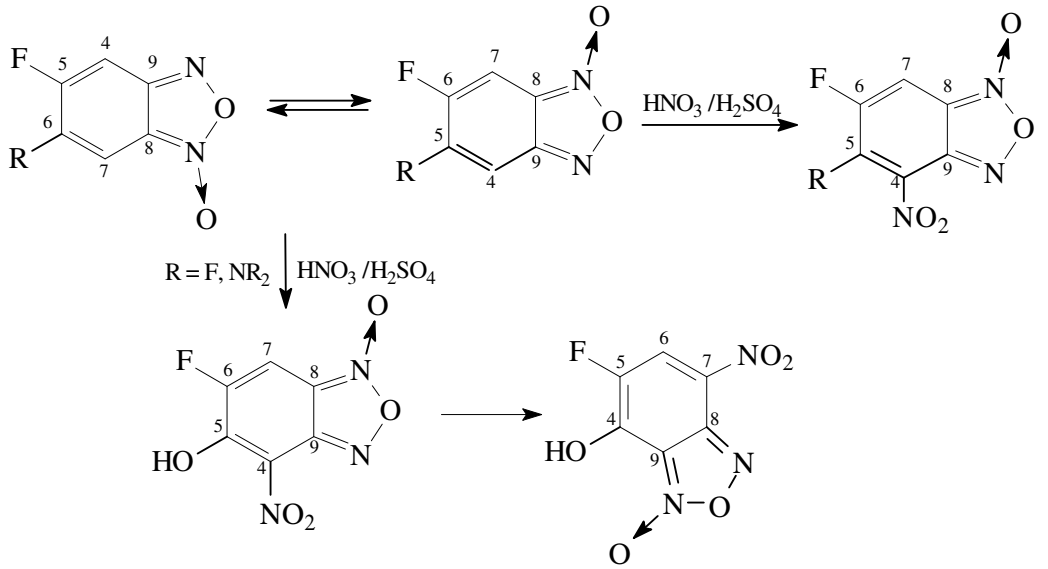
The nitration of 5-methylbenzofuroxan results in a 4-nitro derivative, which on heating is transformed to a more stable 7-methyl isomer according to the Boulton-Katritzky rearrangement. As shown in Scheme 15 the latter compound is obtained by direct nitration of 4-methylbenzofuroxan.[159]



Scheme 15

Similarly, 5-chloro-4,6-dinitrobenzofuroxan prepared by the nitration of 5-chlorobenzofuroxan by HNO_3/H_2SO_4, 0→21 °C[162] undergoes the Boulton-Katritzky rearrangement (28 °C, 51 hrs, $CHCl_3$) to give 7-chloro-4,6-dinitro-benzofuroxan (Scheme 15).

It has been pointed out[155] that in the presence of fluorine atom in the position 5 in 4-nitrobenzofuroxan no Boulton-Katritzky rearrangement occurs. Later it has been established[161] that fluoro-containing benzofluoroxans are fairly easily nitrated, however, not all nitration products are involved in the Boulton-Katritzky rearrangement. 5,6-Difluorobenzofuroxan and 5(6)-amino substituted 6(5)-fluorobenzofuroxans are nitrated with HNO_3 (*d* 1.54) and H_2SO_4 acids on cooling to form 4-nitro-5-hydroxy-6-fluorobenzofuroxan (Scheme 16).[161]



R = F, $N(CH_3)_2$, morpholino, thiomorpholin-4-yl, pyrrolidin-1-yl, OCH_3, OC_2H_5, tetrohydrofuran-2-yl methoxy

Scheme 16

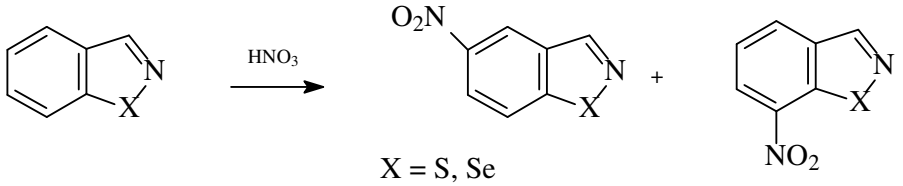
Under nitration conditions the substituted fluorine (or the amine group) in the position 5 are easily hydrolized to hydroxy group. 4-Nitro-5-hydroxy-6-fluorobenzofuroxan, on dissolving in polar solvent (DMSO), partly transforms to 4-hydroxy-5-fluoro-7-nitrobenzofuroxan as a result of the Boulton-Katritzky

rearrangement (Scheme 16).[161] Under nitration of 5(6)-alkoxy 6(5)-fluoro-benzofuroxan the corresponding 4-nitrobenzofuroxans were obtained. In this reaction the C-4 atom in the *ortho*-position to the electron-donating substituent and remote from the *N*-oxide group is also the center of electrophilic attack. In this case, however, no products of the Boulton-Katritzky rearrangement are formed.

4,6-Dichlorobenzofuroxan is nitrated by HNO_3 and oleum 30% to form 4,6-dichloro-5,7-dinitrobenzofuroxan, one of the most perspective precursors of explosive compounds.[162]

2.4. Benzisothiazoles, benzothiazoles, benzothiadiazoles

Like 1,2-benzoselenazole,[163] 1,2-benzothiazole[164-166] on heating forms a mixture of 5-nitro- and 7-nitro-isomers (Scheme 17).



X = S, Se

Scheme 17

The introduction of substituents into the position 3 does not change the reaction course.[165,167-169] 4-Amino-7-nitrobenzisothiazole in the sulfuric-nitric mixture forms 5,7-dinitro derivative in low yield.[170] 4-Chloro-7-nitro-1,2-benzisothiazole was obtained as a result of the nitration of 4-chloro-1,2-benzisothiazole.[171,172] 5-Hydroxy-1,2-benzothiazole is nitrated to the position 4, and in case of 5-hydroxy-4,6-dibromo-1,2-benzisothiazole a substitutive nitration to form 5-hydroxy-6-bromo-4-nitro isomer occurs.[173]

The main product of the nitration of 2,1-benzisothiazole (thioanthranil) is 5-nitro-2,1-benzisothiazole (57%), however, alongside significant amounts of other isomers such as 7-nitro- (26%) and 4-nitro-2,1-benzisothiazole (17%) are formed.[174] The nitration of several other substituted thioanthranils has also been carried out.[174-177]

6-Nitrobenzothiazole is the main product of the nitration of benzothiazoles.[178-184] In several works it has been noted that along with this product some other hardly separable isomers are formed. Ward and Poshe[178] have developed a method to separate mixtures of isomers and showed that on nitration four isomers can be formed (Table 1).

Table 1. Isomers ratio in the nitration of benzothiazole with sulfuric-nitric mixture.

t, °C	Total yield, %	Yield of isomeric nitrobenzothiazoles, %			
		4-NO_2	5-NO_2	6-NO_2	7-NO_2
10±2	83.0	22.6	6.4	49.6	21.3
35±2	91.6	21.4	8.5	50.1	20.0

2-Substituted derivatives of benzothiazole are also nitrated principally into the position 6.[134,185-194] In 2-phenylsubstituted benzothiazoles the nitro group first enters into the benzothiazole cycle.[179,188,195] Like

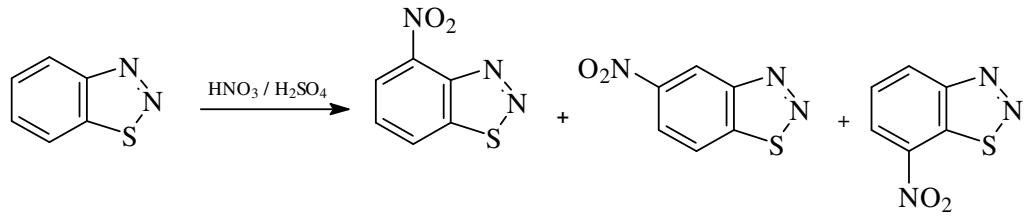
2-aminothiazoles, 2-aminobenzothiazoles first form with the sulfuric-nitric mixture nitramines, which later are rearranged to 2-amino-6-nitrobenzothiazoles. If the benzothiazole position 6 is already occupied by a rather strong electron-withdrawing substituent (NO_2, RSO_2), the nitro group enters into the position 4. Strong electron-donating substituents at the C-6 atom (NH_2, OCH_3) orient the incoming nitro group mainly to the position 7.[195-198] Nitration of other benzothiazole derivatives has also been carried out.[134,199-203]

As a result of the nitration of benzothiazolones-2[136,204,205] and benzo-thiazolylthiones-2[206,207] with the sulfuric-nitric mixture 6-nitro isomers are obtained.

The nitration of benzothiazoles with ethylnitrate[208] is analogous to that with the sulfuric-nitric mixture.

Unlike 1,2,3-benzoxadiazoles the existence of which is open to question,[209-211] 1,2,3-benzothiadiazoles are well known and their nitration has been described in the literature. On nitration of 1,2,3-benzothiadiazoles with sulfuric-nitric mixture Overberger and his colleagues obtained 4-nitro-1,2,3-benzothiadiazole.[212]

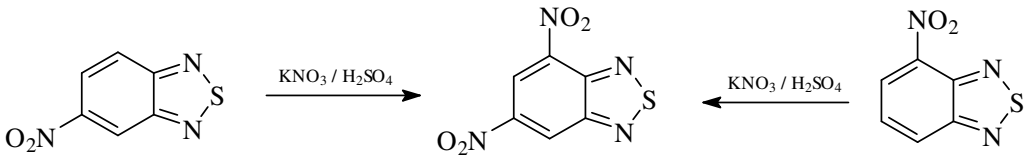
Freis and Reitz, using potassium nitrate in sulfuric acid on heating, have obtained two mononitrated products and assigned them the structures of 4- and 7-nitro isomers.[213] Later, this structure has been proved by a secondary synthesis,[214] and the other isomer turned out to be 5-nitro-1,2,3-benzothiadiazole.[215,216] On a more careful study all three isomers were found among the reaction products as shown in Scheme 18.[217]



Scheme 18

Substituted 1,2,3-benzothiadiazoles are nitrated to the position 5 or 7 if they are vacant.[198,218-220] The data[219] on the synthesis of 4-nitrosubstituted 1,2,3-benzothiadiazoles need to be checked.

Like benzofurazan, 2,1,3-benzothiadiazole is also nitrated to the position 4(7).[221,222] If there are electron-donating substituents (CH_3, OH, OCH_3) at the C-5 atom, 4-nitro derivatives are readily obtained in high yield.[223-230] The electron-withdrawing substituents (nitro group) at the same carbon atom direct the incoming nitro group to the 7(4) position.[231] So, on heating 5-nitro- and 7-nitro-2,1,3-benzothiadiazoles turn into 5,7-dinitro-2,1,3-benzothiadiazole (Scheme 19).



Scheme 19

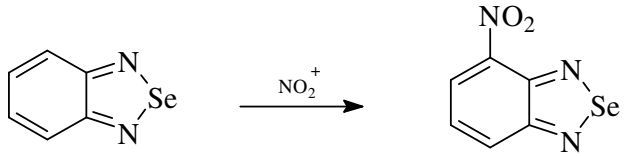
Electron-donating substituents at the C-4 atom direct the incoming nitro group to the position 5 or 7, however, the amount of 7-nitro isomer is higher that of 4-nitro isomer.[223-235] The direction of the nitration of

di- and tri-substituted 2,1,3-benzothiadiazoles is determined by the position and electron nature of substituents.[224,228,230,231,233,236-240] Substitutive (*ipso*) nitration of 4,7-dibromo-2,1,3-benzothiadiazole to form 4-bromo-7-nitro derivative has been reported.[236]

2.5. Benzoselenazoles, benzoselenodiazoles

Benzoselenazoles and their derivatives are also nitrated at the position 6.[241,242] The nitration can be accompanied by the oxidation of the azole ring and 6-nitrobenzoselenazolone-2 can be isolated as a by-product.

The nitration of 2,1,3-benzoselenodiazoles proceeds in the same way as with their thio analogs. For example, 2,1,3-benzoselenodiazole, in the sulfuric-nitric mixture, is transformed into a 4-nitro derivative in a yield of 90-98% (Scheme 20).[224,231,243-246]



Scheme 20

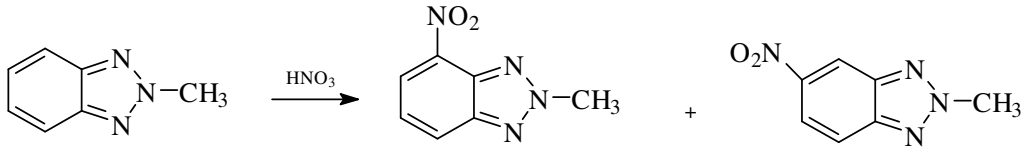
From the preparative point of view, especially when working with small amounts of the substrate, it is reasonable to use nitration with a mixture of sodium nitrate and sulfuric acid.[246,247] This method allows simultaneous introduction of two nitro groups into 4 and 7 positions of the annelated benzene ring. Under nitration of 5,6-disubstituted 2,1,3-benzothia- and 2,1,3-benzoselenodiazoles a regular enhancement of deactivating effect of the substituent on the reactivity of 2,1,3-benzothia- and 2,1,3-benzoselenodiazole is observed (in the following order - CH_3< Cl< NO_2). Under these conditions neither 5,6-dinitro-2,1,3-benzoselenodiazole or its thio analog undergo nitration.[247]

The direction of substitution upon the nitration of 2,1,3-benzoselenodiazole derivatives[231,248-250] is the same as that for their thio analogs.

2.6. Benzotriazoles

On nitration of unsubstituted benzotriazole the nitro group enters into the position 4(7).[43,251-256] Earlier the nitration of 1-methylbenzotriazole was considered to lead to 7-nitro isomer,[251,253] but later the formation of 1-methyl-4-nitrobenzotriazole was proved.[257] Other 1-substituted benzotriazoles are also nitrated to the position 4.[258-262] Arguments of Feldman and Usovskii in favor of their synthesis of 5-alkoxy-6-nitrobenzotriazoles turned out to be incorrect,[263] actually, the authors obtained 4-nitro isomers.[264] On boiling in the mixture of sulfuric and nitric acids 1-picrylbenzotriazole is nitrated into 5,7-dinitro-1-picrylbenzotriazole.[265] It is interesting to note that 6-nitro-1-picrylbenzotriazole in nitric acid gives 5,6-dinitro derivative whereas in the sulfuric-nitric mixture 5,6,7-trinitro derivative is formed. In fact, we can prove the formation of the latter only indirectly, since one of the nitro groups is easily substituted by the methoxy-group on dissolving the reaction product in methanol.[265] At the same time 1-(2,4-dinitrophenyl)-5-nitrobenzotriazole was obtained from 1-(2,4-dinitrophenyl)benzotriazole with the sulfuric-nitric mixture.[266] The main product of the nitration of 5-R-benzotriazole is 5-R-4-nitrobenzotriazole.[251,256,267,268]

Previously it was believed that only one 4-nitro isomer was obtained on nitration of 2-methylbenzotriazole,[269] however, later it was shown that the authors dealt with a mixture of 4- and 5-nitro isomers (Scheme 21).[270]



Scheme 21

Under nitration, benzotriazolyl-2 acetic acid gave only one 4-nitro isomer.[271] The same results were achieved with the nitration of 2-(4-nitrophenyl)benzotriazole.[272] Structure of the nitration products of some benzotriazoles has not been determined till the present time.[273]

The use of acetyl nitrate in place of sulfuric-nitric mixture as a nitrating agent leads to 1-nitro derivatives.[28] These compounds have also been obtained by the nitration of 1-chlorobenzotriazole with a silver nitrate complex with trimethylphosphite.[274]

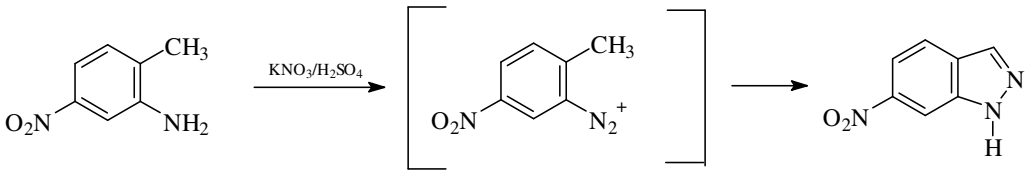
1-Hydroxybenzotriazole is nitrated with nitric acid in glacial acetic acid to give 6-nitro derivative, whereas the use of the sulfuric-nitric mixture does not lead to positive results.[275] 1- and 2-Aminobenzotriazoles react with nitronium tetrafluoroborate to form nitroimides isolated as alkali metal salts, involving no nitro group in the phenylene fragment.[109]

Quantum-chemical studies (MP2/cc-pVDZ treatment) of the reactivity of benzazoles indicate the preferred nitration of benzotriazoles and their protonated cations into the 4- and/or 7-position that is in good agreement with the experiment.[43]

3. Synthesis of nitrobenzazoles *via* heterocyclization

3.1. Nitroindazoles

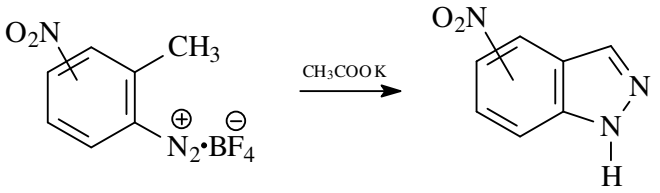
The reactions of heterocyclization are also of a wide preparative use in the synthesis of nitrobenzazoles. Here the nitro group first enters into one of the fragments of which the heterocyclic system is being built. In this case the presence of the nitro group often influences much the course of the process. The diazotization of *o*-toluidine results in the formation of indazole in a yield not more than 5%.[276] At the same time 4-nitro-2-aminotoluene in the same conditions transforms to 6-nitroindazole in high yield as shown in Scheme 22.[277-280]



Scheme 22

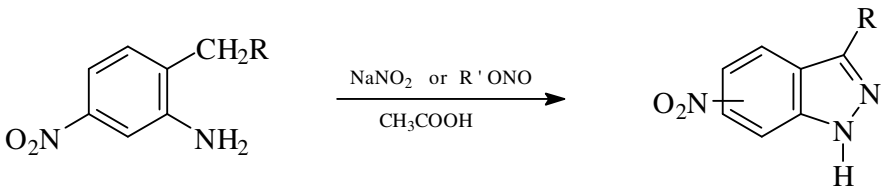
4-Nitro-,[281] 5-nitro-[278,279,282] and 7-nitroindazoles[279,281,283-286] are obtained in an analogous manner. The diazonium salt, obtained from 2-amino-6-nitro-*m*-xylol, gives a mixture of 7-methyl-4-nitro- and 7-methyl-6-

nitroindazoles. It should be noted that the reaction of diazotization of *o*-toluidines, having other substituents apart from the nitro group, is often used to obtain different nitroindazoles.[11,18-22,24,25,280,281,287,288] An original method of the synthesis of nitroindazoles involves the reaction of *o*-tolyldiazonium tetrafluoroborate with potassium acetate in the presence of crown-ethers (18-crown-6) (Scheme 23).[289-291] The reaction of cyclization has a high rate at room temperature (yield 60-90%).



Scheme 23

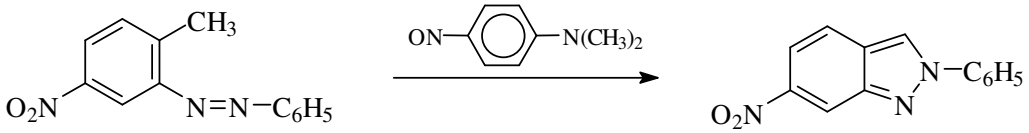
The diazotization of 2-alkylaminoanilines containing a nitro group in the phenyl ring leads to 3-substituted indazoles (Scheme 24).[11,17,283,292,293]



R = CH_3, CF_3, R' = Alk

Scheme 24

Diazoamino compounds are formed, and sometimes they can be obtained as intermediates.[277,283] In some cases nitroindazoles as by-products are determined on diazonation of non-nitrated *o*-toluidines with isoalkylnitrite.[294] 2-Phenylazo-4-nitrotoluene gives 2-phenyl-6-nitroindazole on boiling with *p*-nitroso-dimethylaminobenzene (Scheme 25).[295]

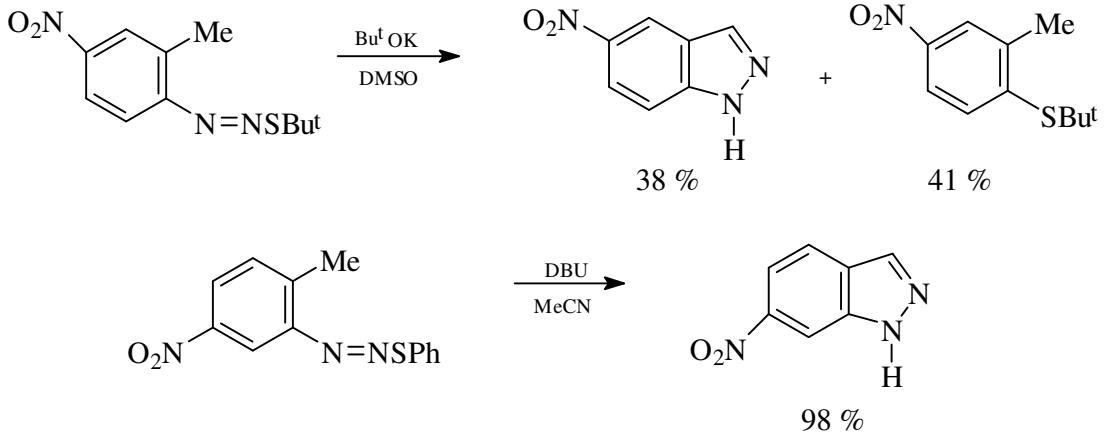


Scheme 25

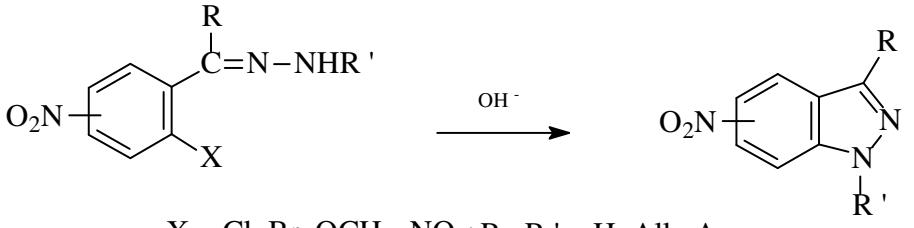
In this case the activation of the methyl group by the nitro group is a necessary reaction condition. Moreover, the nitro group has to be in the *ortho*- or *para*-position to the methyl group.[295,296] If it is in the *meta*-position, no indazole is formed. This is in good agreement with larger yields of 6-nitroindazole in comparison with the ones of 5-nitroindazole (Scheme 26).[297]

It means that more drastic reaction conditions are necessary for the cyclization with a methyl group in the *meta*-position.

Another widespread synthetic route to nitroindazoles is the reaction of intermolecular cyclization of *o*-substituted arylhydrazones as shown in Scheme 27.[10,298-305]

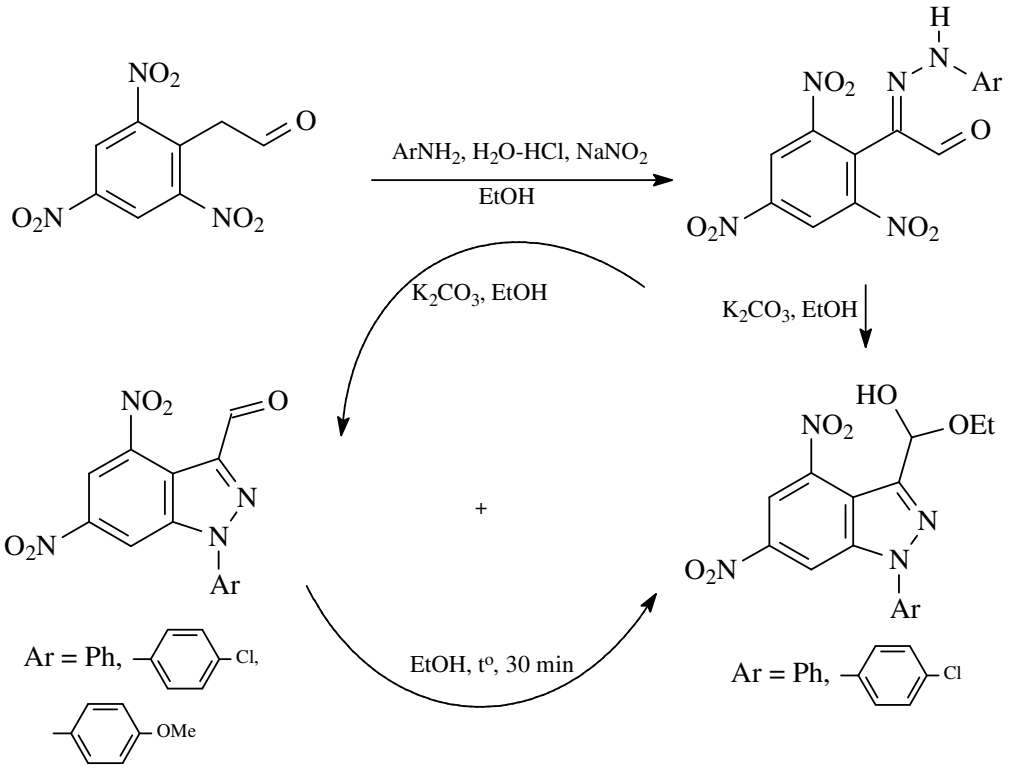


Scheme 26



X = Cl, Br, OCH_3, NO_2; R, R ' = H, Alk, Ar

Scheme 27



Scheme 28

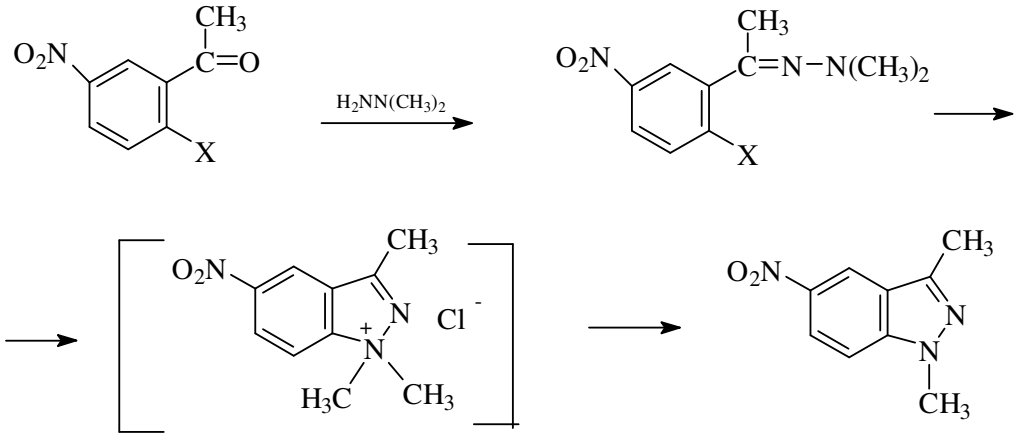
Besides, in this case the aromatic ring nitro group influences much the reaction pathway. 2-Bromobenzophenone, when heated up to 200 °C with hydrazinium hydrate, gives 3-phenylindazole in a very small yield; whereas bromo-5-nitrobenzophenone reacts at 140 °C to form 5-nitro-3-phenylindazole in a

yield of 65%.[298] In analogous conditions the corresponding indazole is obtained from 2-bromo-3,5-dinitrobenzophenone in high yield.[298]

1-Aryl-4,6-dinitro-3-formyl-1*H*-indazoles are obtained by treatment with alkaline metal carbonates of the corresponding hydrazones.[303-305] The latter are formed from picryl acetal aldehydes with aryldiazonium salts. Scheme 28 demonstrates that the cyclization of hydrazones occurs due to intramolecular nucleophilic substitution of the nitro group.

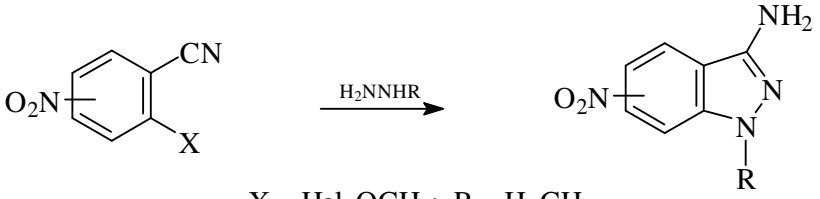
Stable semiacetals can be formed in parallel with dinitroformylindazoles in the absence of electrono-donating groups such as 4-MeO-C_6H_4, for example, in the *N*-aryl substituent. Dinitroformylindazoles readily transform to the corresponding semiacetals when boiled in ethanol for 30 min. At the same time, on heating of crystalline semiacetal (Ar = Ph) in the air (80 ^oC, 8 h) an ethanol molecule is abstracted and the corresponding dinitroformyl indazole is regenerated.[303,304]

The pathway of the reaction of 2-chloro-5-nitrobenzophenone with excess *N,N*-dimethylhydrazine is rather interesting (Scheme 29). In this case 1,3-dimethyl-5-nitroindazole is formed fast and in high yield.[306]



Scheme 29

When boiled with hydrazine hydrate, the esters of nitrated *o*-halogenobenzene acids transform to the corresponding nitroindazolones-3.[307,308] 2-Halogeno- or 2-methoxy-X-nitrobenzonitriles are also involved in an analogous reaction (Scheme 30).[309-315]



X = Hal, OCH_3; R = H, CH_3

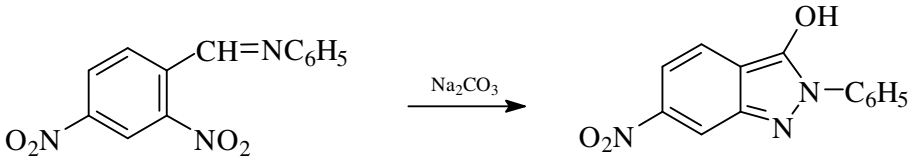
Scheme 30

It should be noted that in earlier publications the reaction products were wrongly assigned a structure of 2-cyano-4-nitrophenylhydrazine,[309-311] (see ref. 312).

In order to simplify the synthetic technology of 3-amino-5-nitroindazole and to improve the target product quality it is reasonable to use 2-cyano-4-nitroaniline. The latter is subjected to diazotization and the

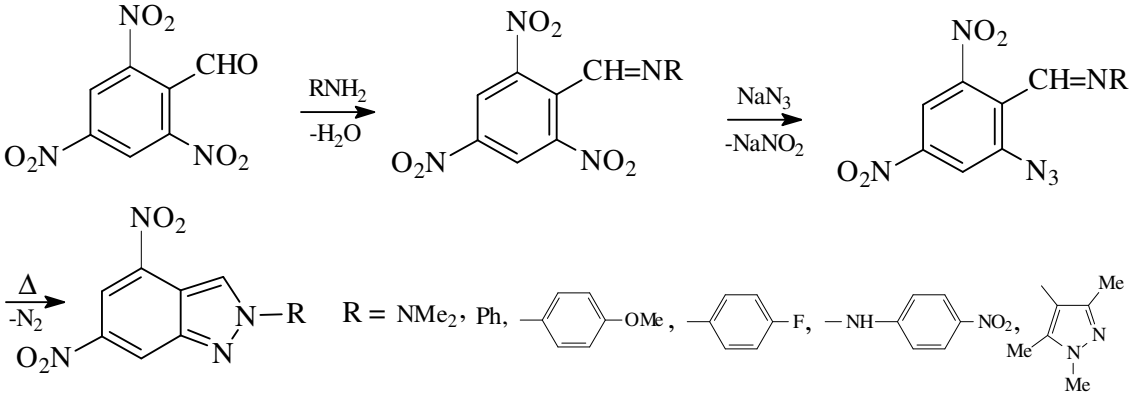
azo compound thus formed is reduced with simultaneous closure of the indazole cycle with sulfur dioxide in 5-15% sulfuric acid.[316]

There are some ways of preparing nitroindazoles by the reactions of heterocyclization and recyclization. For example, if some Schiff's bases containing a nitro group in the *ortho*-position to the methylene fragment are boiled in an ethanolic sodium carbonate solution, nitro derivatives of indazole are formed (Scheme 31).[286,317-319]



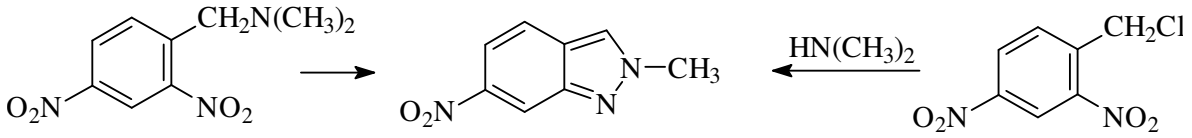
Scheme 31

Chemical utilisation of explosive 2,4,6-trinitrotoluene (TNT) can lead to 4,6-dinitroindazoles. An original method of preparing 2-substituted 4,6-dinitroindazole involves the formation of C-(2,4,6-trinitrophenyl)-*N*-R-azomethines from TNT or the product of its transformation, 2,4,6-trinitro-benzaldehyde with further regiospecific substitution of the nitro group under the action of NaN_3.[320] Thermolysis of the azides in ethylene glycol at 150-180 °C gives the corresponding 4,6-dinitroindazole derivatives in high yields (Scheme 32).[320]



Scheme 32

An interesting event of intermolecular cyclization has been found on nitrating 4-nitrobenzyldimethylaniline.[321] On standing the 2,4-dinitro-*N,N*-dimethyl-benzylamine formed spontaneously transforms to 2-methyl-6-nitroindazole, which is also obtained in the reaction of dimethylamine with 2,4-dinitrobenzylchloride (Scheme 33).

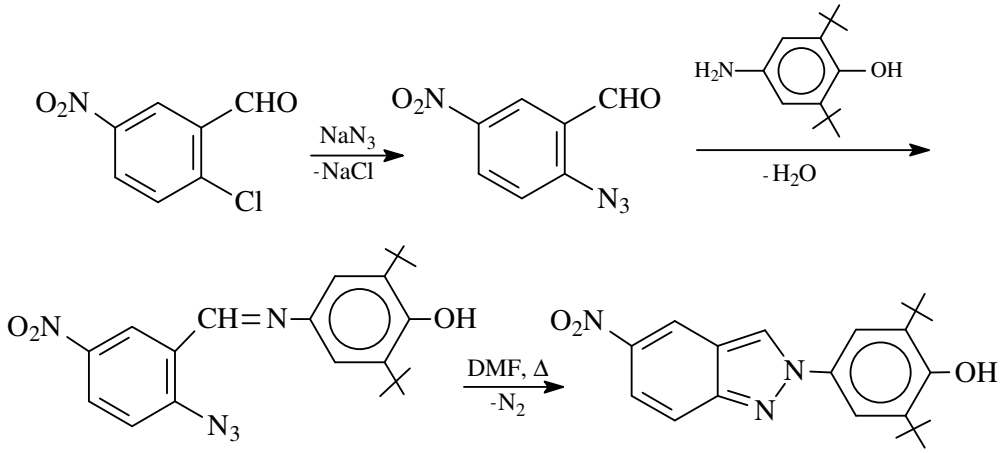


Scheme 33

Previously, 2-methyl-6-nitroindazole-*N*-oxide was suggested to be the reaction intermediate. However, it was not possible to determine its formation in the experimental conditions by means of IR and NMR

spectroscopy.[322] That is why a more probable reaction pathway seems to as follows. The reaction is catalyzed with bases and slowed down with acids that proves the suggested scheme.[322]

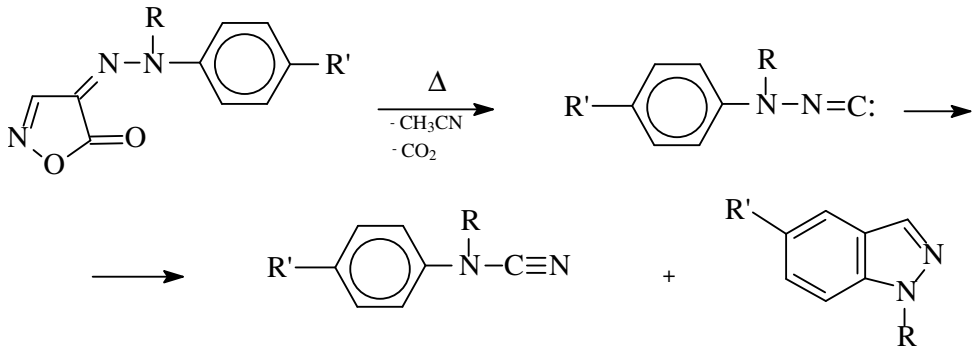
For the synthesis of antioxidants containing fragments of sterically hindered phenol and indazole a method involving thermal decomposition of 2-azidobenzylidenamines to 1,2-dichloro- or 1,2,4-trichlorobenzene and resulting in 2-substituted indazoles was used.[323] So, as seen from Scheme 34, 2-chloro-5-nitrobenzaldehyde gives the corresponding azidoaldehyde and 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-nitroindazole.



Scheme 34

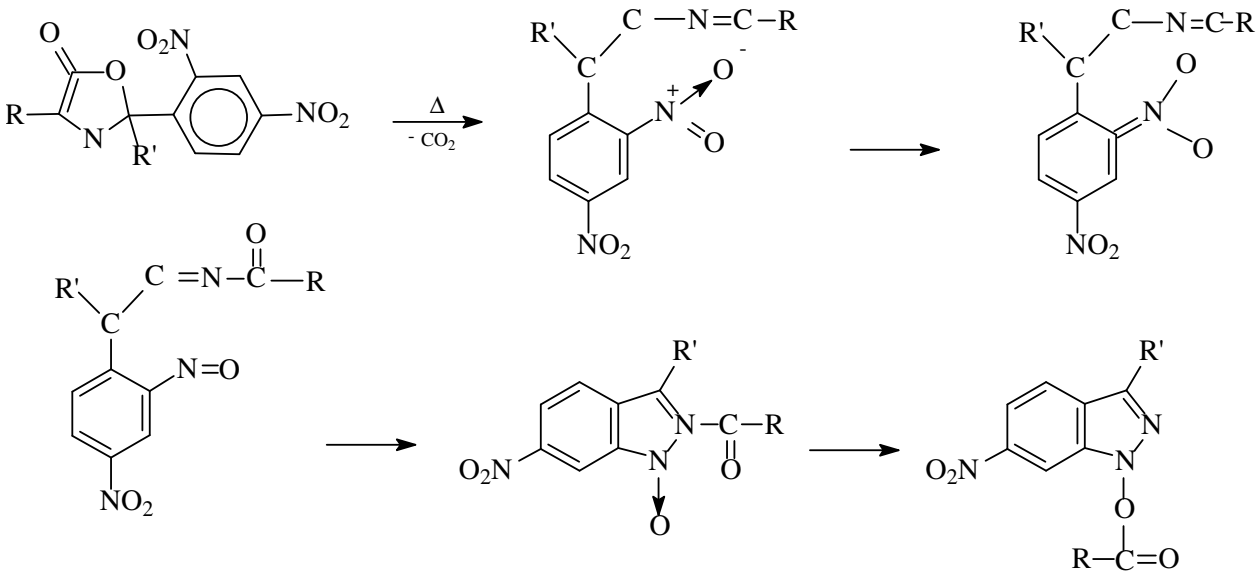
Intermediate azomethine could not be isolated. Upon heating of *N*-(2-azido-5-nitrobenzyliden)aniline in dimethylformamide affords to 2-phenyl-5-nitroindazole, the structure of which has been confirmed by X-ray diffraction.[323]

The pyrolysis of 4-arylhydrazono-3-methylisoxazolone-5 gives isocyanoamines, which undergo rearrangement to cyanoamides and corresponding indazoles (Scheme 35). Among other compounds 5-nitroindazole was obtained in an analogous way.[324]



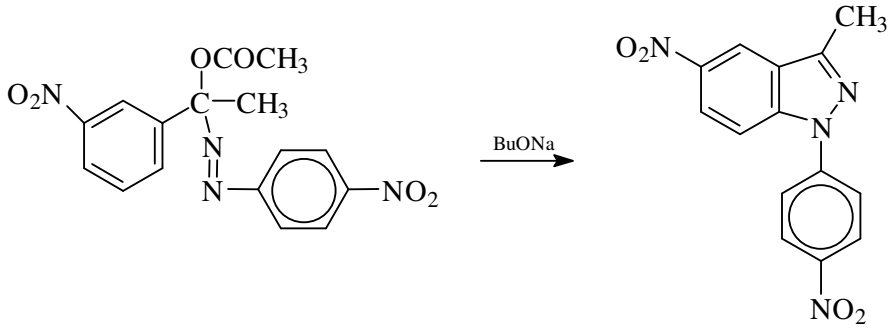
Scheme 35

2-(2,4-Dinitrophenyl)-3-oxazolinones-5 behave in a similar way on heating: the elimination of carbon dioxide leads to (2,4-dinitrophenyl)-nitrylimide from which (2-nitroso-4-nitrophenyl)-*N*-acylimine is formed after intermolecular oxygen migration. The *N*-acylimine undergoes cyclization to unstable 2-acetyl-6-nitroindazole-*N*-oxide with a fast migration of the acyl group to 3-substituted 1-acyloxy-6-nitroindazole (Scheme 36).[325]



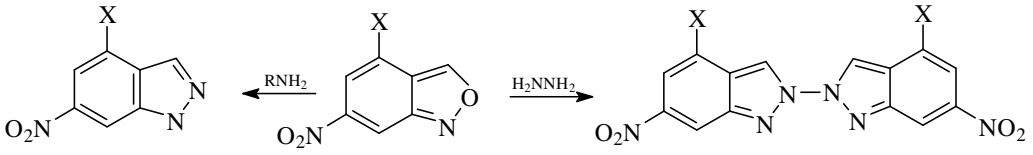
Scheme 36

α-Methyl-3-nitro-4-nitrophenylazobenzylacetate on heating with sodium butoxide transforms to 3-methyl-5-nitro-1-(4-nitrophenyl)indazole (Scheme 37), but the yield of the final product is 15% in this case.[301]



Scheme 37

6-Nitroanthranils react with primary amines or with phenylhydrazine to form 2-substituted 6-nitroindazoles.[326,327] 6,6'-Dinitro-2,2'-bis-indazolyls were obtained in the reaction with hydrazine (Scheme 38).[326,327]

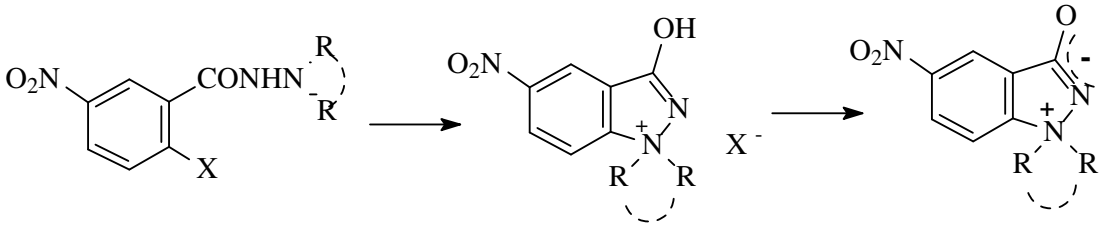


X = H, Cl, Br, I; R = C_6H_5, C_6H_5NH

Scheme 38

Nitroindazolones are prepared on heating from the corresponding 2-bromo-3-nitrobenzoates with hydrazine hydrate.[328]

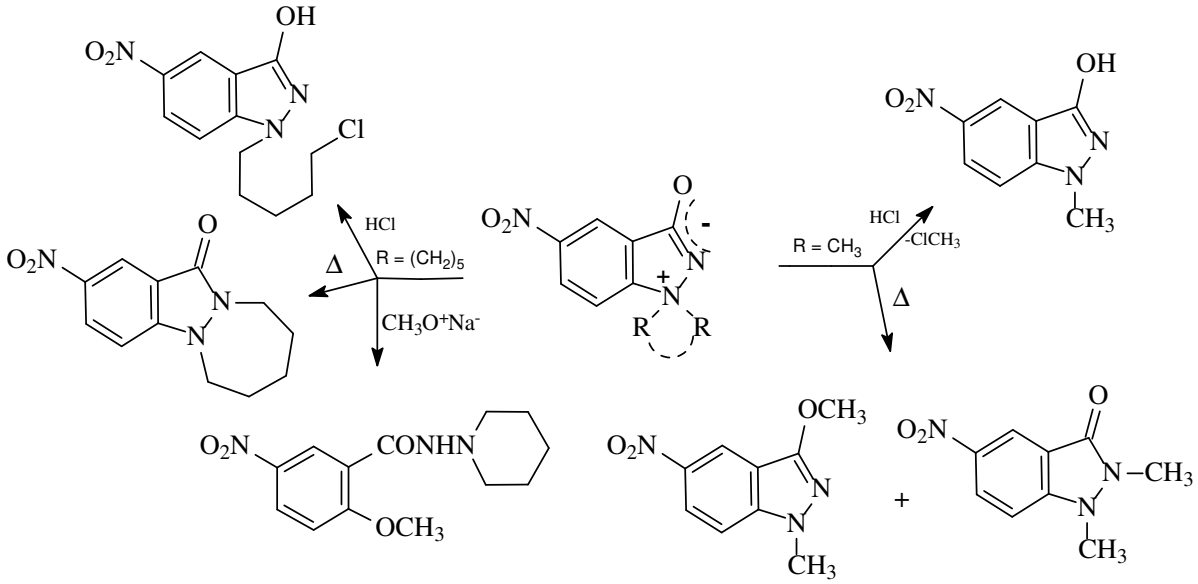
Stable nitroindazolyl-3 oxides (betaines) were obtained in 80-90% yield from the corresponding 2-halogenobenzohydrazides (Scheme 39), moreover, from chlorobenzohydrazides the betaines are formed in more rigorous conditions.[329]



X = F, Cl; R = CH_3; R = $(CH_2)_5$

Scheme 39

The treatment of betaines with concentrated sulfuric acid leads to the corresponding derivatives of 5-nitroindazole (products of alkylhalogenides elimination). Heating of betaines results in other nitroindazoles: a product of Steven's rearrangement or a mixture of *N,O*- and *N,N*-alkyl shift-products as shown in Scheme 40.[329]



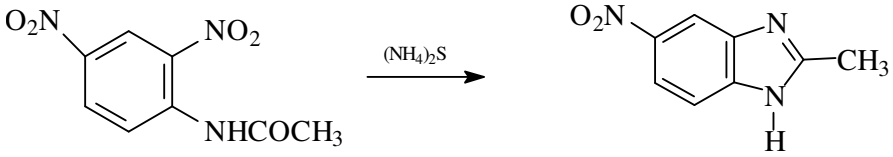
Scheme 40

3.2. Nitrobenzimidazoles

Benzimidazoles containing a nitro group in the arylene fragment are obtained in the reaction of carboxylic acids or their derivatives with nitro-substituted 1,2-diaminobenzenes. This method is especially often used for the synthesis of 4-nitro- and 7-nitrobenzimidazoles, since the latter cannot be obtained by direct nitration of benzimidazoles. In most cases the reaction is carried out in the presence of HCl (the Phillips reaction).[46,47,52,53,75,79,100,330-341] Nitrobenzimidazoles can also be obtained by simple boiling of 1,2-phenylendiamine nitro derivatives with excess lower aliphatic acids (formic or trifluoroacetic acid, for example).[61,342-345] Sometimes nitrobenzimidazoles can be obtained by heating the nitrated

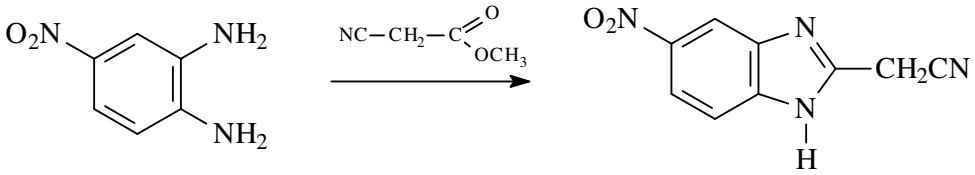
o-phenylendiamines, but in this case more rigorous conditions should be applied (the yields are significantly lower).[50,346-348] The cyclization is even a more difficult process when aromatic or heterocyclic acids are used.[346] In these conditions polyphosphoric acid is used as a condensing agent. [330-341] Derivatives of acids may be employed in the synthesis of nitrobenzimidazoles in place of acids themselves. More often anhydrides or chloroanhydrides are used for this purpose.[44,45,50,59,257,342,343-345,350-353] Usually this reaction is carried out in two stages: acylation of the corresponding 1,2-diaminonitrobenzenes with anhydrides or chloroanhydrides of carboxylic acids followed by cyclization of the forming *o*-aminoacylanilines.[45,50,257,350-354] 1,2-Diaminobenzene nitro derivatives react with iminoesters,[59,355-363] nitriles,[361,364] hydrazides[365] and *o*-esters[366,367] to form nitrobenzimidazoles.

A reaction of 4-nitro-1,2-phenylendiamine with benzotrichloride in the presence of sodium methylate[368] has been described. In this case 2-phenyl-5(6)-nitrobenzimidazole is obtained without preliminary extraction of the *o*-ester of benzoic acid. Sometimes acylated polynitroanilines, with one of the groups in the *ortho*-position to the amino group, are used as the initial products. On partial reduction of such compounds the cyclization to benzimidazoles takes place.[85,369] For example, the reduction of 2,4-dinitroacetanilyde with ammonium sulfide has afforded 2-methyl-5(6)-nitrobenzimidazole (Scheme 41)[85].



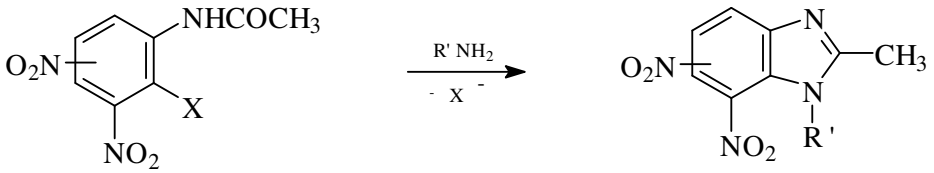
Scheme 41

5(6)-Nitro-2-cyanomethylbenzimidazole, an intermediate in the synthesis of cyanine dyes, was prepared from 1,2-diamine-4-nitrobenzene and methyl cyanoacetate in nitrobenzene (Scheme 42).[370]



Scheme 42

The introduction of the nitro group in azoles leads to a long-wave shift of the visible absorption maximum and an enhancement of the sensitizing properties of cyanine dyes. A long-wave shift of the sensitivity of photographic materials is observed as well.[370]



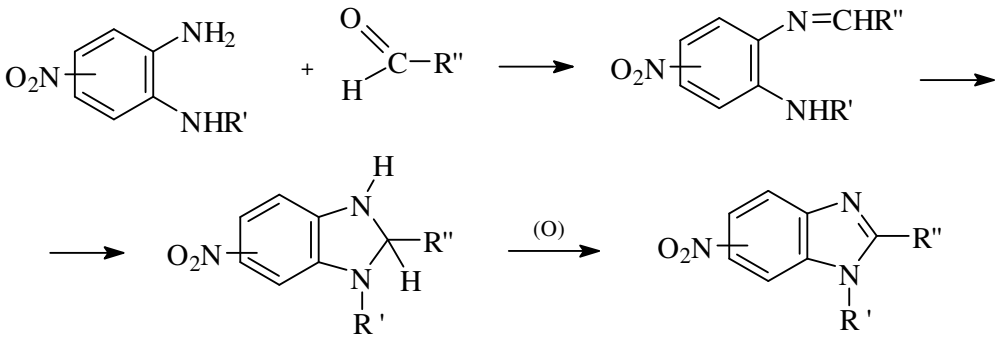
X = NO_2, Cl

Scheme 43

7-Nitrobenzimidazoles can be obtained in the reaction of primary amines with 2-R-3-nitroacetanylides (Scheme 43). On nucleophilic substitution the forming 2-NHR-3-nitroacetanylides transform to benzimidazoles without isolation.[371]

An interesting reaction has been described by Simonov and his colleagues.[372] Studying the reaction of some aromatic *o*-dinitro- and trinitrocompounds with benzylamine they have discovered that under special conditions the reaction of substitution of the nitro group with the benzylamine-group is accompanied by reduction of the second nitro group and cyclization into 2-phenylbenzimidazole derivatives. In this case benzyl alcohol forming from benzylamine serves as a reducer. In this way they obtained 4,5-dimethoxy-7-nitro-2-phenylbenzimidazole in 89% yield from 3,4,5-trinitroveratrole.[372]

The reaction of 1,2-diaminonitrobenzenes with aldehydes is a widely accepted synthetic route to nitrobenzimidazoles.[57,62,63,66,351,373-384] This reaction passes sequentially through a stage of the formation of azomethines (Schiff's base) and benzimidazolines. On oxidation the latter forms the corresponding benzimidazole derivatives (Scheme 44).

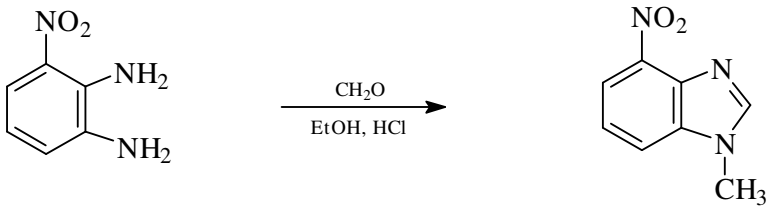


R' = H, Alk, Ar; R" = Alk, Ar, Hal

Scheme 44

Copper (II) salts are often used here as oxidizer,[62,63,66,351,375-380,382-384] and atmospheric oxygen can also be used for this purpose.[384] For the preparation of nitrobenzimidazole derivatives the corresponding Schiff's bases are often boiled.[57,62,63,66,373,374,381]

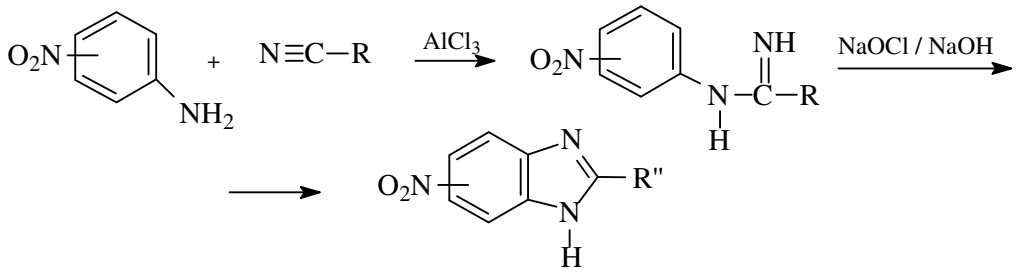
An easy and convenient method has been employed for the synthesis of 1-methyl-4-nitrobenzimidazole (Scheme 45).[385]



Scheme 45

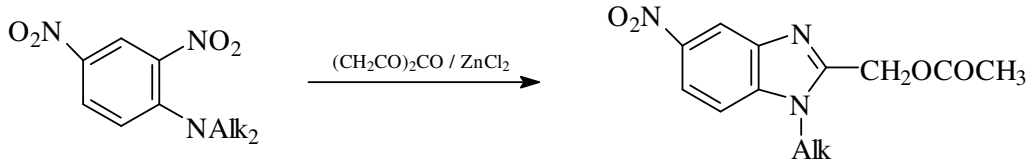
A one-stage reaction of 3-nitro-1,2-phenylenediamine with formaldehyde in an ethanol solution of hydrochloric acid leads to the formation of nitrobenzimidazole in high yield (77%).[385]

Nitroanilines react with organic cyanides in the presence of dry aluminum chloride. Under the influence of sodium hypochlorite in the presence of a base, the resultant amidines undergo cyclization to the corresponding benzimidazoles (Scheme 46).[386-389]



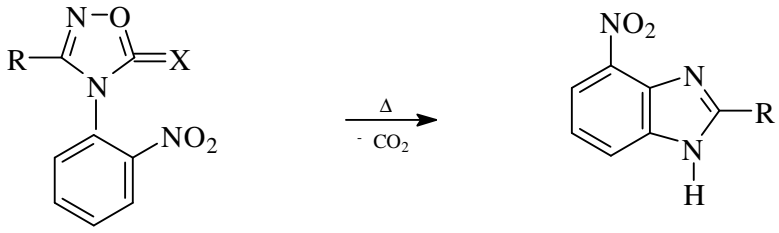
Scheme 46

2,4-Dinitroalkylanylines react with acetic anhydride in the presence of zinc chloride to form 2-acetoxymethyl-1-alkyl-5-nitrobenzimidazoles (Scheme 47).[390]



Scheme 47

On thermal decomposition 3-substituted-4-(2-nitrophenyl)-1,2,4-oxadiazolones-5 form 2-substituted-4-nitrobenzimidazoles (Scheme 48).[391-395]

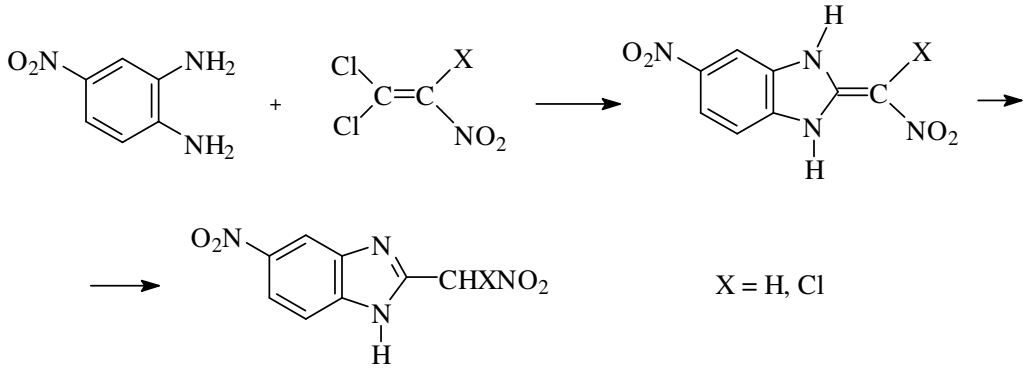


X = O, S

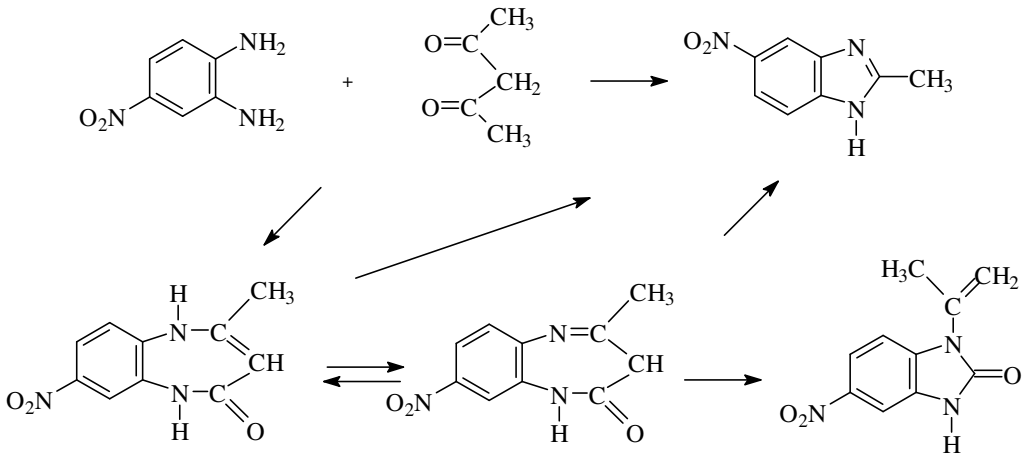
Scheme 48

1,1-Dichloro-2-nitroethylene and trichloronitroethylene react with 4-nitro-1,2-phenyldiamine to afford nitrobenzimidazoles with the nitro group in both the phenylene fragment and side-chain.[396] Evidently, the reaction mechanism consists in nucleophilic substitution of halogen atoms at the multiple bond with subsequent prototropic rearrangement to a benzimidazole system as shown in Scheme 49.

2-Methyl-5-nitrobenzimidazole is formed on heating 4-nitro-1,2-phenylendiamine and its derivatives with the ester of acetoacetic acid (Scheme 50).[397,398] Depending on the experimental conditions, isomeric 8-nitro-4-methyl-2,5-dihydro-1*H*-1,5-benzodiazepinone-2 and 8-nitro-4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepinone-2 easily transforming into each other and 5-nitro-1-isopropenylbenzimidazolone-2 can be obtained (in this case).

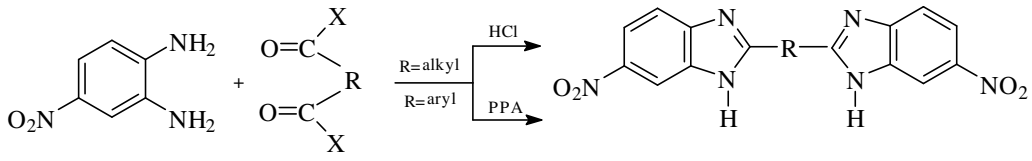


Scheme 49



Scheme 50

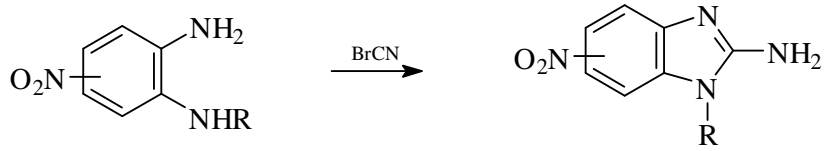
In a similar manner the bis(5-nitrobenzimidazolyl-2) derivatives formed were obtained (Scheme 51).[399]



X = NH_2, OH; R = alkyl, aryl

Scheme 51

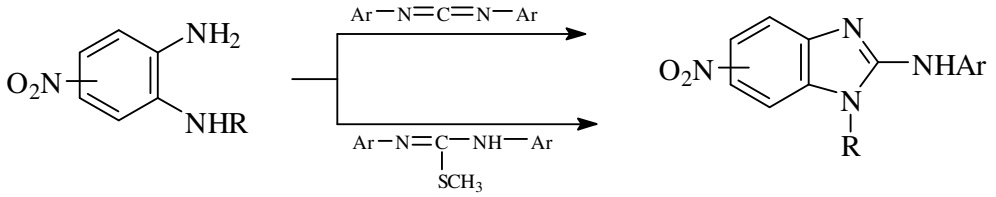
In the synthesis of aromatic derivatives polyphosphoric acid is used.[399] A synthesis of 1-(5-nitrobenzimidazolyl)-3-benzimidazolyl-2-oxapropane by the reaction of 4-(2-benzimidazolyl)-2-oxabutanoic acid hydrochloride and 4-nitro-*o*-phenylendiamine has been reported.[400]



Scheme 52

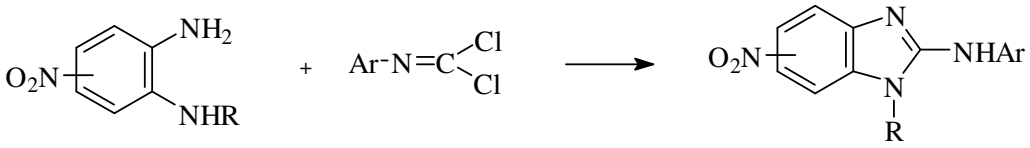
Like unsubstituted *o*-phenylendiamine, its nitro derivatives react with bromocyane to form the corresponding 2-aminobenzimidazoles (Scheme 52).[401-404]

Diarylcarbodiimines or derivatives of *S*-methylurea react with nitrated 1,2-diaminobenzenes in a similar way to lead to 2-arylaminobenzimidazoles (Scheme 53).[405,406]



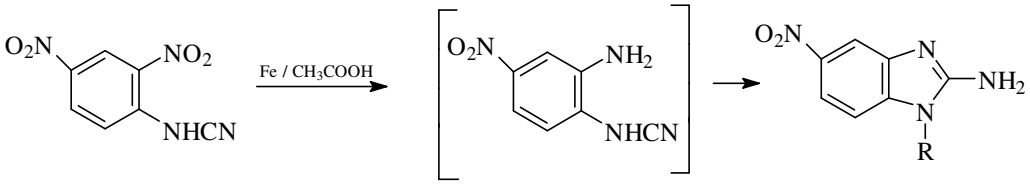
Scheme 53

The same products can be obtained using carboimidoyldichlorides (Scheme 54).[407]



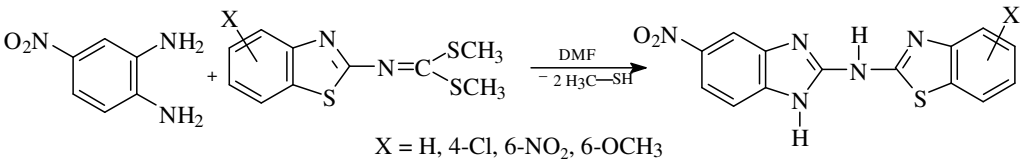
Scheme 54

A convenient synthesis of 2-amino-5(6)-nitrobenzimidazole involves reductive cyclization of 2,4-dinitrophenylcyanamide (Scheme 55).[408,409]



Scheme 55

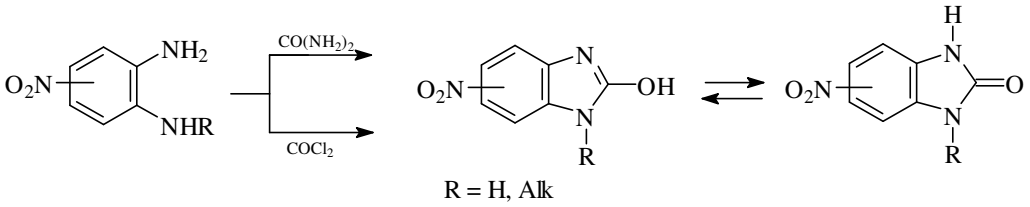
2-(5-Nitrobenzimidazolyl-2-amino)-benzothiazoles are obtained from *o*-phenylenediamines and *S,S*-dimethyl-*N*-(-2-bensothyazolyl)-carbonimidodithioates in dimethylformamide (Scheme 56).[410]



Scheme 56

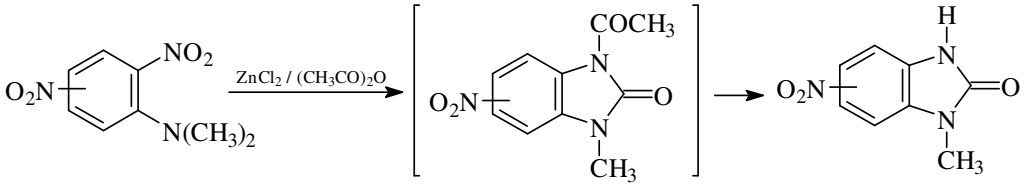
The most widely spread synthetic route to benzimidazolone-2 nitro derivatives is provided by the reaction of *o*-phenylenediamine with phosgene or urea (Scheme 57).[105,406,408,409,411-413]

1-Methyl-5- or 6-nitro derivatives were obtained as a result of intermolecular cyclization of *N,N*-dimethyl-2-nitro-5- or 5-nitroaniline with zinc chloride in acetic anhydride (Scheme 58).[412]



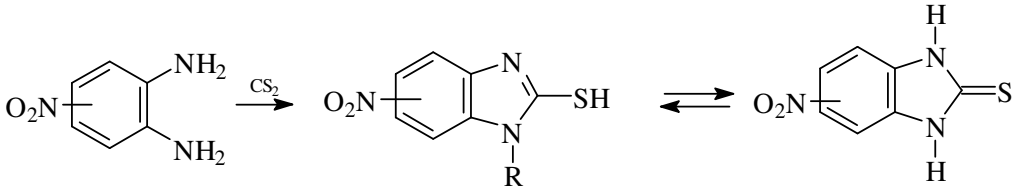
R = H, Alk

Scheme 57



Scheme 58

Benzimidazolthione-2 nitro derivatives are obtained in a similar way under the influence of CS_2 (Scheme 59).[100,408,409,414]



Scheme 59

A simple method for the preparation of 5-nitrobenzimidazolone-2, based on chemical[408,409] or electrochemical reduction of 2,4-dinitrophenylurea,[415] has been proposed. The electrochemical reaction is carried out in a cell with an interelectrode space in aqueous solution of mineral acid at 85-95 ^{o}C in the range of potentials from 0 to –200 mV relative to the silver electrode.

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