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Dear Reader,

The Volume 6 (2002) keeps the international standard of THS series and contains fourteen Chapters, covering the synthesis and reactivity, as well as some medicinal properties of different heterorings. In various way, Austria, Egypt, France, Hungary, Italy, Portugal, and Spain 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.

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ENANTIOSELECTIVE RING EXPANSION VIA AZIRIDINIUM INTERMEDIATES. SYNTHESIS OF SUBSTITUTED PIPERIDINES FROM SUBSTITUTED PYRROLIDINES. SYNTHETIC APPLICATIONS

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Abstract. Enantioselective ring expansion of 2-(halomethyl)pyrrolidines and 2-(hydroxymethyl)pyrrolidines to 3-substituted piperidines via aziridinium intermediates implies a two step process: displacement of a leaving group by the nitrogen of the pyrrolidine via an internal backside nucleophile substitution (S_Nib) mechanism and an attack of a nucleophile on the formed aziridinium by a S_N2-type of displacement. This rearrangement is used to synthetize a great variety of biologically active compounds in a very efficient way.

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1. Introduction

Functionalized piperidines are among the most ubiquitous heterocyclic building blocks of natural and synthetic compounds with important biological activities. Therefore, a huge amount of synthetic effort has been spent on the preparation of these systems. With respect to biologically active target molecules there is an increasing interest in the diastereo- and enantioselective synthesis of piperidines. The most important process for obtaining substituted piperidines from pyrrolidines is probably a ring expansion via aziridinium intermediates.

2. Mechanism

In 1947, it was noticed that β-chloroamine hydrochlorides undergo a rearrangement under basic conditions. The products from hydrochlorides 1 and 2, are identical and possess structure 3. This rearrangement is believed to occur through the cyclic aziridinium intermediate A (Scheme 1).

This behaviour of β-chloroamines suggested the interesting possibility that 2-chloromethyl heterocyclic amine compounds might undergo a similar rearrangement to produce ring expanded products. This hypothesis was verified when 1-ethyl-2-(chloromethyl)pyrrolidine hydrochloride 4 was treated with sodium hydroxide.
The free base obtained was not the pyrrolidine derivative 5 but the isomeric 1-ethyl-3-chloropiperidine 6.\textsuperscript{5a} This rearrangement proceeds through intermediate B which is attacked at the more substituted carbon by the nucleophile (Scheme 2).

It was only in 1966 that the isolation of the aziridinium intermediate C as the perchlorate salt, as well as its independent synthesis were reported.\textsuperscript{6} The reaction of 1-azabicyclo[3.1.0]hexane 7 in dry ether with ethyl perchlorate in absolute ethanol produced a semi-solid, which gave a \textsuperscript{1}H NMR spectrum similar to the \textsuperscript{1}H NMR spectrum of the oil obtained from the reaction of N-ethyl-3-chloropiperidine 6 with silver perchlorate in dry acetone consistent with the aziridinium perchlorate salt C (Scheme 3).

To verify that aziridinium C was the intermediate in the rearrangement of C(2)-substituted pyrrolidines to C(3)-substituted piperidines, the aziridinium intermediate C was heated in the presence of NaOH. Under these conditions, the 2-(hydroxymethyl)pyrrolidine 8 and the 3-hydroxypiperidine 9 were formed in a ratio 68/32 in 68\% yield. Furthermore, treatment of the N-ethyl-3-chloropiperidine hydrochloride 10 with NaOH led to a mixture of 8 and 9 in a similar ratio of 68/32. It should be pointed out that N-ethyl-2-(chloromethyl)pyrrolidine 5 cannot be isolated pure as it rearranged easily into 6. But, in contrast, the 3-chloropiperidine 6 did not rearrange to 5.\textsuperscript{6} It is worth noting that this rearrangement takes place under thermodynamic control (Scheme 4).

Synthetic, kinetic and stereochemical evidence has confirmed that 5 reacts with nucleophiles \textit{via} a two steps neighbouring group participation mechanism involving the intervention of the bicyclic aziridinium ion intermediate B (Scheme 4), formed by the initial rate-determining displacement of chloride by nitrogen \textit{via} an “internal” backside nucleophilic substitution (S\textsubscript{N}ib) mechanism.
The second step involves the attack of a nucleophile on \( B \) by a \( S_N2 \)-type of displacement to give 5- and 6-membered ring products. It is worth noting that the entire process is stereospecific since complete retention of configuration is observed when \((S)-4\) was converted to \((R)-10\) by simple heating or to \((R)-9\) when treated with NaOH, thereby ruling out a dissociated carbocation intermediate (Scheme 5). 

3. Synthesis of 3-halogenopiperidines

2-, 4-, 5- or 6-Alkyl substituted 3-halogenopiperidines can be obtained stereoselectively from the corresponding unstable alkyl \( N \)-alkyl-2-(halogenomethyl)pyrrolidines. \(^8\) Pyrrolidines 11 and 12 rearranged readily when dissolved in chlorinated solvents to form the corresponding thermodynamically stable piperidines 13 and 14 in quantitative yield (Scheme 6). \(^8f\)

5,5-Disubstituted-3-chloropiperidines can be obtained from 2,2-disubstituted-4-pentenylamines. It has been found that the addition of bromine at room temperature to a dichloromethane solution of 2,2-diphenyl-4-pentenylamine 15 gave fair to excellent yields of a bromohydrobromide salt to which the five-membered structure 16 was assigned. Treatment of this salt with two equivalents of sodium hydride in DMF gave the aziridine 17 which subjected to the action of dry hydrogen bromide led to the six-membered structure 18 in 63% yield (Scheme 7). \(^9\)
A stereospecific nucleophilic substitution via anchimeric assistance by the nitrogen of 2-(α-iodoalkyl)-
N-methoxymethylene oxypyrrolidine 19 was observed during its thermolysis at 55 °C as the
dialkylsubstituted 3-iodopiperidine 20 was isolated in 24% yield along with butyrolactone 21 in 60% yield
(Scheme 8). This stereoselective rearrangement was also used to prepare trisubstituted
3-bromopiperidines. When pyrrolidinium salt 22 was treated with KCN in a biphasic system
(THF/H₂O:1/1), the 2-cyano-5-bromopiperidine 24 was obtained in good yield via pyrrolidine 23 and
aziridinium intermediate D (Scheme 9).
Bicyclic compounds such as the substituted 1-azabicyclo[3.3.1]nonane 27 were obtained from the thermal rearrangement of 7a-trichloromethyl-2,3,5,6,7,7a-hexahydro-1H-pyrrolizidine 26 which was synthesized from 25. Taking into account of the difficulties involved in the synthesis of 1-azabicyclo[3.3.1]nonanes 28\textsuperscript{12a} and analogues,\textsuperscript{12b} the readily availability of compound 25 and related heterocyclic enamines, the ring expansion rearrangement provides an easy access to compounds of type 28 after reduction of the rearranged product by LiAlH\textsubscript{4} (Scheme 10).

The rearrangement of N-ethyl-2-(chloromethyl)pyrrolidines to 3-chloropiperidines has been used to synthesize compounds 30a-b, precursors of N-methyl-D-aspartic acid (NMDA) non-competitive antagonists. Haloamines 29a and 29b were thermally rearranged to the thermodynamically favored azabicyclo[3.1.1]octane 30a and 30b. This process was more efficient in the presence of NaI or KBr in acetone. It is worth noting that the chloride 29c failed to rearrange under these conditions (Scheme 11).\textsuperscript{13}
As the ring expansion of C(2)-substituted pyrrolidines is highly stereoselective, enantiopure 3-halopiperidines could be prepared from (S)-prolinol. For example, alkylation of (S)-prolinol with ethyl iodide gave (S)-8, which was treated with thionyl chloride in chloroform to give (S)-4, which rearranged to (R)-10 upon heating. The free base (R)-6 was isolated from the hydrochloride salt after treatment with NaHCO₃ (Scheme 12).  

\[ \text{(S)-Prolinol} \xrightarrow{\text{EtI, NaOH}} \text{(S)-8} \xrightarrow{\text{SOCl₂, CHCl₃}} \text{(S)-4} \xrightarrow{\Delta} \text{(R)-6} \xrightarrow{\text{NaHCO₃}} \text{(R)-10} \]

Scheme 12

This procedure was used to synthesize 3-halogenopiperidines 32 and 34 which are respectively the precursors of cardiovascular compounds 14 and troglitazone analogues 15 (Scheme 13).
A similar reaction was observed with \(N\)-benzyl prolinol (S)-35, which was smoothly converted to 3-bromopiperidine (\(R\))-37 by using thionyl bromide in the presence of DMF. The addition of DMF as a catalyst was found to accelerate significantly the reaction through a Vilsmeier-Haack type \(\text{SOBr}_2\)-DMF complex. Cyclohexane was the solvent of choice to achieve this reaction. On the contrary, polar solvents such as dichloromethane were avoided because undesired side reactions were observed. As usual, the neighbouring amino group facilitates the reaction rate and intermediate 36 was transformed to aziridinium salt F to produce (\(R\))-37 (Scheme 14).\(^{16}\)

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \quad \text{Ph} \\
\text{(S)-35} & \quad \xrightarrow{\text{SOBr}_2, \text{DMF}, \text{cyclohexane} \ 80\%} \quad \text{Br} \\
& \quad \text{Ph} \quad \text{Br} \\
& \quad \text{36} \quad \rightarrow \quad \text{37} \\
\end{align*}
\]

**Scheme 14**

Another reagent that allowed the formation of 3-chloropiperidines from \(N\)-alkyl prolinols is mesyl chloride in the presence of triethylamine in THF.\(^{17,18}\)

Thus, treatment of \(N\)-benzyl prolinol (S)-35 with mesyl chloride in the presence of triethylamine in THF, led to 3-chloropiperidine (\(R\))-39 in 77% yield. Under these conditions, no trace of 3-mesyloxypiperidine (\(R\))-40 was detected. It is postulated that mesylate 38 is formed and that internal assistance of the nitrogen produces the aziridinium salt G which was attacked by the more nucleophilic anion present in the reaction medium e.g. the chloride anion (\textit{versus} mesylate anion) (Scheme 15).\(^{17}\)

\[
\begin{align*}
\text{Bn} & \quad \text{OH} \quad \text{Bn} \\
\text{(S)-35} & \quad \xrightarrow{\text{MsCl, Et}_3\text{N}, \text{THF, reflux} \ 77\%} \quad \text{Cl} \\
& \quad \text{Bn} \quad \text{Cl} \\
& \quad \text{39} \quad \rightarrow \quad \text{38} \\
\end{align*}
\]

**Scheme 15**
By using this latter procedure, the enantioselective synthesis of the 2,3-disubstituted piperidine (2S,3R)-42 was achieved from prolinol (2S,6R)-41 in quantitative yield and the 3,4,5-trisubstituted piperidine 44 was obtained from prolinol 43 in 67% yield (Scheme 16).

(2S,6R)-41

\[
\overset{\text{MsCl}}{\text{Ph}} \overset{\text{Et}_{3}N}{\text{Ph}} \overset{100\%}{\rightarrow} \overset{\text{Cl}}{\text{Ph}} \overset{\text{H}_{2}N}{\text{H}_{2}N} \overset{\text{H}_{2}O}{\text{H}_{2}O}
\]

(2S,3R)-42

(2S,3R,4S)-43

\[
\overset{\text{MsCl}}{\text{Ph}} \overset{\text{Et}_{3}N}{\text{Ph}} \overset{67\%}{\rightarrow} \overset{\text{Cl}}{\text{Ph}} \overset{\text{H}_{2}N}{\text{H}_{2}N} \overset{\text{H}_{2}O}{\text{H}_{2}O}
\]

(3S,4R,5S)-44

Scheme 16

(3S,4R,5S)-45

\[
\overset{\text{1/ MsCl}}{\text{DCE}} \overset{84\%}{\rightarrow} \overset{\text{2/ Et}_{3}N}{\text{Ph}} \overset{\text{Ph}}{\text{Ph}} \overset{\text{CO}_{2}^\text{Bu}}{\text{CO}_{2}^\text{Bu}} \overset{\text{Cl}}{\text{C}} \overset{\text{Ph}}{\text{Ph}} \overset{\text{F}}{\text{F}}
\]

(3S,4R,5S)-46

71%

\[
\overset{n\text{-Bu}_{3}SnH}{\text{AlBN}} \text{Ph} \overset{\text{Ph}}{\text{Ph}} \overset{\text{CO}_{2}^\text{Bu}}{\text{CO}_{2}^\text{Bu}} \overset{\text{Cl}}{\text{C}} \overset{\text{Ph}}{\text{Ph}} \overset{\text{F}}{\text{F}}
\]

(3S,4R)-47

(3S,4R)-(-)-Paroxetine

Scheme 17
This procedure was used to synthesize (–)-paroxetine which is a selective serotonin reuptake inhibitor (SSRI). This drug (Paxil®, Deroxat®) is used in the treatment of depression, obsessive compulsive disorder and panic disorder. The precursor of (–)-paroxetine, 3-chloropiperidine 46 was obtained from prolinol 45 which was synthesized from L-pyroglutamic acid. When the prolinol derivative 45 was treated with MsCl in 1,2-dichloroethane and then refluxed in the presence of Et$_3$N, 3-chloropiperidine 46 was obtained in 84% yield. After selective reduction of the chloride by Bu$_3$SnH in the presence of AIBN, the disubstituted piperidine 47 was isolated and transformed to (–)-paroxetine (Scheme 17).

When aziridinium intermediates were treated with tetraalkylammonium halides, they were transformed to 3-halogenopiperidines. The ring opening of 1-aziridinium[3.1.0]hexane intermediate H by chloride ion is the key step in the synthesis of (±)-virantmycine, an antibiotic agent. This intermediate was prepared from azide 48 via the aziridino carboxylic acid 49. The racemic aziridine 49 was treated with trifluoroacetic acid in the presence of tetraethylammonium chloride to produce (±)-virantmycine (Scheme 18).

4. Synthesis of 3-oxygenated and 3-amino-piperidines derivatives

3-Hydroxy-piperidine derivatives as well as 3-amino piperidine derivatives are present in a great number of natural products and/or biologically active compounds. The reaction of N-alkyl-2-(halogenomethyl)pyrrolidines with amine- or oxygen-nucleophiles should led to 3-aminopiperidine and 3-hydroxypiperidine derivatives via an aziridinium intermediates of type J. N-alkyl-2-(chloromethyl)pyrrolidine of type I rearranged so easily to 3-chloropiperidine of type K that they could not be isolated and, as previously observed, treatment of 5 or 6 in refluxing aqueous sodium hydroxide gave a mixture of 8 and 9 with a similar ratio of 68/32. These two latter isomers could be distilled without rearrangement and the products were stable under the reaction conditions. Furthermore, the 68/32 ratio of 8/9 is essentially the same as the one obtained from the treatment of aziridinium B with NaOH (Scheme 4 and Scheme 19, Table 1, entry 1). As the displacement of the halide by nucleophiles produced the same ratio of pyrrolidine and piperidine by starting either from compound of type I or K, the studies were conducted on 3-chloropiperidines of type K.
The reaction of these 3-chloropiperidines with an excess of amines gave exclusively the corresponding pyrrolidines of type a in yields between 35% and 80% (Table 1, entries 2–8). When these 3-chloropiperidines were treated with oxygenated nucleophiles such as alcoholates and carboxylates, a mixture of pyrrolidines of type a and piperidines of type b were obtained. The ratio of a and b depends on the reaction conditions (Table 1, entries 9–17). For example, when 6 was treated with potassium acetate in acetic anhydride at 139 °C for 6 h, a mixture of acetates 57a/57b was obtained in a ratio 17/83. When the reaction was repeated at 90 °C for 8 h, the ratio of 57a/57b was 75/25 (Table 1, entries 9 and 10). Heating the latter mixture at 106 °C for one day left the ratio unchanged. However elevating the temperature to 126 °C for 6 days resulted in a slow rearrangement of 57a to 57b. The preponderance of 57b in the reaction run at 139 °C is apparently due to the rearrangement of the predominant initial product 57a.\(^7\) Compound 8 reacts with refluxing acetic anhydride to give the same product ratio of 57a and 57b as found from the reaction of 6 with sodium acetate in refluxing acetic anhydride. No rearrangement was encountered in synthetizing 57b by refluxing 9 in acetic anhydride.\(^23\) From the above results,\(^24\) it is evident that strong nucleophiles (amines) give mainly 5-membered ring products of type a, whereas, weaker nucleophiles (–OH and –OAc) give a mixture of 5-membered ring products of type a and 6-membered ring products of type b except when sodium benzylate or sodium phenate were used. In this case, pyrrolidine 59a (R= Me, Nu= OBn) and piperidine 60b (R= Me, Nu= OPh) respectively were the only obtained product (Table 1, entries 13 and 14).

From the above results, it is evident that strong nucleophiles (amines) give mainly 5-membered ring products of type a, whereas, weaker nucleophiles (–OH and –OAc) give a mixture of 5-membered ring products of type a and 6-membered ring products of type b except when sodium benzylate or sodium phenate were used. In this case, pyrrolidine 59a (R= Me, Nu= OBn) and piperidine 60b (R= Me, Nu= OPh) respectively were the only obtained product (Table 1, entries 13 and 14).

\[ \text{Scheme 19} \]

It is worth noting that substituted N-alkyl-2-(halogenomethyl)pyrrolidines can be prepared from 5-(halogenomethyl)-1-pyrrolidinium salts and transformed to 3-oxygenated piperidines. When 5-(bromomethyl)-1-pyrrolidinium salt 64 was treated with an excess of sodium methoxide in methanol under reflux, the N-tert-butyl-2-(bromomethyl)pyrrolidine 65 intermediate rearranged cleanly to one major isomer, presumably the trans-dimethoxypiperidine 66 (>95%) via the aziridinium salt L. After reduction of 66 with LiAlH\(_4\), the 3-methoxypiperidine 67 was isolated in good yield (Scheme 20).\(^32\)

The transformation of 2-(halogenomethyl)pyrrolidines to 3-hydroxypiperidines was used to synthesized 14-α-hydroxyvincadifformine and (±)-pseudoconhydrine.
<table>
<thead>
<tr>
<th>entry</th>
<th>K (R=)</th>
<th>Compounds a / b (yield, ratio)</th>
<th>Nucleophile</th>
<th>Subst (—Nu)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>8 / 9 (65%, 68/32)</td>
<td>NaOH</td>
<td>—OH</td>
<td>7a</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>50a / 50b (56%, 100/0)</td>
<td>NH₃</td>
<td>—NH₂</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>51a / 51b (80%, 100/0)</td>
<td>PhCH₂NH₂</td>
<td>—NHCH₂Ph</td>
<td>7a</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>52a / 52b (43%, 100/0)</td>
<td>PhCH₂NH₂</td>
<td>—NHCH₂Ph</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>53a / 53b (43%, 100/0)</td>
<td>(PhCH₂)₂NH</td>
<td>—NH(CH₂Ph)₂</td>
<td>7a</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>54a / 54b (68%, 100/0)</td>
<td>NH₂NH₂</td>
<td>—NHNH₂</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>55a / 55b (69%, 100/0)</td>
<td>NH₂(CH₂)₃N(CH₃)₂</td>
<td>—NH(CH₂)₃N(CH₃)₂</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>56a / 56b (37%, 100/0)</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>57a / 57b (66%, 17/83)⁺</td>
<td>KOAc</td>
<td>—OAc</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>Et</td>
<td>57a / 57b (75/25)b</td>
<td>NaOAc</td>
<td>—OAc</td>
<td>7a</td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>57a / 57b (84%, 75/25)c</td>
<td>NaOAc</td>
<td>—OAc</td>
<td>5b</td>
</tr>
<tr>
<td>12</td>
<td>Et</td>
<td>58a / 58b (67%, 30/70)</td>
<td>NaOEt</td>
<td>—OEt</td>
<td>23</td>
</tr>
<tr>
<td>13</td>
<td>Me</td>
<td>59a / 59b (53%, 100/0)</td>
<td>NaOBn</td>
<td>—OBn</td>
<td>5b</td>
</tr>
<tr>
<td>14</td>
<td>Me</td>
<td>60a / 60b (83%, 0/100)</td>
<td>NaOPh</td>
<td>—OPh</td>
<td>28</td>
</tr>
<tr>
<td>15</td>
<td>Et</td>
<td>61a / 61b (89%, 60/40)</td>
<td></td>
<td></td>
<td>29,30</td>
</tr>
<tr>
<td>16</td>
<td>Me</td>
<td>62a / 62b (70/30)</td>
<td></td>
<td></td>
<td>5b,31</td>
</tr>
<tr>
<td>17</td>
<td>Et</td>
<td>63a / 63b (61%, 70/30)</td>
<td></td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>

*The reaction with acetate gave different product ratios, depending on the reaction conditions. Refluxing in acetic anhydride at 139 °C for 6 hr. *²* Heating in acetic anhydride at 90 °C for 8 hr. *ã* Refluxing in 2-propanol at 83 °C for 6 hr.
The former was prepared by ring expansion of (chloromethyl)-D-norvincadifformine 68. When this latter compound was heated in aqueous DMF, 14-α-hydroxyvincadifformine 69 was generated as the major isomer accompanied by traces of 70 (Scheme 21).  

(±)-Pseudoconhydrine was obtained from 2-(iodomethyl)pyrrolidine 72 which was obtained by aminomercuration of the unsaturated carbamate 71. After treatment of 72 with HBr in acetic acid and then with Na₂CO₃, the bicyclic aziridine 73 was formed and transformed to a mixture of 2-(hydroxymethyl)pyrroline 74 and 3-hydroxypiperidine 75 by slow addition of trifluoroacetic acid. The major compound, 3-hydroxypiperidine 75 was obtained in 85% yield and, after hydrolysis of the trifluoroacetyl group with Na₂CO₃ in methanol, (±)-pseudoconhydrine was isolated in 50% yield (Scheme 22).

Intramolecular attacks of aziridinium salts by a carbonyl oxygen lone pair have been observed to produce exclusively 3-oxygenated piperidine derivatives. In tuning up new routes to the morphinan ring system, compound 78 has been isolated after thermolysis of 77.
The formation of 78 can be explained by the generation of an aziridinium cation M which is then attacked intramolecularly by the oxygen lone pair of the ketone. After treatment of 78 by 1,3-propanethiol in the presence of BF$_3$.OEt$_2$, tricyclic compound 79 was isolated in 73% yield (Scheme 23).$^{35}$

2-(Hydroxymethyl)pyrrolidines can also be transformed to 3-hydroxypiperidines and 3-aminopiperidines via N-alkyl-2-(methanesulfonylmethyl)pyrrolidines. N-Alkyl-2-(methanesulfonylmethyl)pyrrolidines can be prepared under specific conditions and can be used to prepare 3-oxygenated and 3-aminopiperidines. Thus, when substituted (S)-prolinol 80 was treated with methanesulfonyl chloride in pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine at room temperature for two hours, the mesylate 81 was isolated in 98% yield (Scheme 24). We have to point out that under these conditions, the corresponding 3-chloropiperidine 87 was not detected. The reactivity of the mesylate 81 with
NaOH (3 equiv) in water/dioxane and with AcONa (2 equiv) in DMF, respectively afforded diastereomERICALLY pure substituted piperidines 82c and 83c in 52-54% yield along with the pyrrolidine isomers 82d and 83d in 26-34% yield. It is worth noting that DMF itself could serve as a nucleophile in this reaction. When mesylate 81 was treated in DMF at 100 °C for five hours, diastereomerically pure products 84c (38%) and 84d (50%) were obtained after standard work-up. The formation of 84c and 84d further indicates that this reaction must proceed via a highly reactive aziridinium intermediate N since DMF is much less nucleophilic compared with other nucleophiles. Similar reactions of mesylate 81 with NaN₃ in N,N-dimethylformamide was observed. When 81 was heated at 100 °C in the presence of NaN₃ for one hour, the diastereomerically pure piperidine 85c was obtained in 63% yield along with pyrrolidine 85d in 28% yield. Neither the replacement of NaN₃ with LiN₃ or changes of reaction temperature and reaction time had any effect on the total yield and on the product selectivity (Table 2, entries 4–7). The azide 85c could be transformed to the corresponding 3-aminopiperidine. Furthermore, treatment of 81 with TBAF in refluxing THF led to 86c as the major product (54% yield) accompanied by 86d (26% yield).36,37

Table 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Nucleophile (mol equiv.)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Products c/d (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>NaOH (3.0)</td>
<td>H₂O–1,4-dioxane</td>
<td>reflux</td>
<td>0.5</td>
<td>82c (54)/ 82d (26)</td>
</tr>
<tr>
<td>2</td>
<td>OAc</td>
<td>NaOAc (2.0)</td>
<td>DMF</td>
<td>100</td>
<td>5</td>
<td>83c (52)/ 83d (34)</td>
</tr>
<tr>
<td>3</td>
<td>OCHO</td>
<td>DMF</td>
<td>DMF</td>
<td>100</td>
<td>0.5</td>
<td>84c (38)/ 84d (50)</td>
</tr>
<tr>
<td>4</td>
<td>N₃</td>
<td>NaN₃ (1.1)</td>
<td>DMF</td>
<td>100</td>
<td>1</td>
<td>85c (63)/ 85d (28)</td>
</tr>
<tr>
<td>5</td>
<td>N₃</td>
<td>LiN₃ (1.1)</td>
<td>DMF</td>
<td>100</td>
<td>1</td>
<td>85c (61)/ 85d (29)</td>
</tr>
<tr>
<td>6</td>
<td>N₃</td>
<td>NaN₃ (1.1)</td>
<td>DMF</td>
<td>60</td>
<td>15</td>
<td>85c (64)/ 85d (24)</td>
</tr>
<tr>
<td>7</td>
<td>N₃</td>
<td>LiN₃ (1.1)</td>
<td>DMF</td>
<td>60</td>
<td>15</td>
<td>85c (65)/ 85d (25)</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>TBAF (3.0)</td>
<td>THF</td>
<td>reflux</td>
<td>5</td>
<td>86c (54)/ 86d (26)</td>
</tr>
</tbody>
</table>
The precursor of the neuropeptide substance-P (neurokinin-1) receptor antagonist \( \text{89} \) has been prepared \( \textit{via} \) the piperidine intermediate \((2S,3S)-3\)-hydroxy-2-phenylpiperidine \( \text{88} \). Piperidine \( \text{88} \) was obtained easily from prolinol \( \text{90} \) by treatment with \( \text{MsCl} \) in the presence of \( \text{Et}_3\text{N} \), to produce the aziridinium intermediate \( \text{O} \) which was subsequently treated with tetra-\(n\)-butylammonium acetate (4.5 equiv) to afford the desired acetoxy piperidine \( \text{91} \) in 85% yield and 99% ee.

Interestingly, only a small amount of the isomeric pyrrolidinyl acetate \( \text{92} \) (~5%) was detected in the crude reaction mixture. For obtaining \( \text{88} \), the next step involved a selective \( N \)-debenzylation/Boc protection
using Pd/C, H₂ in the presence of Boc₂O followed by the hydrolysis of the acetyl group using NaOH in methanol (Scheme 25).³⁸

An intramolecular trapping of the aziridinium salt by an amino group can lead to the total conversion of a 2-(hydroxymethyl)pyrrolidine to a 3-aminopiperidine. When the bicyclo[3.2.1]octane 93 was treated with MsCl/Et₃N, aziridinium salt P was formed and was attacked intramolecularly by the sulfonamido group to produce the bicyclo[2.2.1]octane compound 94 (Scheme 26).³⁹

As it was noticed previously, intermolecular attack of pyrrolidines of type Q by oxygenated nucleophiles (–OH, –OAc, –OR) produced a mixture of 3-oxygenated piperidines of type R and pyrrolidines of type S (Scheme 27, eq. 1). In contrast, when prolinol (S)-35 was treated with trifluoroacetic anhydride (TFAA), then with triethylamine in THF, followed by NaOH the corresponding 3-hydroxypiperidine (R)-95 was the only isolated product (Scheme 27, eq. 2).⁴₀

The enantiomeric excess of (R)-95 was determined to be superior to 95%. The ring expansion of (S)-35 did not proceed in solvents such as toluene or hexane. In CH₂Cl₂ at reflux, the only product formed was the 3-chloropiperidine (R)-39.
The first step in the formation of 3-hydroxypiperidine \((R)-95\) from 2-(hydroxymethyl)pyrrolidine \((S)-35\) involves esterification of the hydroxy group by trifluoroacetic anhydride and formation of the corresponding quaternary ammonium salt \(96\). In the absence of triethylamine, no rearrangement was observed. The addition of \(\text{Et}_3\text{N}\) produced the aminoester \(97\) which underwent an \(\text{S}_\text{N}i\) process to give a tight ion-pair \(T\) that reacted to generate the stable ester \(98\). Finally, saponification of ester \(98\) by \(\text{NaOH}\) (2.5 M) afforded the 3-hydroxypiperidine \((R)-95\) (Scheme 28).\(^{17,40}\)

\[
\begin{align*}
\text{R}_1 \quad &\text{OH} \\
\text{R}_2 \quad &\text{OH} \\
\rightarrow \quad &\text{R}_1 \quad &\text{OH} \\
\end{align*}
\]

Scheme 29

**Table 3. Formation of 3-hydroxypiperidine from pyrrolidine-methanol derivatives**

<table>
<thead>
<tr>
<th>starting material</th>
<th>product (yield)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>((S)-35)</td>
<td>((R)-95)</td>
<td>17,40</td>
</tr>
<tr>
<td>((S)-99)</td>
<td>((R)-100)</td>
<td>17</td>
</tr>
<tr>
<td>((S)-101)</td>
<td>((R)-102)</td>
<td>17,40</td>
</tr>
<tr>
<td>((S)-103)</td>
<td>((R)-104)</td>
<td>40</td>
</tr>
<tr>
<td>((2SR,4R)-105)</td>
<td>((3SR,5R)-106)</td>
<td>17</td>
</tr>
<tr>
<td>((2S,4R)-107)</td>
<td>((3R,4R)-108)</td>
<td>17</td>
</tr>
<tr>
<td>((2S,3S)-109)</td>
<td>((3S,4S)-110)</td>
<td>41</td>
</tr>
</tbody>
</table>
Table 3 (continuation). Formation of 3-hydroxypiperidine from pyrrolidine-methanol derivatives

<table>
<thead>
<tr>
<th>starting material</th>
<th>product (yield)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBDMSO</td>
<td>TBDMSO</td>
<td></td>
</tr>
<tr>
<td>(2S,4F)-111 R = Bn</td>
<td>(3R,5R)-112 R = Bn (65%)</td>
<td>17</td>
</tr>
<tr>
<td>(2S,4F)-113 R = PMB</td>
<td>(3R,5R)-114 R = PMB (100%)</td>
<td>42</td>
</tr>
<tr>
<td>(2R,3R,4S)-115</td>
<td>(3S,4R,5S)-116</td>
<td>17</td>
</tr>
<tr>
<td>R' = H</td>
<td>(67%)</td>
<td></td>
</tr>
<tr>
<td>(S)-117 R' = H</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>(S)-118 R' = p-NpPh</td>
<td></td>
<td>17</td>
</tr>
</tbody>
</table>

The ring expansion of N-alkylated prolinols appears to be general (Scheme 29) and highly stereoselective as shown in Table 3, except for (S)-prolinol 117 and for the N-(4-nitrophenyl) derivatives (S)-118. In these two cases, the ring expansion products were not detected. The nucleophilicity of the amino moiety of the prolinol derivative has to be high enough for the rearrangement to occur. We note that acid sensitive hydroxy protecting groups (compounds 111, 113, 115) were tolerated under these conditions. The (4R)-hydroxyprolinol derivative 107 was isomerized smoothly into a single diastereomeric diol 108 with a yield of 54%. The [α]_{D}^{20} value [(α)_{D} = + 151] of this compound is consistent with the (3R,5R) configuration in 108 and strongly supports the mechanism of Scheme 26, (2 eq.) (inversion of configuration during the nucleophilic attack at C(2) of aziridinium intermediate T).

2-(Hydroxymethyl)pyrrolidine derivatives with secondary alcohols were also submitted to this rearrangement. 2-(Hydroxymethyl)pyrrolidine 119 was transformed to substituted piperidinol 121 in 100% yield, with an enantiomeric excess of 95%. In contrast, the diastereomer 122 was not reactive under the same conditions (Scheme 30). The non-reactivity of 122 can be attributed to a gauche effect (steric interactions) between the phenyl and the C(2)-C(3) bond in the aziridinium ion intermediate V. In contrast, 2-(hydroxymethyl)pyrrolidine 119 was transformed to piperidinol 121, as no serious steric repulsions were developed during the formation of the aziridinium intermediate U, the phenyl group and the C(2)-C(3) bond being antiperiplanar (Scheme 30). This interpretation implies that the amino moiety participates (anchimeric effect) in the heterolysis of the trifluoroacetate intermediate generated by esterification of the benzyl alcohol 119 (Scheme 30).^{17}

The N-benzyl-2-(hydroxymethyl)pyrrolidine 41 was also studied in the aim of synthesizing the neuropeptide substance-P (neurokinin-1) receptor antagonist 88 (Scheme 25). However, the yield in the ring expansion 125 is not as high as for the transformation of 90 to 91 (Scheme 31 and Scheme 25).^{18}
Treatment of 2-(hydroxymethyl)pyrrolidine derivatives 126 and 128, did not lead to the ring expansion products under the TFAA conditions as 126 was recovered, whereas 128 underwent dehydration to produce alkene 129 (55% yield) (Scheme 32). These results are consistent with the fact that 126 and 128 can generate ion-pairs without the participation of the amino moiety, giving stable tertiary carbocation intermediates.

A ring expansion of pyrrolidine to piperidine was used for the diastereoselective synthesis of azabicyclo[4.3.0]nonane systems. Treatment of the bicyclic 2-(hydroxymethyl)pyrrolidine derivative 130 with trifluoroacetic anhydride in THF followed by addition of Et$_3$N led, after hydrolytic work-up with NaOH, to the formation of 131 which corresponds to the ring expanded product with a diastereomeric ratio
>95/5. The formation of bicyclic 3-hydroxypiperidines 131a-e from 2-(hydroxymethyl)pyrrolidine derivatives 130a-e is general and does not depend on the N-alkyl group (Scheme 33, Table 4).  

![Scheme 32](image)

![Scheme 33](image)

**Table 4.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>131a</td>
<td>CH₂C₆H₅</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>131b</td>
<td>CH₃</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>131c</td>
<td>CH₂CH₃</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>131d</td>
<td>CH₂(CH₃)₃</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>131e</td>
<td>CH₂CH₂C₆H₅</td>
<td>36</td>
</tr>
</tbody>
</table>

The TFAA/Et₃N/NaOH procedure was also applied to the synthesis of 2,6-dihydroxy-9-azabicyclo[3.3.1]nonane 135 (Scheme 34).  

The ring expansion of prolinols induced by TFAA allowed the synthesis of polyhydroxyindolizidinones. For example, 3,5-dihydroxypiperidine (3R,5R)-112, obtained from prolinol (3S,4R)-111 was transformed to nitrone 136 which, after treatment with dimethyl maleate, led to two diastereomeric adducts 137 and 138 in a ratio 8/1. Reductive cleavage of the N-O bond afforded polyhydroxyindolizidinone 139 in 88% yield (Scheme 35).  

Substituted 3-hydroxypiperidines which are present in natural products and/or biologically active compounds such as (−)-pseudoconhydrine, (−)-velbanamine or (+)-zamifenacin can be prepared from ring expansion of optically active prolinols.
Scheme 34

Scheme 35

Scheme 36
(L)-Proline was transformed in 6 steps to 2,5-disubstituted prolinol $140$. After treatment of $140$ with TFAA, with Et$_3$N and then with NaOH, 3-hydroxypiperidine $141$ was obtained and transformed to $(-)$-pseudoconhydrine after hydrogenation (Scheme 36).$^{46}$

Ring expansion of the trisubstituted prolinol $142$ by the TFAA/Et$_3$N/NaOH procedure, led to the trisubstituted piperidin-3-ol $143$ in 93% yield. This intermediate was transformed to the indole compound $145$ than can be used to achieve the synthesis of $(-)$-velbanamine (Scheme 37).$^{47}$
The selective muscarinic M<sub>3</sub> antagonist, (+)-zamifenacin has been obtained with high enantiomeric excess by ring enlargement of prolinol 149 by the TFAA/Et<sub>3</sub>N/NaOH ring expansion method. By this method, (+)-zamifenacin was synthetized in four steps from the (L)-proline methyl ester 146 (Scheme 38).<sup>48</sup>

5. Synthesis of C(3)-alkylated piperidine derivatives

Aziridinium ions can be opened by cuprates. For example, aziridinium intermediate W was formed from the hydrochloride 151 by using one mole of 3-methoxyphenylmagnesium bromide as a base. Addition of another mole of Grignard reagent gave no coupling products. However, by adding a catalytic amount of cuprous cyanide or cuprous iodide to the reaction mixture, the nucleophilic attack on the aziridinium intermediate was successfully initiated and the pyrrolidine derivative 152 as well as the piperidine compound 153 were obtained in a ratio 82/12 respectively (82% yield). Demethylation of 153 by using HBr gave (–)-3-PPP in 84% yield. This compound is a selective dopamine (DA) autoreceptor agonist devoid of any appreciable postsynaptic DA-mimetic activity (Scheme 39).<sup>49</sup>

In contrast, the intramolecular attack on an aziridinium cation, which comes from a 2-(chloromethyl)pyrrolidine, by an internal carbon nucleophile allowed the formation of C(3) alkylated piperidines. In an approach to the morphinan ring system, compound 154 was transformed to 155 by treatment with AgSbF<sub>6</sub>. This product arises through intramolecular attack by the silyl enol ether on the aziridinium intermediate X (Scheme 40).<sup>35</sup>

Alklyation at the C3 position of the piperidine ring was achieved from a 3-chloropiperidine. When diphenylacetonitrile was allowed to react with N-methyl-3-chloropiperidine 156 in the presence of sodium amide and toluene, compounds 157 and 158 were obtained, via aziridinium Y, in 80% yield in a ratio 1 to 1. After hydrolysis with 90% sulphuric acid, the corresponding diphenylacetamides 159 and 160 were separated (Scheme 41).<sup>50</sup>

It should be pointed out that upon treatment of N-ethyl-3-chloropiperidine with NaCN, the only isolated product was the 2-(cyanomethyl)pyrrolidine.<sup>7a</sup>
6. Conclusions

In summary, ring expansion reactions (RER) of 2-(halomethyl)pyrrolidines and 2-(hydroxymethyl)pyrrolidines to form substituted piperidines are highly stereo- and enantioselective and can be used to synthesize a great diversity of substrates for obtaining biologically active compounds in a very efficient way. In the future, it will be of great interest to further extend ring expansions of 2-(halomethyl)- and 2-(hydroxymethyl)pyrrolidine by using carbanions as nucleophiles.

Acknowledgements

We sincerely acknowledge Ph. D. students, C. Dumas, O. Mirguet, P. Michel, and B. Burger for their fruitful efforts in this area. Financial support for our research program by the Ville de Paris, the CNRS, and Rhodia is gratefully acknowledged. We thank also the MRET for a grant to O. M.
References


37. For related ring expansion from other substrates see: (a) Setoi, H.; Takeno, H.; Hashimoto, M. Heterocycles 1986, 24, 1261; (b) Zhi-cai, S.; Chun-min, Z.; Guo-Quang, L. Heterocycles 1995, 41, 277; (c) Knaack, M.; Fleischhauer, I.; Charpentier, P.; Emig, P.; Kutscher, B.; Muller, A. Liebigs Ann. 1996, 1477.


THE FORMATION OF THE CARBON-CARBON BOND CATALYSED BY METALLOPORPHYRINS

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Abstract. In this review, the results reported in the literature during the last twenty years for the metalloporphyrins-catalysed formation of the carbon-carbon bond are described. Cyclopropanation reactions, Diels-Alder additions, olefination of aldehydes and cyclotrimerization of alkynes are important processes in organic chemistry and all of them are catalysed by metalloporphyrins. Such catalysts afford interesting results in terms of chemical yields and stereospecificity, due to the differences in the electron densities of the substituted macrocycles and the possibility to have the access to flat or saddle-shaped conformations of the tetapyrrolic rings, depending on the substituents located on their skeleton.

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1. Introduction
The formation of the carbon-carbon bond is a step of great importance in organic synthesis and several industrial processes for the production of valuable chemicals are based on reactions that involve the formation of new C-C bonds.\(^1\text{ }^3\) Many procedures involve carbanions, obtained from organometallic compounds or activated methyl or methylene groups.\(^4\text{ }^6\) The Grignard reaction, the Claisen condensation, the Diels-Alder reaction and many other processes have been discovered in the last century but even if the catalytic formation of this bond has been well studied, many general and efficient methods for affecting this
reaction still remaining to be found or optimized. From many points of view, catalysis by metal complexes is an important and powerful tool in organic chemistry and within this field of research, the metalloporphyrin catalysts have achieved important results. In this review, the formation of carbon-carbon bond catalysed by synthetic metalloporphyrins and their application in organic chemistry is reported.

1.1. Catalysis by metalloporphyrins: general remarks

The investigations on the natural and synthetic porphyrins and their metallo-derivatives are a fundamental field of research to better understand how some classes of natural enzymes work and their structural relation with the substrates. Natural enzymes like cytochrome P450 are able to perform the epoxidation of olefins and the hydroxylation of alkanes with great efficiency and stereospecificity. Such systems, all of them containing the heme group, are ubiquitous in the living organisms and their main task is the intracellular transformation of non-polar organics into polar compounds, making the excretion easier and eliminating by way the most likely toxic and mutagenic substances. The structure of the porphyrins skeleton is reported in Figure 1.

![Figure 1](image_url)

The skeleton of porphyrins enclosing the IUPAC(left) and the classical Fischer (right) numeration of the substituents.

For our convenience, the methine bridges ($\alpha$, $\beta$, $\gamma$, $\delta$) will be also called *meso* positions.

The use of synthetic metalloporphyrins as model catalysts in oxidation reactions, like epoxidation of olefins and hydroxylation of saturated hydrocarbons, has been largely documented during the last decade. Among the metalloporphyrins tested for such reactions, much attention has been devoted to the *meso*-tetraphenyl substituted ones, which show the most interesting properties. The first report on the catalytic activity of the iron (III) *meso*-tetraphenylporphyrin in the oxidation reactions came from Groves and co-workers, who used iodosilbenzene as oxygen donor. This class of macrocycles is known as the “first generation” of porphyrin catalysts. Following this pioneering work, other authors showed that manganese(III) and iron(III) *meso*-tetraphenylporphyrins bearing suitable substituents (Cl, OCH$_3$, Br, F, CH$_3$, etc.) on the 2’, 6’ positions of all the phenyl groups, are able to catalyse the oxygen transfer, showing a
high resistance to the oxidative conditions. These sterically hindered groups prevent the formation of the $\mu$-oxo dimeric complexes, which are not catalytically active.

This class of compounds is actually known as the “second generation” of porphyrin catalysts. The “third generation” of porphyrin catalysts is formed by the aforementioned second class bearing further electron-withdrawing groups, like halogens, nitro or cyano, in some or all the beta positions. Examples of porphyrins of the second and third generation are reported in Figure 2.

![Figure 2](image_url)

Such catalysts are able to perform the hydroxylation of aromatic compounds giving phenols or quinones as the final products. Furthermore, the iron porphyrins of the third class are also able to catalyse the hydroxylation of simple and short hydrocarbons, like propane or isobutane using the molecular oxygen in the suprabiotic catalytic systems.

2. Cyclopropanation reactions

The cyclopropyl ring formation is an important reaction in organic synthesis, due to the presence of such structure in a number of interesting natural products. Many methods have been developed in the past for obtaining such reaction and several copper, rhodium and osmium complexes have been reported to be efficient catalysts for the synthesis of cyclopropanes from diazocompounds. In comparison with the copper catalysts, like CuCl, which do not afford synthetic useful cis/trans ratios of the final products, the porphyrin catalysts give larger selectivities, depending on the nature of the metal. The reaction mechanism of the metalloporphyrins catalysed cyclopropanation reaction is not completely elucidated, because of the lability of the bond between the central metal and the acetate residue.
The intermediate of the reaction, showed in Scheme 1, proposed, in the case of rhodium, by Callot et al.\textsuperscript{23} was later studied by Kodadek, who used the NMR spectroscopy for detecting the tentatively suggested carbene species, A.\textsuperscript{26,30}

\begin{center}
\begin{tikzpicture}
    \node (A) at (0,0) {\text{A}}; \node (B) at (-1.5,0) {\text{Rh}}; \node (C) at (-1,0) {\text{III}}; \node (D) at (0,0) {\text{N}_2\text{CHCO}_2\text{Et}}; \node (E) at (1,0) {\text{Rh}}; \node (F) at (1.5,0) {\text{III}}; \node (G) at (1.5,1) {\text{CHCO}_2\text{Et}}; \node (H) at (0,1) {\text{CHCO}_2\text{Et}}; \node (I) at (1.5,1) {\text{cis+trans}};
    \draw[->] (B) -- (C); \draw[->] (C) -- (D); \draw[->] (D) -- (E); \draw[->] (E) -- (F); \draw[->] (F) -- (G); \draw[->] (G) -- (H); \draw[->] (H) -- (I);
\end{tikzpicture}
\end{center}

Scheme 1

2.1. Rhodium porphyrin catalysts

Almost twenty years ago, Callot and co-workers reported the first study on the rhodium(III) porphyrins catalysed cyclopropanation reaction of olefins.\textsuperscript{23} They used the easily obtainable rhodium(III) meso-tetraphenylporphyrin iodide, Rh(TPP)I as catalyst for the decomposition of EDA in the presence of different olefins, obtaining the cyclopropanation products with remarkable cis selectivities.

In Table 1, the total yields of the reactions and the \textit{cis/trans} ratios for all the substrates are reported and compared with the results obtained using different catalysts, such as rhodium pivalate or copper chloride.

From the reported data, it is clear that the structure of the catalysts influence the stereochemical results, giving larger cis selectivity and this fact was used for planning the synthesis of more hindered porphyrins, able to give higher selectivities. In fact, in the presence of rhodium 2',6' phenyl substituted porphyrins, the \textit{cis} selectivities changes and using rhodium meso-tetra-(2', 4', 6'-trimethylphenyl)porphyrin, Rh(TMPP)I instead of Rh(TPP)I in the case of cyclohexene, the \textit{cis/trans} ratio increases from 0.84 to 1.17 and for norbornene from 1.85 to 2.14.\textsuperscript{24}

These first studies prompted other groups in the searching of more sterically hindered porphyrins and for such reason Kodadek and co-workers synthesised the so-called rhodium “chiral wall”, Rh(TBPNP)I and “chiral fortress” Rh (TPBNP)I porphyrins.\textsuperscript{25,31,32} The non-metalated macrocycles were synthesised by inserting, in all the \textit{meso}-positions, the optically active binaphtyl or 1’-pyrenyl-1-naphtalene groups. In scheme 2 is reported the synthetic pathway for obtaining one of them. The rhodium derivatives of such porphyrins were used for the EDA cyclopropanation of simple olefins and the enantiomeric excesses were determined on both the \textit{cis} and \textit{trans} isomers. In this way, two sterically hindered and optically active catalysts have been made available and the \textit{cis} selectivities of the cyclopropanation reactions of standard olefins by EDA were the best ever reported in the literature for this reaction.

Furthermore, such intrinsically chiral catalysts afforded diastereoselectivities in moderate or good excess but the difficult to prepare large quantities of such porphyrins made them not useful for large scale preparations. Some results of the use of these chiral catalysts are collected in Table 2.

As to the mechanism of the reaction for the rhodium porphyrins catalysis, Kodadek\textsuperscript{33,34} proposed that the olefin could approach the metalallocarbene intermediate in a perpendicular orientation relative to the
metal-carbon bond axis, giving after a rotation the arrangement found in the final cis or trans product. In Scheme 3, a simplified representation of the transition state is reported.

**Table 1.** The total yields and the cis/trans ratios obtained using Rh(TPP)I, compared with the results obtained using other catalysts, such as rhodium pivalate or copper chloride. (According to ref. 23. Reprinted from *Tetrahedron Lett.* 1980, 21, 3489-3492, Callot, H. J. and Piechocki, C.: Cyclopropanation using rhodium(III) porphyrins: large cis vs trans selectivity. Copyright 1980, with permission from Elsevier Science).

<table>
<thead>
<tr>
<th>olefin</th>
<th>cis and trans products</th>
<th>catalyst</th>
<th>cis/trans ratio</th>
<th>Total yield(%)</th>
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<tbody>
<tr>
<td></td>
<td>E=CO₂Et</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RhTPPI</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhpiv</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CuCl</td>
<td>0.12</td>
<td>62</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.85</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RhTPPI</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhpiv</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CuCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.9</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RhTPPI</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhpiv</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CuCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.13</td>
<td>71</td>
</tr>
</tbody>
</table>

In this early suggestion, the transfer of the acetate residue to an unsymmetrical alkene, bearing a smaller, Rₛ and a larger, Rₜ, substituent, is obtained maintaining the large substituent far from the ester group while the olefin, rotating clockwise or counterclockwise around an axis orthogonal to the metal-carbon bond, can reach the transition state in a concerted fashion. This fact is also supported by the absence of a secondary isotope effect, determined in a competitive experiment with styrene and d₈-styrene, which gave the value of 1.0±0.07. For bulky porphyrins, like the 2’, 6’ phenyl substituted ones, the interaction between ligand and
substrate dominates, giving a clockwise rotation and the final *cis* product. If the interaction ester-substrate is stronger, the rotation will be counterclockwise leading to the *trans* product.

![Chemical Structures](image)

(Reprinted from *Organometallics* 1992, 11, 2299. Copyright 1992 American Chemical Society)

**Scheme 2**

**Table 2.** Selected yields and enantiomeric excesses for the cyclopropanation reactions catalysed by Rh (TPBNP)I. (According to ref. 31. Reprinted from *Organometallics* 1992, 11, 2299. Copyright 1992 American Chemical Society).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products</th>
<th>cis</th>
<th>trans</th>
<th>cis/trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenyl[3]</td>
<td>H H EtO2C H H Ph</td>
<td>15</td>
<td>nd</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[3]methyl</td>
<td>H H EtO2C H H Ph</td>
<td>25</td>
<td>20</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[3]tolyl</td>
<td>H H EtO2C H H Ph</td>
<td>10</td>
<td>10</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This model was successively refined by using the $^1$H NMR spectroscopic observation of another reactive intermediate, the iodoalkyl rhodium derivative, B which has been proved to be the possible active catalyst.$^{30}$ The proposed modified mechanism for the cyclopropanation of olefins catalysed by rhodium porphyrins is reported in Scheme 4.

The possibility to vary the electronic properties and steric hindrance of the meso-tetraphenylporphyrins, introducing different groups on the $\beta$-positions and/or on the phenyl rings, prompted us to investigate which parameters govern the stereochemical results obtained in the cyclopropanation reactions using their rhodium derivatives as catalysts.$^{35}$ It is well known from previous studies$^{36,37}$ that (PorBr$^x$)M, where PorBr$^x$ is the dianion of different $\beta$-halogenated 5, 10, 15, 20-tetraphenylporphyrins, M is Fe, Co, Zn or H$_2$ and x $\geq$ 3 or 4, show saddle-shaped distortion of the macrocycles.

This fact suggested the possibility to direct the cyclopropanation reaction to give the most hindered isomer in excess without building complicated porphyrinic structures.$^{31,32}$ For this purpose we decided to use the rhodium derivatives of 5, 10, 15, 20-tetra(2', 6'-dimethoxyphenyl)porphyrin, Rh(TDMPP)Cl and 5, 10, 15, 20-tetra(2', 6'-dichlorophenyl)porphyrin, Rh(TDCPP)Cl which both show good steric hindrance on both
sides of the macrocycle due to the presence of bulky groups. The starting free bases of such metal derivatives are now available in grams quantity by new synthetic methods, much cheaper than those previously reported in the literature and comparable with those for obtaining the simple 5, 10, 15, 20-tetraphenylporphyrin. Furthermore, we examined the possibility to quantify the influence of the β-bromine groups on the stereoselectivity of the reaction and we report all the new data obtained for styrene, comparing with CuCl and Rh(TPP)Cl catalysts in Table 3.

![Scheme 4](image)


It is clear that there is a small but evident influence of the β-bromination on the stereoselectivity of the reaction and, plotting the logarithm of the cis/trans ratio against the sum of the Hammett’s σ_p of the β-bromine groups, a good linear correlation (r^2=0.98, ρ=-0.132) is evident (see Figure 3). The selectivity changes on increasing the number of the halogens and this fact, in our opinion, is due to different factors; the
The electrophilic character of the metal is clearly enhanced by the electron-withdrawing effects of the β-substituents and this is in agreement with the mechanism proposed by Kodadek but we also believe that, during the catalytic process, styrene can approach the core of the macrocycle through a π–π interaction with the higher halogenated pyrrole rings stabilising the transition state which leads to the trans product.

Table 3. cis/trans Molar ratios and yields in parentheses for the cyclopropanation reaction of styrene with EDA catalysed by rhodium porphyrins (According to ref. 35. Reprinted from J. Mol. Cat. A: Chemical 2002, 185, 127-133, Tagliatesta, P. and Pastorini, A.: Electronic and steric effects on the stereoselectivity of cyclopropanation reactions catalysed by rhodium meso-tetraphenylporphyrins. Copyright 2002, with permission from Elsevier Science.)

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Catalyst</th>
<th>Molar ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>0.6(79.3)</td>
</tr>
<tr>
<td>2</td>
<td>RhTPPCl</td>
<td>1.3(70.4)</td>
</tr>
<tr>
<td>3</td>
<td>Rh(Br2)TPPCl</td>
<td>1.1(95.0)</td>
</tr>
<tr>
<td>4</td>
<td>Rh(Br3)TPP]Cl</td>
<td>1.0(90.1)</td>
</tr>
<tr>
<td>5</td>
<td>Rh(Br4)TPPCl</td>
<td>0.9(91.2)</td>
</tr>
<tr>
<td>6</td>
<td>Rh(Br8)TPPPCl</td>
<td>0.7(26.5)</td>
</tr>
<tr>
<td>7</td>
<td>RhTDMPPCl</td>
<td>0.4(88.8)</td>
</tr>
<tr>
<td>8</td>
<td>RhTDCPPCl</td>
<td>1.7(43.7) [b]</td>
</tr>
</tbody>
</table>

[a] Reactions were carried out at 60 °C with a molar ratio substrate/EDA/catalyst=2500:1000:1; [b]Room temperature

The situation is different for cyclohexene and norbornene, which show different behaviours with the β-brominated porphyrins. For cyclohexene, the most conformationally flexible substrate among those examined, we obtained almost the same cis/trans ratio for all the above mentioned catalysts (0.5÷0.8). This is not surprisingly and such effect can be attributed to the possibility for cyclohexene to have the access to different conformations.

On the contrary, norbornene, a more rigid substrate, shows a non-linear decrease in the stereochemical ratio on increasing the number of the halogen atoms on the β-positions. Rh(TDCPP)Cl shows the most interesting results when compared with the data obtained by Callot and co-workers, who used the rhodium derivatives of porphyrins bearing other bulky substituents as catalysts for the reaction of EDA with the same substrates. This catalyst is able to give good improvement of the stereochemical results with all the substrates reported above. For styrene, we obtained a cis/trans ratio of 1.7 vs 0.98, for cyclohexene 1.5 vs 1.17 and for norbornene 3.5 vs 2.14, at room temperature. These last results are quite remarkable for several reasons, first of all because of the low cost of the starting free base.

Furthermore, the result for norbornene, to the best of our knowledge, is the higher so far reported in the literature and also the other ratios obtained for styrene and cyclohexene are interesting when compared with the values obtained by Kodadek who used more complicated and expensive porphyrin catalyst.31,32

**Figure 3**


<table>
<thead>
<tr>
<th>olefin</th>
<th>Catalysta</th>
<th>ratio of trans/cis products</th>
<th>ratio of cyclopropane/diethyl maleate products</th>
</tr>
</thead>
<tbody>
<tr>
<td>styrene</td>
<td>Fe(PFP)Cl</td>
<td>6.0</td>
<td>75:25</td>
</tr>
<tr>
<td></td>
<td>Fe(TPP)Cl/40º C</td>
<td>5.5</td>
<td>76:24</td>
</tr>
<tr>
<td></td>
<td>Fe(TPP)Cl/CoCp2</td>
<td>8.7</td>
<td>80:20</td>
</tr>
<tr>
<td></td>
<td>Fe(TTP)</td>
<td>8.8</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>Fe(TPP-p-OMe)Cl/CoCp2</td>
<td>9.0</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>Fe(TMP)Cl/CoCp2</td>
<td>13</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>Fe(OEP)Cl/CoCp2</td>
<td>10</td>
<td>b</td>
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<td>α-methylstyrene</td>
<td>Fe(PFP)Cl</td>
<td>1.1</td>
<td>67:33</td>
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<td>Fe(TPP)Cl/40º C</td>
<td>3.4</td>
<td>70:30</td>
</tr>
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<td></td>
<td>Fe(TMP)Cl/CoCp2</td>
<td>3.0</td>
<td>97:3</td>
</tr>
<tr>
<td></td>
<td>Fe(OEP)Cl/CoCp2</td>
<td>3.7</td>
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<tr>
<td></td>
<td>Fe(TTP)</td>
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</tr>
<tr>
<td>p-methoxystyrene</td>
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<td>5.8</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>Fe(TPP)Cl/40º C</td>
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<td>b</td>
</tr>
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<td></td>
<td>Fe(TMP)Cl/CoCp2</td>
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<td>b</td>
</tr>
<tr>
<td>ethyl vinyl ether</td>
<td>Fe(PFP)Cl</td>
<td>3.3</td>
<td>67:33</td>
</tr>
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<td></td>
<td>Fe(TMP)Cl/CoCp2</td>
<td>4.1</td>
<td>82:18</td>
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<td></td>
<td>Fe(OEP)Cl/CoCp2</td>
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<tr>
<td>2-ethyl-1-butene</td>
<td>Fe(PFP)Cl</td>
<td></td>
<td>30:70</td>
</tr>
</tbody>
</table>

a0.02-0.05% catlyst. bTrace diethyl maleate observed. PFP=meso-tetra(2’, 3’, 4’, 5’, 6’-pentafluorophenyl)porphyrin; TMP=meso-tetra(2’, 4’, 6’-trimethylphenyl)porphyrin; TTP=meso-tetra(4’-methylphenyl)porphyrin; OEP= 2, 3, 7, 8, 12, 13, 17, 18 octaethylporphyrin
2.2. Iron porphyrin catalysts

The first report on the catalytic activity of the iron(II) porphyrins in the cyclopropanation reactions was published in 1995 and came from Kodadek’s laboratory.\textsuperscript{39} Although the iron(II) porphyrins are isoelectronic with the rhodium(III) ones, their stereoselectivity is completely opposite. In fact the iron(II) meso-tetraphenylporphyrin was found to be quite active in catalysing for example the reaction between styrene and EDA but a ratio of 8.8 to 1 of trans to cis isomers was produced. In Table 4 we report some results obtained by Kodadek using different catalytic systems on five standard olefins.

The active intermediate of the reaction was attributed to an iron(II) carbene species which can be formed from a starting iron(III) porphyrin by the chemical reduction with cobaltocene (CoCp\textsubscript{2}) and subsequent complexation or generated \textit{in situ} by the direct reaction with EDA. The same observation was reported by Kodadek, who observed the EDA direct reduction of the iron(III) meso-tetra(2', 3', 4', 5' 6'-pentafluorophenyl)porphyrin chloride and it was attributed to the presence of the electron-withdrawing groups on the phenyl rings which make easier the reduction of the iron by EDA. The secondary kinetic isotope effect was determined using styrene and d\textsubscript{8}-styrene in a competitive experiment and gave the value of 0.87±0.07, suggesting a rehybridization of the olefin in the transition state. This proposal implied the presence of a carbocation or radical species which is formed in a non-concerted insertion of the acetate residue into the olefin. A simple scheme of this mechanism is reported in Figure 4.

Moreover, the iron(II) porphyrins catalyse the carbene transfer with a great preference for the aromatic olefins or those bearing π-heteroatoms. At variance with the rhodium catalysed reactions, the aliphatic olefins are poor substrates and almost no reaction was observed for cyclohexene, indene and 1-methyl-cyclohexene. For the cyclopropanation of such substrates, only diethyl fumarate and/or maleate were detected as reaction by-products. In our opinion this fact could be due to the presence of two separate mechanisms involved in the cyclopropanation of the aromatic olefins. For iron catalysts, an asynchronous
transfer can be present and, in this case, the intermediate after rotation along the carbon-carbon bond, can give a mixture of the *cis* and *trans* isomers.

This mechanism is reminiscent of that reported for the epoxidation of *cis*-stilbene catalysed by manganese porphyrins\(^\text{40}\) which involves two different routes, depending on the electron withdrawing substituents on the macrocycle ring.

In our opinion, for the iron catalysis, the rotation can depend on the steric hindrance of the substituents on the porphyrin ring and also on the relative stability of the radical intermediates. Another observation which supports our interpretation, derives from the fact that only rhodium porphyrins give the carbene transfer for both aromatic and aliphatic substrates. In the case of iron, only styrenes undergo to the formation of cyclopropanes because the radical intermediate can be stabilised by the resonance effect. The effect of the DMSO seems to be related to the coupling interaction of the unpaired electron of the radical with the lone pair of the sulfoxide, stabilizing the radical intermediate.

**Table 5.** Catalytic cyclopropanation of olefins with EDA using Fe(TDCPP)Cl as catalyst (According to ref. \(^\text{41}\)).

<table>
<thead>
<tr>
<th>Entries</th>
<th>Olefin</th>
<th>Catalyst(^a)</th>
<th>Reaction time(h)(^b)</th>
<th>Ratio of <em>trans/cis</em> products(reaction yield)(^c)</th>
<th>Ratio of cyclopropane/diethyl maleate products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>styrene</td>
<td>Fe(TDCPP)Cl</td>
<td>2</td>
<td>20(80)</td>
<td>82:12</td>
</tr>
<tr>
<td>2</td>
<td>Fe(TDCPP)Cl/CoCp(_2)</td>
<td>1.5</td>
<td>30(97)</td>
<td></td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td><em>p</em>-chlorostyrene</td>
<td>Fe(TDCPP)Cl</td>
<td>0.5</td>
<td>13(80)</td>
<td>80:20</td>
</tr>
<tr>
<td>4</td>
<td>Fe(TDCPP)Cl/CoCp(_2)</td>
<td>0.5</td>
<td>78(94)</td>
<td></td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td><em>p</em>-methoxystyrene</td>
<td>Fe(TDCPP)Cl</td>
<td>6</td>
<td>8.3(85)</td>
<td>d</td>
</tr>
<tr>
<td>6</td>
<td>Fe(TDCPP)Cl/CoCp(_2)</td>
<td>2</td>
<td>50(95)</td>
<td></td>
<td>d</td>
</tr>
<tr>
<td>7</td>
<td><em>α</em>-methylstyrene</td>
<td>Fe(TDCPP)Cl</td>
<td>8</td>
<td>1.6(80)</td>
<td>d</td>
</tr>
<tr>
<td>8</td>
<td>Fe(TDCPP)Cl/CoCp(_2)</td>
<td>3</td>
<td>2.0(95)</td>
<td></td>
<td>d</td>
</tr>
<tr>
<td>9</td>
<td><em>β</em>-methylstyrene</td>
<td>Fe(TDCPP)Cl</td>
<td>18</td>
<td>-</td>
<td>e</td>
</tr>
<tr>
<td>10</td>
<td>Fe(TDCPP)Cl/CoCp(_2)</td>
<td>16</td>
<td>-</td>
<td>e</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)0.03-0.07% catalyst. \(^b\)Room temperature. \(^c\)Determined by GC analysis. \(^d\)Trace diethyl maleate observed. \(^e\)Only diethyl maleate observed

This coupling could be depressed by the methoxy substituent in *p*-methoxystyrene which destabilises the radical intermediate. This is also in agreement with other observations on the reaction performed on styrene. By using Rh(TDCPP)Cl as catalyst, in neat CHCl\(_3\), we have been able to obtain an *trans/cis* ratio of 0.58 while with 0.5% of DMSO the result increases to 3.0. This last result is also in agreement with value of 2.8 obtained adding 1% of 3-carbamoyl tempo, a free radical, in the reaction media instead of DMSO and strongly support our interpretation of the obtained data.

Interesting results were recently obtained in our laboratory using the Fe(TDCPP)Cl, a sterically hindered and electron-poor metalloporphyrin.\(^\text{41}\) In the reactions catalysed by such macrocycle, we obtained,
for some aromatic olefins, the highest trans/cis ratios ever obtained, going from a value of 30 for styrene to 78 for p-chlorostyrene. The total yields were also very interesting and the number of turnovers reached the value of 3 \times 10^3.

Interesting results have been recently obtained by Woo and co-workers who used aromatic diazocompounds as carbene source. They were able to obtain a trans/cis ratio of 14 for the reaction of styrene with p-tolylidiazomethane, catalysed by Fe^{II}TPP. Furthermore, they reported the reaction of EDA with styrene catalysed by Fe^{II}TDMPP which gives a remarkable ratio of 21 and the 1H NMR spectroscopic identification of a carbene iron(II) porphyrin derivative from the stoichiometric addition of mesityl diazomethane to Fe^{II}TPP.

2.3. Osmium porphyrin catalysts

Woo and co-workers reported in 1992 the first use of an osmium porphyrin in the synthesis of olefins from diazocompounds. This method afforded the cis isomers in great excesses and with remarkable yields. An example of this reaction is given in scheme 5 for the EDA conversion to diethyl fumarate or maleate.

![Scheme 5](image.png)


<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>Yield</th>
<th>Olefin&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cyclopropane</th>
<th>a/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TPP)Os(CO)(Py)</td>
<td>styrene</td>
<td>11(2)</td>
<td>b</td>
<td>54(1)</td>
<td>9.0(1)</td>
</tr>
<tr>
<td>(TPP)Os(CO)(Py)</td>
<td>styrene</td>
<td>12(1)</td>
<td>b</td>
<td>65(3)</td>
<td>9.5(2)</td>
</tr>
<tr>
<td>(TPP)Os(CO)(Py)</td>
<td>styrene</td>
<td>26(1)</td>
<td>b</td>
<td>44(1)</td>
<td>9.0(3)</td>
</tr>
<tr>
<td>[Os(TPP)]&lt;sub&gt;2&lt;/sub&gt;</td>
<td>styrene</td>
<td>trace</td>
<td>b</td>
<td>79(2)</td>
<td>10.2(1)</td>
</tr>
<tr>
<td>(TPP)Os=CHCO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>styrene</td>
<td>trace</td>
<td>b</td>
<td>63(2)</td>
<td>8.9(6)</td>
</tr>
<tr>
<td>(TPP)Os=CHCO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>PhC≡CH</td>
<td>41(1)</td>
<td>b</td>
<td>11(1)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>d</td>
</tr>
<tr>
<td>[Os(TPP)]&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PhC≡CH</td>
<td>20(1)</td>
<td>b</td>
<td>46(2)&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>d</td>
</tr>
<tr>
<td>(TPP)Os(CO)(Py)</td>
<td>1-decene</td>
<td>31(1)</td>
<td>b</td>
<td>32(1)</td>
<td>4.3(1)</td>
</tr>
<tr>
<td>(TPP)Os(CO)(Py)</td>
<td>α-methylstyrene</td>
<td>29(1)</td>
<td>b</td>
<td>39(1)</td>
<td>2.8(1)</td>
</tr>
<tr>
<td>(TPP)Os(CO)(Py)</td>
<td>(E)-β-methylstyrene</td>
<td>43(2)</td>
<td>23</td>
<td>13(2)</td>
<td>f</td>
</tr>
<tr>
<td>(TPP)Os=CHCO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>styrene</td>
<td>73(5)</td>
<td>11.5(4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Diethyl maleate/diethyl fumarate products. <sup>b</sup>(Z)-isomer is the only one detected. <sup>c</sup>Bicyclobutanes are the only cyclopropane products detected. No cyclopropene has been observed. <sup>d</sup>Only one isomer observed. <sup>e</sup>Ten-hour addition. <sup>f</sup>Ethyl-trans-2-phenyl-cis-3-methylcyclopropane-(r)-carboxylic acid ester was the only isomer.

After this first report on the catalytic activity of the osmium porphyrins, another paper appeared in the literature on the cyclopropanation of olefins by EDA. In that contribution, several catalysts have been tested using styrene, α-methylstyrene, β-methylstyrene or 1-decene as substrates. Furthermore, such catalysts were also used for the cyclopropanation of phenylacetylene, giving the bicyclobutanes as the final product.
products. All results are reported in Table 6. Two osmium porphyrin carbone complexes have been later isolated and fully characterised.  

The x-ray analysis of the trans-(TPP)Os=CHSi(CH₃)₃•THF and trans-(TPP)Os=C(C₆H₄-p-CH₃)₂•THF shows distorted geometries due to the steric interactions of the metal ligand with the macrocycle. The molecular structures provide new information about the intermediate of the reaction and in Figure 5 we report the ORTEP drawing of the trans-(TPP)Os=CHSi(CH₃)₃•THF.

Figure 5

(Reprinted from Organometallics 1994, 13, 3020. Copyright 1994 American Chemical Society)

\[
\text{(TPP)Os=CHCO₂Et + N₂CH(Mes) + 2 Ph} \xrightarrow{-2 \text{ N₂}} \begin{array}{c}
\text{CO₂Et} \\
\text{Mes}
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \quad (6)
\]

\[
\text{(TPP)Os=CH(Mes) + N₂CHCO₂Et + 2 Ph} \xrightarrow{-2 \text{ N₂}} \begin{array}{c}
\text{CO₂Et} \\
\text{Mes}
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \quad (7)
\]

\[
\text{(TPP)Os=CH(Mes) + Ph} \xrightarrow{} \text{No reaction} \quad (8)
\]

(Reprinted from Organometallics 2001, 20, 5189. Copyright 2001 American Chemical Society)

Scheme 6

The reaction mechanism has been recently studied in detail by Woo and co-workers.  They used the isolated (TPP)Os=CH(Mes) carbene complex for a key experiment using it stoichiometrically with styrene at room temperature. No reaction was observed, whilst this was not the case when the reaction was performed in the presence of EDA and a mixture of two cyclopropanated products was obtained. This last result was also obtained generating (TPP)Os=CHCO₂Et directly in solution by stoichiometric amount of EDA on the
osmium porphyrin and reacting the obtained carbene compound with N$_2$CH(Mes) and styrene. For clarity, in scheme 6 we report the simple equations of these experiments.

All the above cited experiments demonstrate that the active species in the reaction is probably a bis(carbene) complex and this conclusion is also supported by the evidence that (TPP)Os=CHCO$_2$Et, generated in situ by the stoichiometric addition of EDA to (TPP)Os, in the presence of styrene, gives the cyclopropanated product after many hours. The authors concluded that the attack of the olefin to the second carbene ligand is favoured by the electron-withdrawing effect of the first one.

### 2.4. Ruthenium porphyrin catalysts

Few reports appeared in the literature for the cyclopropanation reactions of olefins catalysed by ruthenium porphyrins. The first paper was published in 1997 as a short communication and reported on the cyclopropanation of styrene derivatives performed with different ruthenium meso-tetraphenylporphyrins, one of which bearing chiral residues. The results for the non-chiral catalysts are reported in Table 7.


<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Ratio of trans:cis products$^a$</th>
<th>Alkene yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrene</td>
<td>Ru(TPP)CO</td>
<td>13.1</td>
<td>7</td>
</tr>
<tr>
<td>Styrene</td>
<td>Ru(TMP)CO</td>
<td>7.9</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Styrene</td>
<td>Ru(TMP)(O)$_2$</td>
<td>7.1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>α-methylstyrene</td>
<td>Ru(TPP)CO</td>
<td>3.1</td>
<td>7</td>
</tr>
<tr>
<td>α-methylstyrene</td>
<td>Ru(TMP)CO</td>
<td>1.6</td>
<td>&lt;5</td>
</tr>
<tr>
<td>α-methylstyrene</td>
<td>Ru(TMP)(O)$_2$</td>
<td>1.5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>p-chlorostyrene</td>
<td>Ru(TPP)CO</td>
<td>14.0</td>
<td>8</td>
</tr>
<tr>
<td>p-chlorostyrene</td>
<td>Ru(TMP)CO</td>
<td>8.2</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

$^a$Determined by GC. $^b$Diethyl maleate and fumarate

The *trans* selectivities are very similar to those reported for iron and osmium porphyrin catalysts and only a low increase in the diastereoselectivity is observed using Ru(TPP)CO instead of the more crowded Ru(TMP)CO. The enantioselectivity was tested on the styrene using the dioxoruthenium(VI) picket-fence complex bearing optically active α-methoxy-α-(trifluoromethyl)phenyl acetyl residues on both sides of the porphyrin plane (α, β, α, β isomer) and the enantiomeric excesses obtained for the *trans* and *cis* products were 14 and 34% respectively. The formation of an active carbene ruthenium derivative was demonstrated by $^1$H NMR spectroscopy when Ru(TMP)CO was used as the catalysts. The α-carbon proton of the coordinated carbene appeared at δ 13.23 due to the deshielding effect of the porphyrin ring.

In the same year, two other communications from different groups appeared in the literature, reporting interesting results in the asymmetric catalytic cyclopropanation of styrene, both based on the same
ruthenium catalyst.\textsuperscript{48,49} This enantiomerically pure catalyst was the metal derivative of the D\textsubscript{4} porphyrin (H\textsubscript{2}P\textsuperscript{*}), which was reported, for the first time, by Halterman and Jan and is shown in Figure 6.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure6}
\caption{Figure 6}
\end{figure}

In the first paper, the results obtained using other ruthenium porphyrins were also reported. However the most interesting results were the enantiomeric excesses obtained for the \textit{trans} isomer which were reported in both the papers between 80 and 91\%. For the \textit{cis} isomer the results were less interesting and for this reason two further studies were later performed by other research groups.\textsuperscript{50,51} They used the approach developed by Gross for the synthesis of chiral porphyrins, consisting in the alkylation of the \textit{meso}-tetra(2', 6'-dihydroxyphenyl)porphyrin with chiral residues. The molecular structure of such catalysys are reported in Figure 7.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure7}
\caption{Figure 7}
\end{figure}

The Gross’ group was able to obtain 23\% of enantiomeric excess for the \textit{cis} isomer obtained by the reaction of EDA on styrene catalysed by ruthenium derivatives of the above cited chiral porphyrins.\textsuperscript{50} More recently, the structure of a ruthenium porphyrin carbene has been reported by Simonneaux and co-workers.\textsuperscript{52} Such complex was obtained by reacting Ru(TPP) with diethyl diazomalonate and it is stable at room temperature. The isolated carbene was kept to react with styrene and gave a \textit{trans/cis} ratio of 14, similar to the value of 13.8 obtained for the one-pot reaction.
Some interesting developments have been recently obtained by Che and co-workers. In a first paper they reported the immobilization of the catalysts on a soluble polymer and the use of such system for the epoxidation, aziridination and cyclopropanation of several alkenes. In particular they reported the cyclopropyl ring formation from EDA and para substituted styrenes. The yields of these reactions are quite good and the trans/cis ratio are all around 10. The second paper reports on the use of the ruthenium porphyrins as catalysts in the reactions of diazo ketones with \(\pi\)-unsaturated compounds with the formation of interesting cycloadducts.

3. Diels-Alder reaction

The Diels-Alder reaction is one of the most important synthetic process in organic chemistry and belongs to the general class of the cycloaddition reactions. In this reaction a 1, 3-diene reacts with an olefinic or acetylenic compound, the dienophile, to give a six-membered adduct. Two \(\sigma\)-bonds are formed from two \(\pi\)-bonds of the diene. Sometimes, with unreactive starting products, vigorous reaction conditions are necessary and catalysts can be useful for accelerating the process.

3.1. Catalysis by aluminium and rhodium porphyrins

It is well known from the literature that the Lewis acids are efficient catalysts for promoting the addition of the \(\alpha,\beta\)-unsaturated compounds to a diene and compounds like diethyl aluminium chloride (DEAC) catalyses this reaction affording good yields in cycloadducts. The simple reaction equation is reported in Scheme 7.

\[
\text{R}^+ + \text{Catalyst} \rightarrow \text{R}^\text{+Catalyst}
\]

### Scheme 7


<table>
<thead>
<tr>
<th></th>
<th>Cyclopentadiene</th>
<th>Isoprene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>DEAC</td>
</tr>
<tr>
<td>R=H</td>
<td>7.5%</td>
<td>67.4%</td>
</tr>
<tr>
<td>R=CH₃</td>
<td>15.7%</td>
<td>64.9%</td>
</tr>
<tr>
<td>R=CH₂CH₃</td>
<td>10.8%</td>
<td>70.8%</td>
</tr>
<tr>
<td>R=OCH₃</td>
<td>0.0%</td>
<td>77.0%</td>
</tr>
</tbody>
</table>

The mechanism of this reaction is based on the complexation of carbonyl oxygen of the \(\alpha,\beta\) unsaturated compounds by the metal which acts as a Lewis acid making the double bond more electrophilic. This fact suggested the possibility to use a metalloporphyrin as catalyst for the cycloaddition of carbonyl.
compounds to simple dienes and in Table 8 are reported the results obtained by Kodadek using Al(TPP)Cl as catalysts.\textsuperscript{64} It is interesting to note that the reaction is selective toward the substrates and only ketones and aldehydes are enough reactive to give the final compounds, while the esters are completely unreactive.

This selectivity can give the possibility to discriminate between different groups within the same starting compounds.

4. Olefination of aldehydes

The formation of the carbon-carbon double bond is an interesting and important reaction because it can be found in the synthesis of natural products and polymers.\textsuperscript{65,66} There are several methods in the literature for the conversion of different organic groups into the double bond and many are based on the catalysis by the organometallic compounds and the iron systems are particularly efficient and not expensive.

4.1. Catalysis by iron porphyrins

Recently, in the literature appeared a new application of the porphyrins catalysis based on the reaction of an iron porphyrin carbene, formed from EDA and Fe\textsuperscript{II}(TPP), with aldehydes.\textsuperscript{67} Such new method involves the formation of an olefinic compound as described in Scheme 8.

\[
\text{RCHO} + \text{N}_2\text{CHCO}_2\text{Et} + \text{Ph}_3\text{P} \xrightarrow{\text{Fe}^{\text{II}}(\text{TPP})} \text{RCH=CHCO}_2\text{Et} + \text{Ph}_3\text{P}=\text{O}
\]

\[
\text{R} = \text{Ph}, \text{p-CH}_3\text{C}_6\text{H}_4\text{-, p-ClC}_6\text{H}_4\text{-, p-NO}_2\text{C}_6\text{H}_4\text{-, PhCH}_2\text{-, Ph}_2\text{CH-}
\]

\text{Scheme 8}

Such reaction gives excellent yields of final compounds at room temperature in toluene, with good \textit{trans} selectivities. In the reaction pathway is present the triphenylphosphine which acts as oxygen scavenger forming the phospine oxide which must be separated from the other products. The yields, the selectivities and other important parameters of the above cited reaction for different substrates are reported in Table 9.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>aldehyde</td>
<td>reaction time (h)</td>
<td>yield (%)</td>
<td>turnover no.</td>
<td>\textit{trans/cis} selectivity</td>
<td>aldehyde</td>
<td>reaction time (h)</td>
<td>yield (%)</td>
<td>turnover no.</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>94</td>
<td>128</td>
<td>24:1</td>
<td>4</td>
<td>2</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>99</td>
<td>119</td>
<td>24:1</td>
<td>5</td>
<td>23</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>95</td>
<td>98</td>
<td>13:1</td>
<td>6</td>
<td>12</td>
<td>93</td>
<td>64</td>
</tr>
</tbody>
</table>

The proposed mechanism of the reaction involves the formation of a phosphorane intermediate which is actually the active species. In fact, when a phosphorane is isolated from the reaction of the carbene with
the phosphine, it produces the olefin and the phosphine oxide when reacting with the aldehyde. The formation of the phosphorane, with the final step of the reaction is reported in Scheme 9.

The reaction rates and the tran/cis selectivities seems to be affected by the nature of the aldehyde, the most reactive being those bearing electron-withdrawing groups, i.e. chlorine or nitro.

\[
\text{Ph}_3\text{P} = \text{CHCO}_2\text{Et} + \text{RCH}=\text{O} \rightarrow \text{RCH} = \text{CHCO}_2\text{Et} + \text{Ph}_3\text{P}=\text{O}
\]


**Scheme 9**

5. Cyclotrimerization of acetylene derivatives

The activation of the triple bond, namely the Reppe’s reaction, to give aromatic compounds is a well known process\(^6\)\(^8\)\(^-\)\(^7\)\(^0\) and several catalysts have been used to promote it. Such reaction, starting from mono or disubstituted acetylenes, usually gives a mixture of symmetrical (1,3,5) and unsymmetrical(1,2,4) substituted benzenes.\(^7\)\(^1\),\(^7\)\(^2\)

\[
\text{M} + \text{RC} \equiv \text{CR'} \rightarrow \text{M} \rightarrow \text{M} \rightarrow \text{R'} \rightarrow \text{R'}
\]

**Scheme 10**

The mechanism of the formation of the 1,2,4 substituted isomer was established to involve the consecutive presence of metallocyclopropene and metallocyclobutadiene compounds formed from the consecutive addition of three molecules of acetylene to the metal residue, as shown in Scheme 10.\(^6\)\(^9\)

However, a simple trend in the formation of the products was tentatively proposed on the basis of the different metals and the steric interaction between the catalysts and the intermediates. Cobalt, rhodium, nickel, aluminum and other metal complexes were used as catalysts for such reaction, which can give also the cyclooctatetraene (COT) derivatives as by-products.

5.1. Substituted benzenes from acetylenes: catalysis by iron porphyrins

In this review we want to report our recent results on the investigation of the remarkable properties, in catalysing the formation of benzene derivatives from substituted acetylenes, of Fe\(^{II}\)(Cl\(_8\))TDCPP, where
(Cl₈)TDCPP is the dianion of 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetrakis-(2’,6’-dichlorophenyl) porphyrin. The reactions were performed, when possible, without solvents at 120 °C or in boiling dry chloroform and under strictly anaerobic conditions. The catalyst was generated in situ by the cobaltocene stoichiometric chemical reduction of the iron(III) porphyrin chloride precursor. This porphyrin catalyst precursor was synthesised by literature method and its structure is reported in Figure 8.

![Figure 8](image)

An interesting observation derived from the fact that, in our experiments, only iron(II) catalyst, bearing eight chlorine atoms on the beta positions of the macrocycle, is able to catalyse the reaction while other iron(II) porphyrins, like FeTPP or FeTDCPP systematically fail. This fact, in our opinion, is related to the stabilization in the +2 oxidation state of the iron due to the presence of beta halogen atoms on the porphyrins skeleton. Furthermore, running the experiments in the presence of oxygen, which maintains the iron to +3 oxidation state, the reaction does not occur. In addition, it should be also considered the difficulties of the acetylenic compounds to be coordinated on an electron-rich iron(II). We report the molecular structures of the phenylacetylene derivatives used for the experiments in Figure 9.

![Figure 9](image)

The reaction performed on the substrates using our catalyst always give a mixture of the 1,2,4 and 1,3,5 triphenyl substituted benzenes as reported in Scheme 11 for the case of phenylacetylene. We report the
reaction yields and the selectivities for several phenyl acetylene derivatives in Table 10. The final conversions were always between 72 and 90% depending on the nature of the substituents.

![Scheme 11](image)

**Scheme 11**

**Table 10.** Catalytic cyclotrimerization of substituted phenylacetylenes using Fe$^{II}$Cl$_8$TDCPP as Catalyst (According to ref. 73).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>Conditions</th>
<th>Conversion</th>
<th>Yield(%)</th>
<th>ratio of 1, 2, 4 /1, 3, 5 products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>120° C, 18h</td>
<td>90</td>
<td>86</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>H</td>
<td>120° C, 18h</td>
<td>72</td>
<td>70</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>H</td>
<td>120° C, 36h</td>
<td>72</td>
<td>70</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td>OCH$_3$</td>
<td>H</td>
<td>120° C, 24h</td>
<td>85</td>
<td>78</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*Reaction performed in CHCl$_3$*

Another interesting reaction has been found running the experiments with phenylacetylene in the presence of benzonitrile, a reagent with a triple bond between carbon and nitrogen. We found that such triple bond acts like a carbon-carbon triple bond, giving a mixture of substituted pyridine in 60% of yield, based on benzonitrile. This reaction affords a mixture of two regio-isomers with an isomeric ratio of 26 as reported in Scheme 12.

![Scheme 12](image)

**Scheme 12**

It is also important to remark that, in our opinion, a complicated reaction mechanism is involved in the porphyrin catalysed reactions but first of all we believe to exclude the formation of the metallocycle intermediates. Such intermediates should involve the formation of two $\sigma$ metal-carbon bonds on the same face of the macrocycle and this possibility can be ruled out for the iron which does not have the suitable orbitals for binding. We propose a tentative mechanism to explain the stereochemistry found for the products and we have reported our interpretation of the obtained results, in the case of phenylacetylene in Scheme 13.
In such a scheme, the iron porphyrin coordinates the first molecule of the alkyne through a $\pi$ orbitals-metal interaction, activating the triple bond for the attack of a second molecule as in A or F, where are reported the two statistical isomers. The subsequent reaction gives unstable cyclobutadiene intermediates, as shown in B or G, still coordinated on the metal. Such adduct undergoes the attack of the third molecule of phenylacetylene, again in a statistical way, giving the intermediates C, E and H, which easily rearranges to the final benzene derivatives. The intermediate G might undergo to the attack of the third molecule of alkyne from the same side giving the 1,2,3 substituted isomer, but this possibility can be ruled out, because of the steric hindrance between the phenyls and the porphyrin.

5.2. Substituted benzenes from acetylenes: catalysis by rhodium porphyrins

As reported in the case of the cyclopropanation of the olefins by EDA, the iron(II) porphyrins are isoelectronic with Rh(III) ones and for this reason we tried to make the ciclotrimerization of alkynes in the presence of different rhodium porphyrins. The reactions were performed as reported above for the iron porphyrins but the deaeration was not necessary because the stability of the Rh(III) porphyrins is high and we did not observe any decomposition of the catalysts, even in the presence of molecular oxygen.

The results of the reactions with phenylacetylene are reported in Table 11. The yields of the reactions are lower if compared with those for the iron catalysts, but the selectivities are higher, giving in many cases, the 1,2,4 substituted isomer as the main product.

It is interesting to note that the electron-withdrawing substituents on the macrocycle seems to have an influence on the selectivities, giving higher quantities of the 1,2,4 isomer. The most intriguing observation on this catalytic system derived from the GC-mass data obtained from all the reactions performed in the presence of rhodium porphyrins. We found a chromatographic peak at a retention time shorter than those for the triphenylbenzenes, giving an m/z=204. This value corresponds to that calculated for diphenyciclobutadiene but this compound could not be isolated from the reaction media due to its high
reactivity. However, it can be concluded that the diphenylciclobutadiene can be a good candidate as a reaction intermediate in the cyclotrimerization of alkynes catalysed by rhodium porphyrins.

Table 11. Catalytic cyclotrimerization of phenylacetylene using rhodium porphyrins as catalysts (According to ref. 75).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield(% conversion)</th>
<th>ratio of 1, 2, 4/1, 3, 5 substituted products</th>
<th>ratio of 1, 2, 4/diphenylciclobutadiene products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh(TPP)Cl</td>
<td>40(48)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Rh(TDCPP)Cl</td>
<td>50(70)</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Rh(TDMPP)Cl</td>
<td>40(50)</td>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Rh(Cl16TDMPP)Cl</td>
<td>40(45)</td>
<td>8.6</td>
<td>80</td>
</tr>
</tbody>
</table>

6. Conclusions

We have reported on the catalytic formation of the carbon-carbon bond by metalloporphyrins and the extreme promising potentiality of such catalysts in the organic synthesis. The selectivities of these systems depend on the steric hindrance experimented by the substrates when approaching the core of the macrocycles and on the electronic situation of the metal. More work is necessary to have the access to new sets of reactions that can be catalysed by the metalloporphyrins and this field of research, in our opinion, can be considered a stimulating challenge for all the scientists involved in the porphyrins chemistry.

Acknowledgements

The author wish to thank all the students cited in the references who worked in his laboratory on the cyclopropanation and cyclotrimerization projects and Prof. Barbara Floris and Dr. Pierluca Galloni for their scientific contribution. He likes also to thank Giuseppe D’Arcangelo and Alessandro Leoni for their valuable technical support in recording mass spectra and GC analysis.

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PYRAZOLES AS DRUGS: FACTS AND FANTASIES

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Abstract. This review examines the past and the present of pyrazole derivatives in medicinal chemistry. From an important past, exemplified in the analgesic and anti-inflammatory pyrazolones and pyrazolindiones, not devoid of severe complications, to a glorious present with some of the most important drugs of recent times (sildenafil, celecoxib) being pyrazole derivatives. The progress of the last twenty years will be emphasized although some older references will be reported when significant.

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6. Conclusions: structure-biological activity relationships and modelling

Acknowledgements

References

1. Introduction

This review deals with the medical applications of pyrazoles and their derivatives (pyrazoles, pyrazolinones, pyrazolidines, pyrazolones, pyrazolidinones, indazoles…), hericidal and other agrochemical compounds being excluded. In general, references are from 1980 onwards but some earlier important papers are quoted; only journals have been considered, thus patents have been excluded.

In the pharmaceutical industry, pyrazoles and their derivatives are not so well considered as other azoles, such as imidazole. This is probably related to the problems associated with the large class of analgesics and anti-inflammatory agents having a pyrazole skeleton (see Sections 2.2.2. and 4.1.). These compounds, known from old, have shown a variety of serious haematological side effects, like agranulocitosis, aplastic and hemolytic anemias and thrombocytopenia.

It is true that compared with imidazoles, natural pyrazoles are rare compounds. In three ouvrages,1-3 four pyrazoles found in nature are reported: whitasomnine 1 (an alkaloid isolated from the roots of an Indian medicinal plant, Withania somnifera), pyrazofurin or pyrazomycin 2 (an antibiotic isolated from the fermentation broth of Streptomyces candidus), formycin 3 (a naturally occurring isomer of adenosine) and L-β-pyrazolyllalanine 4 (found in the seeds of many species of Cucurbitaceae).

Classification by chemical structure is important in medicinal chemistry. This allows direct considerations of structure-activity relationships. Without discarding this concern, a classification4 taking into account the mode of action of the drugs and the nature of the disease was adopted for this review. Four major classes are distinguished: agents acting on the central nervous system, pharmacodynamic and chemotherapeutic agents and agents acting on metabolic diseases and on endocrine functions.
Although in this review no attempt has been made to classify the reported compounds with a chemistry criterion, we will occasionally consider that the pyrazole nucleus is part of the central core of the drug or that it is a substituent of the pharmacophore. When the compounds have been reported in the Merck Index (13th Edition, 2001, hereafter MI) the corresponding number will be quoted in bold.

2. Agents acting on the central nervous system

Most of the novel central BDZ receptor ligands, not related to benzodiazepine, contain a pyrazole ring and thus, pyrazoloquinolines 5\textsuperscript{5}, pyrazoloquinolones 6-8,\textsuperscript{6,7} pyrazolobenzotriazines 9,\textsuperscript{8,9} pyrazolobenzoxazines 10,\textsuperscript{10} pyrazolopyrimidines 11\textsuperscript{11} or chloropyrazolyl-triazoloquinoxalines 12 have been reported in the literature.\textsuperscript{12} There are marked differences in the biological profiles of these ligands.\textsuperscript{13} Full agonist ligands exhibit anticonvulsant, sedative and muscle relaxant effects together with anxiolytic properties. In contrast, partial agonists provide anxiolytic activity without the undesired side effects and inverse agonists cause the opposite behavioural effects such as anxiogenesis and proconvulsant action. Since small modifications in the structure of pyrazole containing ligands can cause a shift from agonistic to antagonistic activities, common structural features responsible for specific intrinsic activity have been studied. Recently, several pharmacophore models have been proposed although they have not achieved yet the ability to correctly predict the intrinsic activity.\textsuperscript{11,12,14} The pyrazoles that display a specific medical application will be reported in the corresponding sections.

2.1. Antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics

The extraordinary variety of subtypes, increasing importance and manifold CNS activities of serotonin receptors,\textsuperscript{15-18} decided us to describe here some pyrazoles acting on 5-HT\textsubscript{1A} (depression, section
2.1.1., references 19-21; anxiety, section 2.1.3., reference 22), 5-HT$_3$ (emesis, section 3.2.2., references 23,24) and 5-HT$_4$ receptors. Close to serotonin is the N-methyl-d-aspartate receptor (NMDA)$^{18,25}$ related to depression (section 2.1.1., reference 26). They will be discussed in the corresponding sections, save a publication dealing with the 5-HT$_4$ receptor, whose proposed therapeutic applications include the treatment of irritable bowel syndrome, atrial arrhythmias, urinary incontinence, and various diseases of the central nervous system.$^{27}$

The authors have identified $\text{LY353433 (1-[(1-methylethyl)-N-[2-[4-[(tricyclo[3.3.1.1$^{3,7}$dec-1-yl-carbonyl)amino]-1-piperidinyl]ethyl]-1H-indazole-3-carboxamide} (\text{13})$ as a potent and selective 5-HT$_4$ receptor antagonist with clinical suitable pharmacodynamics.$^{27}$

\begin{center}
\textbf{13}
\end{center}

2.1.1. Antidepressants

In the search of drugs with antidepressant activities and reduced adverse effects, pyrazoles, as part of a tricyclic structure or not, were found to be interesting compounds. Among a series of indazoles studied in the late seventies, 14 (FS-32) presented antidepressant properties with a pharmacological profile different from conventional benzodiazepine derivatives.$^{28}$ In this context, ten years later, the corresponding pyrazole, fezolamine, $N,N$-dimethyl-(3,4-diphenyl-1H-pyrazole)-1-propanamine (15), was identified by Sterling-Winthrop Research as a potential antidepressant with significant reduced side effects.$^{29}$

Tricyclic structures 9 containing a pyrazole moiety$^8$ and pyrazoloquinolin-3-ones$^{30}$ have been synthesised to evaluate their GABA$_A$-benzodiazepine receptor affinities. 3-Chloropyrazole as substituent of tricyclic heterocycles, triazoloquinoxalines 12, has shown to be efficient for binding to the GABA$_A$-benzodiazepine and A$_1$/A$_2A$-adenosine receptors.$^{12}$ It is worthy to note that most of the adenosine receptor antagonists, which are of interest for the treatment of depression, dementias or morbus Parkinson, are pyrazolopyrimidines or pyrazolopyridines and some of them are currently under clinical development.$^{31}$

Pyrazolopyrimidine structures 16$^{32}$ have been also studied for their antagonistic properties for the corticotropin releasing factor CFR-1 receptor whose activation is related to depression and anxiety. In search of new class of neuroleptic drugs, pyrazolo[1,5-$a$]pyridine structures 17$^{33}$ have been evaluated for presynaptic dopamine autoreceptor agonist activity.

An attempt to substitute the terminal carboxylic group of (S)-$\alpha$-aminoacidipic acid, an excitatory amino acid (EAA) by a 3-pyrazolone failed because the compound did not show significant effects on EAA receptors.$^{26}$

2-Pyrazolines bearing a thiocarbamoyl group 18 have been reported as good leads for BSAO-bovine serum amine oxide inhibitors.$^{34}$ These enzymes, which seem to display biochemical behaviour similar to that of MAOB, are useful models in the search of antidepressant, antiparkinson and anticholinergic agents.

It is assumed that 5-HT$_{1A}$ receptors are implicated in major depressive disorders. Ligands (buspirone, ipsapirone) reported so far are partial agonists and present limited clinical efficacy and long duration of onset. As a consequence, these last years, efforts have been dedicated to design ligands with high intrinsic
activity. Among these studies, pyrazole,\textsuperscript{19,20} as a \( \pi \)-electron-releasing substituent of 6-substituted-2-pyridinylmethylamine, has shown to increase recognition and activation of 5-HT\(_{1A} \) receptors.

\begin{center}
\includegraphics[width=\textwidth]{figures.png}
\end{center}

2.1.2. Antipsychotics

Due to the interest in improving antipsychotic efficacy and neurological side effects of antipsychotic agents such as chlorpromazine, a series of 1,3-dialkyl-4-(iminoaryl)methyl)-1\(H\)-pyrazol-5-ols 19 has been described.\textsuperscript{35} Since they do not act via the brain dopamine receptors like classical antipsychotics do, they do not present neurological side effects such as the extrapyramidal syndrome or dyskinesia; structural modifications were examined to further reduce their toxicity.\textsuperscript{36}

Recent advances in molecular biology have identified five cloned human subtypes of dopamine receptors. The human D\(_4 \) subtype receptors have been reported to be involved with antipsychotic activity. Pyrazolopiperidine 20 and a series of structural analogs have been identified as novel highly and selective human D\(_4 \) receptor antagonists.\textsuperscript{37,38} Structural modifications include incorporation of piperazine in place of piperidine and conformational restriction to give 4,5-dihydro-1\(H\)-benzo[g]indazoles. A recently reported CoMFA study describes the correlation of biological activity with structural parameters of twenty-five dopamine D\(_4 \) antagonists; the lead compound was 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-\(a \)]pyridine, FAUC113.\textsuperscript{39}

\begin{center}
\includegraphics[width=\textwidth]{figures.png}
\end{center}

Modulation of the dopaminergic system by neurotensin (NT) receptor antagonists offers the possibility of a new treatment for psychotic disorders. The first non-peptide antagonist of the NT receptor, pyrazole 21, was reported by Quéré et al.\textsuperscript{40,41} providing a pharmacophoric model of neurotensin non-peptide antagonists and new information about NT receptor subtypes.

2.1.3. Anxiolytics

Lesopitron 22 (E-4424), a pyridinylpiperazine substituted by 1-butyl-4-chloropyrazole, was introduced in 1994 as a new non-benzodiazepine anxiolytic acting on 5-HT\(_{1A} \) receptors, showing greater
anxiolytic potency, lack of sedative effects, sustained activity even on long-term treatments and lack of withdrawal problems. Lesopitron, currently in advanced clinical trials (phase III), has been shown to be efficient and safe in patients with generalised anxiety disorder.

Behavioural effects in mice of pyrazolopyrrolodiazepines 23 have been studied and some of these compounds have shown anxiolytic activity similar to that of diazepam with weak anticonvulsant and sedative actions.

2.1.4. Sedatives and hypnotics

Recent studies of non-benzodiazepine compounds acting at benzodiazepine recognition sites, which form part of the GABA<sub>A</sub> receptor complex, suggested that sedative effects of agonists are mediated by the BZ<sub>1</sub>-benzodiazepine receptor subtype. Of particular interest is zaleplon, N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide 24, a BZ<sub>1</sub>-receptor selective ligand. Zaleplon (Sonata, Wyeth-Pharma, MI 10165) is a non-benzodiazepine sedative hypnotic which has been recently introduced for clinical use, indicated for short-term treatment of insomnia and showing weak anxiolytic activity and reduced risk of tolerance.

2.2. Anticonvulsants, analgesics, anti-Parkinson and anti-Alzheimer drugs

2.2.1. Anticonvulsants

In 1979, Kornet et al. reported pyrazolidines 25 as potential anticonvulsant agents, showing moderate anticonvulsant activity in the maximal electroshock seizure and pentylenetetrazole seizure assays.

Recent investigations on 3-amino-4-arylpyrazoles 26 revealed a strong anticonvulsant activity in vivo. These pyrazole structures have been proposed to fulfil requirements of a suggested pharmacophore for sodium channel blocking compounds. In particular, a derivative of this series, 4-chlorophenyl-3-
(morpholin-4-yl)-1H-pyrazole, blocked sodium channels and was strongly effective in the maximal electroshock seizure test.

Pyrazolopyrimidin-7-ones, e.g. 27, benzodiazepine receptor ligands, have been tested in vitro to determine their agonism/antagonism profiles and in vivo for anticonvulsant activity.\textsuperscript{11}

2.2.2. Analgesics

Although classified in different sections, we should note the close relationship existing between analgesics (this section) and anti-inflammatory drugs (section 4.1). This was, by far, the main area of biological activity of pyrazoles often associated with antipyretic activity. In reference 3 are reported several analgesics which are part of the Merck Index (11\textsuperscript{th} Edition).

They belong to three main classes: pyrazolin-5-ones (piperylone, 7449; benzpiperylon, 1131; antipyrine, 748; pyramidon, 488; metamizol or dipyrone, 3358; aminopropylon, 484; morazone, 6176), pyrazolin-3,5-diones (phenylbutazone, 7248; kebuzone, 5168; sulfinpyrazone, 8926; mofebutazone, 6141; phenopyrazone, 7217; oxyphenylbutazone, 6925) and one pyrazole (actually, an acetic acid, lonazolac, 5445). Other compounds described in the same book are: difenamizole (3123), epirizole (3572), apazone (758), feprazone (3953), pipebuzone (7424), propyphenazone (7884), ramifenazone (8122), suxibuzone (8990) and thiazolinobutazone (9236) (a salt of phenylbutazone with 2-aminothiazoline) (Schemes 1 and 2). Some of them (piperylone, phenopyrazone, oxyphenylbutazone) have dissapeared in the 13\textsuperscript{th} Edition of MI.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{example.png}
\caption{Scheme 1}
\end{figure}

Structural modifications and pharmacological studies of these pyrazoles have been extensively studied in the late 70's and in the 80's. For example, lipophilic derivatives of the analgesic
oxyphenylbutazone 6925 have been designed seeking for locally applicable nonsteroidal anti-inflammatory activity.\textsuperscript{52}

\begin{center}
\begin{tabular}{c}
\includegraphics[scale=0.5]{scheme2}
\end{tabular}
\end{center}

Scheme 2

Another example is the study in 1985 by Beyer et al.\textsuperscript{53} of the metabolites of nifenazon 28, an analgesic that belongs to the pyrazolin-5-ones class used, as already commented, in the management of pain and inflammation. Research focused on this class of analgesics is still very active. New 3-pyrazolin-5-ones 29\textsuperscript{54} and new 2-pyrazolin-5-ones 30\textsuperscript{55} have recently shown in vivo, antinociceptive properties superior to those of antipyrine and acetylsalicylic acid in mice. A review by Mehlisch compared analgesic efficacy of pyrazolinones (dipyrone) with salicylates and acetaminophen:\textsuperscript{56} in comparable amounts, dipyrone seemed to be less effective in reducing mean pain relief, however, it produced greater relief in postepisiotomy pain.

Besides the main families already described, various pyrazole structures display antinociceptive activity. Recently, it has been shown that pyrazolo[3,4-c]pyridazines and related systems are of interest as analgesics and anti-inflammatories.\textsuperscript{57} Analgesic properties of 1-methyl-3-alkyl-3-arylpyrazolidines 31 have been assessed in mice using the hot-plate test. Some of the pyrazolidines were about one half to one-third as active as phenacetin.\textsuperscript{58} Indazole revealed to be an interesting nucleus in this field. Structural modifications of the anti-inflammatory agent bendazac 85 (section 4.1.), an indazole derivative, have provided compounds showing analgesic effects along with anti-inflammatory properties.\textsuperscript{59,60} Pyrazolopyridine hydrazones have been prepared and their antinociceptive activity was evaluated by the classical acetic acid test in mice.\textsuperscript{61} The authors concluded that this series could represent a pharmacophoric tool for the development of more efficacious analgesics. Some \(N\)-substituted 1-(2- or 3-aminopropyl)-3,5-diphenylpyrazoles have shown weak analgesic, antipyretic, anti-arrhythmic and hypotensive activities and marked anti-inflammatory effect in mice and rats.\textsuperscript{62} These pharmacological properties have also been observed in 1-aryl-1\(H\)-pyrazoles\textsuperscript{63} such as 1-phenyl-1\(H\)-pyrazoles 32\textsuperscript{64} and 33\textsuperscript{65} and pyrazoles condensed with a thiophene moiety.\textsuperscript{66} Cizolirtine,\textsuperscript{67} 34 (E-3710; citrate salt: E-4018) is a new analgesic currently undergoing advanced clinical trials. The presence of a chiral centre in this molecule prompted academic and pharmaceutical industry researchers to obtain each enantiomer separately in order to compare their biological activities with that of the racemic. Therefore, the optical resolution of (±)-cizolirtine has been realised by the classic procedure of recrystallising diastereoisomeric salts\textsuperscript{68} and by an efficient enantioselective synthesis;\textsuperscript{69,70} the use of cyclodextrins as NMR chiral resolving agents has also been reported.\textsuperscript{71} With regard to analgesic activity,\textsuperscript{72} no significant difference
was observed between the pure enantiomers and the racemic compound. Epibatidine, a natural alkaloid, isolated from the skin of an equatorial frog is a novel, highly potent, non opioid analgesic agent and a specific agonist of central nicotinic acetylcholine receptors. Replacement of the chloropyridyl ring of the epibatidine structure by 4-pyrazole has been reported.\(^7^3\) The moderate binding potency of the 4-pyrazole analog \(^3^5\) was somewhat disappointing when compared with the high binding potency of the isoxazole analog. The authors suggested that the presence of the N-H functionality in \(^3^5\) hinders efficient hydrogen bond formation with the acetylcholine receptor.

There have been several reports in the literature dealing with pyrazole derivatives which beside analgesic properties show other biological activities, one concerned pyrano[4,3-c]pyrazoles \(^3^6\) which showed analgesic effects together with antipyretic, anti-arrhythmic and hypotensive activity in rats or mice, as well as weak anti-inflammatory, local anesthetic and \textit{in vitro} platelet antiaggregating activity.\(^7^4\) Another one dealt with indazoles \(^3^7\) whose pharmacological evaluation \textit{in vivo} showed a predominant significance as analgesic, antiarrhythmic (section 3.1.1.) and local anaesthetic agents.\(^7^5\) Finally, long-acting fentanyl analogs having a N-(1-phenylpyrazolyl)-N-(1-phenylalkyl -4-piperidyl) propanamide structure \(^3^8\) have been recently described.\(^7^6\)

\begin{align*}
\text{2.2.3. Anti-Parkinson drugs} \\
\text{In the late nineties, Baraldi et al.}^{7^7,7^8} \text{ presented an emerging class of new selective A}_{2\alpha} \text{ adenosine receptor antagonists, pyrazolo[4,3-c][1,2,4]triazolo[1,5-c]pyrimidines} \; 39. \text{ The development of A}_{2\alpha} \text{ antagonists will contribute to a better understanding of the role of A}_{2\alpha} \text{ receptors in physiological and pathological states and will provide potential drugs for the treatment of cerebral ischemia or}
\end{align*}
neurodegenerative disorders, such as Parkinson’s disease. Other pyrazolo[4,3-\(e\)][1,2,4]triazolo[1,5-c]pyrimidines 40 have been reported by the same author to be highly potent and selective human A\(_3\) adenosine receptor antagonists.

As already reported in section 2.1.1. related to antidepressants, thiocarbamoyl pyrazolines 18 represent a new class of BSAO inhibitors. According to their evaluation of experimental parkinsonism \textit{in vivo}, these pyrazolines can be considered leads for anti-parkinson agents. Since neuroleptic drugs may be useful for depression and Parkinson’s disease, pyrazolo[1,5-\(a\)]pyridines 17, dopamine autoreceptor agonists already described in section 2.1.1., might be targets for treatment of neuropsychiatric disorders.

\begin{center}
\includegraphics[width=\textwidth]{images/39_40.png}
\end{center}

**2.2.4. Anti-Alzheimer drugs**

In current strategies to treat the cognitive symptoms of Alzheimer’s disease, the loss of cholinergic transmission is improved either by increasing the availability of acetylcholine \textit{via} cholinesterase inhibitors or by direct stimulation with a cholinergic agonist. Although the search for cholinergic agonists has focussed on ligands selective for muscarinic M\(_1\) cholinergic receptor subtype, Plate \textit{et al}.
\cite{80} have observed that ligands for M\(_3\) receptors might present therapeutic benefit. Thus, from a series of 3-(pyrazolyl)-1,2,5,6-tetrahydropyridine derivatives designed to measure M\(_3\) functional activity, compound 41 has shown some positive mnemonic properties in rats.

\begin{center}
\includegraphics[width=\textwidth]{images/41_42_43.png}
\end{center}

Drugs that combine cholinergic and adrenergic properties are part of the strategies to attenuate symptoms of Alzheimer’s disease, a recent example being that of 3,5-dimethylpyrazoles 42 which have shown moderate activities in both muscarinic and adrenergic receptor binding tests.\cite{81}

Pyrazoles 43, synthesized as heterocyclic analogs of glutamic acid, have shown biological activity at central glutamate receptors.\cite{82} Several diseases such as Alzheimer’s disease, septic shock, inflammatory arthritis, schizophrenia, impotence and susceptibility to infection involve disfunction of the three nitric oxide synthase (NOS) isoforms (neuronal, endothelial or inducible macrophage) which regulate NO production. Recently, 1\(H\)-pyrazole-1-carboxamidines have been shown to be competitive inhibitors of all three isoforms:
the most selective compound, 1\textit{H}-pyrazole-\textit{N}-(3-aminomethylanilino)-1-carboxamidine, was 100-fold selective for neuronal NOS over endothelial NOS.\textsuperscript{83}

In neuroprotection studies, concerning inhibition of NOS by indazole agents, it was confirmed that 5-nitro-, 6-nitro-, and 7-nitroindazoles exert their action by hindering oxygen to bind. 7-Nitroindazole, as selective inhibitor of neuronal nitric oxide synthase, has been studied for neuroprotective activity and was used to investigate the role of nitric oxide.

\textbf{2.3. Pyrazoles acting on the cannabinoid receptors}

Pyrazoles play a major role in cannabinoid chemistry. Two subtypes of cannabinoid receptors are currently recognised, CB\textsubscript{1}, found in brain and neuronal cells, and CB\textsubscript{2}, found mainly in spleen and immune cells.

In 1994, Sanofi\textsuperscript{85} reported pyrazole SR141716A (Rimonabant), \textbf{44}, as the first cannabinoid antagonist possessing nanomolar affinity. This selective and orally active CB\textsubscript{1} antagonist has become an experimental tool for studying CB\textsubscript{1} subtype recognition and activation and for clinical applications such as treatment of psychosis, eating disorders or memory deficits.\textsuperscript{86}

The availability in 1997 of a highly specific antagonist SR144528 (\textbf{45}),\textsuperscript{88} for the CB\textsubscript{2} receptor has allowed to investigate the architecture of ligand binding sites, whose approach was difficult due to the structural disparity of cannabinoid agonists, and to investigate also the respective contribution of cannabinoid receptor subtypes in functional cannabinoid effects \textit{in vivo}. Its potential therapeutic applications include immune disorders such as rheumatoid arthritis, multiple sclerosis, psoriasis, infections and asthma.

Various derivatives of SR141716A have been synthesized\textsuperscript{89,90} and Makriyannis \textit{et al.}\textsuperscript{91} have reported a SAR study of pyrazole derivatives as cannabinoid receptor antagonists and have proposed structural requirements for CB\textsubscript{1} antagonistic activity: they suggested that the structural properties of 1- and 5-substituents are primarily responsible for the antagonist activity.
An iodophenyl derivative of SR141716A, pyrazole 46 $^{[123]}$IAM281, showed to be suitable for in vivo imaging of human brain CB1 receptors using positron emission tomography (PET) or single photon emission computed tomography (SPECT), two techniques already used to study the pharmacokinetics and pharmacodynamics of abuse drugs in the human brain. Recently, the syntheses of two $^{[18]}$F-labeled analogs of 44 and 46, both by incorporation of the label into a fluoromethyl group have been reported.

3-Azido- and isothiocyanato-substituted aryl pyrazoles have been suggested to be useful tools for the investigation of tolerance and receptor down-regulation both in vitro and in vivo studies. Recently, it has been proposed that inverse cannabimimetic effects produced by pyrazoles (CB1 or CB2 antagonists) are due to inverse agonistic rather than pure antagonistic properties. It has also been recently demonstrated, that aryl pyrazole SR141716 and the new synthesized pyrazole CP272871 (47), behave as antagonists and as inverse agonists in G-protein-mediated signal transduction in endogeneous expressed CB1 receptors.

3. Pharmacodynamic agents

3.1. Antiarrrhythmics, antianginals, vasodilators, antihypertensives, diuretics, antithrombotics and anti-allergics

3.1.1. Antiarrrhythmics, antianginals, vasodilators, antihypertensives

In the search of antihypertensive agents, the angiotensin II (AII) levels, involved in the regulation of blood pressure can be reduced either by inhibiting the angiotensin converting enzyme (ACE) or by antagonising the AII receptors directly.

Since the discovery of losartan (DuP753) (48), the first orally active nonpeptide AII receptor antagonist several structurally related compounds have been synthesized. For example, researchers at Yamanouchi have replaced the imidazole ring of DuP753 by a bicyclic ring providing a series of azopyrazolo[5,1-a]imidazoles (49) from which compound 49a was the most interesting. A three-fold improvement in potency was achieved by the introduction at position 6 of the pyrazolotriazoles of a C-linked oxygen functional group which resulted in compound 49b, the most interesting of this series.

Based also on the biaryltetrazole structure of losartan, C-linked pyrazole biaryl tetrazoles have been prepared by Glaxo. Derivatives of general formula 50 are potent orally active AII antagonists selective for the AT1 receptor. Their oral activity seems to be very sensitive to the nature of the nitrogen substituent and thus the cyclopropylmethyl derivative 50a is very effective at lowering blood pressure in hypertensive rats, whereas the closely related cyclobutyl analog 50b is ineffective despite having superior activity in vitro.

Carpibem have also prepared two series of C-linked pyrazole derivatives, 5-oxysubstituted pyrazoles and 5-C-substituted pyrazoles. The biphenyl tetrazole derivatives 5-C-substituted turned out to be the most active and compound 50c, UP 221-78, was claimed to be equipotent to losartan in oral antihypertensive activity in rats.

Independently, researchers at Merck have also reported 3-alkyl-1-phenyl-pyrazole-5-carboxylic acids incorporating also the biaryltetrazole substituent as AII receptor antagonists which can also be represented by the general formula 50. A more recent publication has dealt with 5-(biphenyl-4-ylmethyl) pyrazoles in which the disposition of the ring nitrogen atoms was altered. Compound 51, UR-7280, showed high potency in vitro and in vivo and has been selected for clinical evaluation as an antihypertensive agent.

Computer graphics have been used to design hexahydropyrazolo[1,2-a]pyridazine diones as bicyclic mimetics of the angiotensin converting enzyme (ACE).
A different kind of antihypertensive agents are the $\alpha_1$-adrenoceptor antagonists of which prazosin (52a, MI 7803) is the reference compound. Pyrazole analogs have been synthesised (52b) but all of the compounds displayed lower affinity for the $\alpha_1$ receptor than prazosin.\textsuperscript{104}

Within this context, a series of new 3-aryl-tetrahydropyrazolo[4,3-c]pyridines (53) was synthesised and screened for in vitro \textsuperscript{3}H prazosin displacement activity. Compound 53a (L 16052), was selected for further pharmacological evaluations.\textsuperscript{105}

In what concerns cardiotonic agents, a prototype of them that has both inotropic and vasodilator activities are 6-aryl-tetrahydroprazidin-3-ones. Imazodan (54a) and bemoradan (54b) are two representatives of this family which are supposed to exert their actions by selective inhibition of phosphodiesterase type 3 enzymes (PDE3). Many different structural variations have been performed in this series and related to pyrazoles, two compounds are worth mentioning. One is meribendan (54c), which was the most interesting compound from a series of benzimidazolyl-pyridazinones. Meribendan inhibited myocardial PDE3, showed an interesting calcium sensitising effect and was selected for development as a positive inotrope.\textsuperscript{106} The other interesting compound is the pyrazolo[4,3-b][1,4]benzoxazine 54d derivative, a pyrazole fused analog of bemoradan (54b) which had displayed potent positive inotropic actions in vivo and had more than twice the peak of activity of the parent compound 54b.\textsuperscript{107}

In a conceptually different approach, the pyridazinedione ring of these structures has been replaced by a pyrazolone. Since it is well known that a key element for inotropic activity in this series is an acidic hydrogen adjacent to a polar group, a number of 4,4'-disubstituted pyrazolones, in which the tautomeric keto form is blocked, were synthesised and their inotropic activity studied.\textsuperscript{108} Among these ring contracted
analogs of imazodan, compounds 55a and 55b were the most interesting. The PDE III inhibitory activity of the five-membered pyrazolone 55a was similar to that of its six-membered analog imazodan (54a). The tetrahydrobenzimidazole derivative 55b was the most potent compound of this series.

Pyrazolopyrimidines, such as 56a-c, showed positive inotropic effects similar to milrinone, a potent nonglycosidic cardiotonic agent belonging to the 5-arylpyridinone family. Selective endothelin A (ET\textsubscript{A}) receptor antagonists can be used for the treatment of diseases in which a pathophysiological role for endothelin has been implicated such as hypertension, ischemic diseases and artherosclerosis. In an extensive report dealing with the SAR of 4-phenoxybutanoic acids as ET\textsubscript{A} receptor antagonists, a promising derivative was the pyrazole diacid 57 which was designed to fit the requirements of the cation binding model proposed. The compound did show interesting binding properties but it had negligible oral bioavailability in the rat. Another series of pyrazole-5-carboxylic acids as endothelin antagonists has been described; these compounds have potent ET\textsubscript{A} selective, mixed ET\textsubscript{A}/ET\textsubscript{B}, or moderately ET\textsubscript{B} selective antagonist activities.

Endothelin converting enzyme (ECE) inhibitors are expected to produce therapeutic benefits similar to those proposed for ET receptor antagonists. In the reported approach, SM-19712 {4-chloro-N-{[(4-cyano-3-methyl-1-phenyl-1\textsubscript{H}pyrazol-5-yl)amino]carbonyl} benzenesulfonamide, monosodium salt} proved to be a structurally novel, potent and selective inhibitor of ECE, and represents a new tool for elucidating the pathophysiological role of ECE.

3.1.2. Diuretics

Interesting diuretic activity has been reported for phenylpyrazolo[1,5-\textit{a}]pyridines 58. The most interesting compound 58a, of which only the (\textit{R})-enantiomer was active, turned to be a potent and selective adenosine antagonist.
Although 58a, FK 453, was a potent diuretic in several species it had low bioavailability, poor solubility in water and, in solution, was isomerized to the less active isomer. To overcome these problems, the researchers from Fujisawa used SAR studies and the X-ray crystal structure of FK 453 to improve the pyrazolo[1,5-a]pyridine diuretics by introducing heteroaryl groups at position 3 of the ring. Among these A1 receptor antagonists exemplified by formulae 59, compound 59a, FK 838, incorporating a butanoic moiety, is undergoing clinical trials. A newer, water-soluble derivative within this series is 59b, FR 166124, of which an improved synthesis through a novel Horner-Emmons isomerization has been published.

3.1.3. Antithrombotics

Antithrombotic drugs can act on several steps of the coagulation cascade being of significant importance the control of platelet aggregation. One effective approach is the control of the prostacyclin (PGI2) thromboxane A2 (TXA2) system. A large variety of heterocyclic compounds have been described as TXA2 synthetase inhibitors including a series of ω-carboalkenyl pyrazoles represented by 60, of which 60a was the most interesting.

Monge et al. have reported pyridazino[4,5-b]indole derivatives which have additional inotropic properties. Compound 61a was the first compound described to have both activities as inhibitor of PDE-4 and selective inhibitor of TXA2 synthetase. A further modification of the structure including a triazole moiety 61b which had a good profile as an inodilator with anti-aggregating activity due to the inhibition of phosphodiesterase.
Another approach is to develop analogs of prostacyclin (PGI2), the most powerful endogenous stimulator of blood platelet adenylate cyclase which inhibits platelet activation. Triphenyl-1H-pyrazole-1-nonanoic acid (62) is a non-prostanoid prostacyclin mimetic which inhibited ADP induced human platelet aggregation. Other pyrazole containing PGI2 agonists without the PG skeleton are the di- or tetrahydronaphthalene 5-oxyacetic derivatives with a 4-benzhydryl pyrazole group such as 63.

The synthesis and inhibitory effects on cyclooxygenase, lipoxygenase and thromboxane synthetase of 3-amino-4,5-dihydro-1H-pyrazoles and related compounds have been reported, the trifluorophenyl methyl derivative 64 being the most interesting.

A series of papers by Mosti and others, have dealt with pyrazole derivatives that beside anti-aggregating properties have also analgesic, anti-inflammatory and antipyretic activities such as 4-carboxy-1-phenyl-1H-pyrazole-5-propanamides and thieno[3,4-c]pyrazoles.

Since the final step in platelet aggregation is the binding of fibrinogen to activated glycoprotein IIb/IIIa, inhibitors of this protein are another possibility to obtain anti-aggregating agents. In this context, the design and synthesis of orally active, long-acting non-peptide fibrinogen receptor antagonists have been reported. Compound L-738,167 (65) inhibited the aggregation of human gel-filtered platelets, probably due to its high-affinity binding to GPIIb/IIIa on circulating platelets.

Very recently, direct inhibition of factor Xa, a trypsin-like serine protease holding the central position that links the intrinsic and extrinsic mechanisms in the blood coagulation cascade, has emerged as an attractive strategy for the discovery of novel antithrombotic agents. A SAR study of a series of pyrazoles culminated in the discovery of DPC423, 1-[3-(aminomethyl)phenyl]-N-[3-fluoro-2′-(methylsulfonyl)-1,1′-biphenyl]-4-yl]-3-(trifluoro-methyl)-1H-pyrazole-5-carboxamide, a highly potent, selective, and orally active factor Xa inhibitor which was chosen for clinical development.

In 1991 was identified the protease-activated receptor-1, PAR-1, a thrombin receptor which represents an attractive drug discovery target for the possible treatment of various disorders such as thrombosis, restenosis, atherosclerosis, inflammation, cancer metastasis, and stroke. So far, the only PAR-1 antagonists were synthetic peptides containing the recognition sequence SFLLRN. Ten years later, through a de novo design approach, was generated a novel series of indole-based PAR-1 antagonists. Optimization of this series, through in vivo studies, led to an indazole-based SFLLR peptide mimetic (RWJ-58259). This potent and selective PAR-1 antagonist served as a pharmacological tool for assessing the therapeutical potential of these ligands in different disorders.

Several recent papers have dealt with the synthesis and biological evaluation of pyrazoles and indazoles as activators of the nitric oxide receptor soluble guanylate cyclase (sGC). sGC catalyses the
conversion of GTP to cGMP and is the only known receptor for the signalling molecule nitric oxide, NO. The NO-cGMP signalling pathway is important in many physiological processes including vasodilatation, neurotransmission and platelet aggregation. Using the structure of 66 (YC1, a known activator of sGC) the authors generated 2D substructural queries in commercially available compound databases and found that benzydamine 67 (see also section 4.1.) a known anti-inflammatory and analgesic agent, of unknown mechanism, was a more potent activator of sGC than YC-1.

SAR studies indicated that the indazole ring of 67 could be replaced by appropriately substituted pyrazoles and thus, compounds 68, 69a and 69b showed potent activation of sGC and potent inhibition of platelet aggregation, showing no significant inhibition of phosphodiesterases or NO synthases.

Researches from Bayer have also reported NO-independent stimulators of guanylate cyclase mainly derivatives of pyrazolopyridinylpyrimidine, BAY 41-2272 (70) being selected for further studies.

Finally, a paper dealing with pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives as potent inhibitors of A2A adenosine antagonists will be discussed in this section because the functional studies reported were platelet aggregation inhibition which is one of the biological responses mediated by the A2A receptor subtype (see also section 2.2.3.). Adenosine which has already been mentioned along this review modulates a wide range of physiological functions by interacting with specific cell surface receptors (A1, A2A, A2B and A3), and the efforts made by the medicinal chemists have focused on obtaining selective agonists and antagonists. Baraldi et al. have reported the design and synthesis of pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives bearing alkyl and arylalkyl chains on positions 7 and 8, as represented by general formula 71. Some compounds were potent and selective A2 antagonists and their potential for treating CNS disorders such as Parkinson’s disease should be further studied.

3.1.4. Anti-allergics

Researchers at Dr. Esteve Laboratories have reported the synthesis and SAR studies of a new series of benzimidazoles (72) as H1 antihistaminic agents. The best antihistaminic activity required the
simultaneous presence of a homopiperazinyl benzimidazole system/or a methylene link between the benzimidazole and the piperazine ring and an unsubstituted pyrazole ring.

![Chemical structure]

72

3.2. Drugs acting on gastrointestinal, respiratory and urogenital systems

3.2.1. Antihistaminics

A pyrazole derivative, \([5-(3-N'2,2,2-trifluoroethyl)guanidino]pyrazol-1-yl\) (ICI 162,846) has been reported as a histamine H2-receptor antagonist.\(^{130}\)

3.2.2. Antiemetics

Antagonists of the serotonin 5HT\(_3\) receptor are now used clinically for the treatment of emesis. An example is granisetron (73, MI 4551) in the market since 1991 for the treatment of chemotherapy induced nausea.

![Chemical structures]

73

One of the first 5HT\(_3\) antagonists reported was tropisetron (MI 9853), a tropanyl ester of indole-3-carboxylic acid which was used for performing bioisosteric replacement of the indole moiety by an indazole.\(^{131,132}\) Pyrazolo[1,5-\(a\)]pyridines and pyrazolo[1,5-\(b\)]pyridazines have also been reported as indole isosteres of selective 5HT\(_3\) antagonists.\(^{133}\)

In an extensive SAR study on \(N\)-benzyl-1,4-diazepin-carboxamides, compound 74 was identified to be equipotent to ondansetron (MI 6916) and granisetron (73).\(^{23}\) The resolution of this compound by preferential crystallization has also been reported (see also section 2.1.).\(^{24}\)

3.2.3. Respiratory system

Using solution phase parallel synthesis and SAR studies for the optimization, a series of 3,5-bis(trifluoromethyl)pyrazoles have been reported as a novel class of NFAT transcription factor regulator. The compounds are novel inhibitors of cytokine production and even inhibit IL-2 production with a 10-fold enhancement over the immunosuppressive drug, cyclosporine. The difluoromethoxy ether 75 showed remarkable efficacy in an Ascans-induced nonhuman primate model of asthma.\(^{134}\)

In Pfizer laboratories, high-throughput file screening against inhibition of human lung phosphodiesterase 4 (PDE4) led to the discovery of 3-ethyl-1-(4-fluorophenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1\(H\)-pyrazolo[3,4-\(c\)]pyridine (76) as a novel PDE4 inhibitor. Subsequent SAR development, using
an eosinophil PDE assay, led to analogs which were up to 50-fold more potent than 76, one interesting example being CP-220,629 (77). Almirall-Prodesfarma investigations led to the synthesis and biological evaluation of 2,5-dihydropyrazolo[4,3-c]quinolin-3-ones, a novel series of PDE4 inhibitors, such as 78, with low emetic potential and antiasthmatic properties.

![Chemical Structures](image)

3.2.4. Urogenital system

On 27 March 1998, the US Food and Drug Administration approved sildenafil citrate (Viagra) (80, MI 8563) for treating male erectile dysfunction (MED). The drug works by inhibiting cyclic guanosine monophosphate (cGMP) phosphodiesterase Type 5 (PDE5). Further structural manipulations have included α-thiagra, the thiophene bioisoster, and monagra, a chiral 5-(2-methyl-2,3-dihydro-7-benzofuryl)-pyrazolo pyrimidone analog.

![Chemical Structure](image)

In Bristol-Myers Squibb recent PDE5 screening of a series of pyrazolopyridines identified a lead compound with modest potency. Based on this template and using parallel synthesis, merged a new pyrazolopyridine showing comparable in vitro functional PDE5 inhibition as sildenafil and improved PDE isozyme selectivity. Thus, due to its pharmacokinetic profile, it is expected to have fewer PDE-related side effects than sildenafil.

The synthesis of a series of halogenated 1-benzylindazole-3-carboxylic acids with anti-spermatogenic properties have been described.

3.3. Drugs acting on skin diseases

3.3.1. Psoriasis

Tyrosine kinases are attractive targets for the design of therapeutic agents because deregulated tyrosine kinase activity has been observed in many proliferative diseases such as cancer, psoriasis, etc. A pharmacophore model of the ATP-binding site of the epidermal growth factor receptor (EGFR) kinase has
been built and used successfully to design selective kinase inhibitors such as phenylamino-pyrazolo[4,3-d]pyrimidines.\textsuperscript{142}

4. Agents acting on metabolic diseases and on endocrine functions
4.1. Anti-inflammatory drugs and antiarthritics

The coexistence in the same molecule of analgesic (section 2.2.2.) and anti-inflammatory activities is common, and so, in the present section, these compounds previously commented will no longer be discussed. Many compounds are also described as antipyretics.

This field has many subsections related to the different ways to attack inflammatory processes. One is the arylacetic acids,\textsuperscript{3} related to fenclofenac and sulindac, for instance bufezolac 81, lonazolac 82 (MI 55587) and trifezolac \textsuperscript{83} or Schering’s pirazolac 84 (MI 7571).\textsuperscript{144-146} Somewhat related to them are benzadac 85 and benzydamine 67 (MI 1124). Egyptian authors have studied pyrazol-4-yl-propenoic acids and found some compounds more potent than ketoprofen.\textsuperscript{147}

\begin{center}
\includegraphics[width=\textwidth]{4.png}
\end{center}

Progress in the understanding of the inflammatory processes led to the search of inhibitors of both the cyclooxygenase (COX) and lipoxygenase (LOX) pathways of the arachidonic acid cascade. In this way tepoxalin 86 was prepared and found to be a potent anti-inflammatory agent.\textsuperscript{148,149}

The discovery of a second, inducible form of cyclooxygenase (COX-2) that exists along with the constitutive form (COX-1) led to the hypothesis that selective inhibitors of COX-2 would be anti-inflammatory without causing the side effects associated with inhibition of COX-1 in the gastrointestinal tract and kidney. This is for the moment most promising approach, which ultimately led Searle to SC-58125 87 and then to celecoxib SC-58635 88 (MI 1968) useful for the treatment of rheumatoid arthritis and osteoarthritis.\textsuperscript{150,151} Fujisawa has developed 89\textsuperscript{152} and Uriach presented a series of pyrazolo[1,5-a]pyrimidines as potent and selective COX-2 inhibitors.\textsuperscript{153}

Other groups, like ASTA, have approached the problem by inhibiting the enzyme 5-LOX. By analogy with zileuton, one of the first launched 5-LOX inhibitors for the treatment of asthma (see section 3.2.3.), they prepared a series of 1,5-disubstituted indazol-3-ols, the most potent being 90.\textsuperscript{154} Mosti \textit{et al.} also reported indazoles related to angelicin, like compound 91a, which shows good anti-inflammatory and antipyretic properties, while 91b shows significant local anaesthetic activity.\textsuperscript{155}

A completely different approach was used by Sanfilippo \textit{et al.} who defined as target the cell adhesion molecules (CAMs).\textsuperscript{156} These molecules are important in the regulation of the immune response and inflammation. An agent that inhibits leukocyte adhesion and transmigration represents a novel mechanism of
action as an immunosuppressive (section 5.2.) and/or anti-inflammatory drug. In this way, these authors identified RWJ-50271 92 as a potent anti-inflammatory.

For the treatment of hyperuricemia and chronic gout, the antiurolitic agent allopurinol 93 (MI 276) an inhibitor of xanthine oxidase is still in much use as the numerous publications about it testify. Leonard has prepared prox-benzoisoallopurinols 94 and 95 that inhibit xanthine oxidase only in concentrations comparable to their $K_m$.

Recently, looking for novel anti-allergic agents, indazole-3-ols and indazole-2-ones were synthesized and exhibited a high anti-inflammatory activity both i.p. and orally; one of the pyrazoles is expected to be useful in the treatment of a variety of eosinophilia-mediated disorders, including bronchial asthma.

**4.2. Hypoglycemic, hypolipidemic and antiobesity agents**

For the treatment of diabetes, a series of hypoglycemic agents derived from pyrazoles have been prepared and tested. Thus, the metabolism of sulfonylurea SPC-703 96 was reported by Polish authors. Shroff et al. have described the synthesis of thirty-eight benzimidoyl-pyrazoles, the two more interesting compounds 97 and 98, combine in one molecule some of the biological activities of the $\beta$-cytotrophic sulfonylureas and some of the activities of the biguanides.
Derivatives of 4,5,6,7-tetrahydro-7,8,8-trimethyl-3-phenylamino-4,7-methano-2H-indazoles 99 with hypotensive and hypoglycemic activities have been described by Italian authors.\(^\text{161}\) But the most interesting antidiabetic in this field is WAY-123783 (100), obtained after extensive SAR studies; it acts by blocking SGTL (sodium-glucose cotransporter) in the kidney.\(^\text{162}\)

The approach to the treatment of diabetes by means of arginin-vasopressin (AVP) receptor antagonists has lead Wyeth-Ayerst to N-[4-[(4,5-dihydropyrazolo[3,4-d]thieno[3,2-b]azepin-6(2H)-yl)carbonyl]phenyl]benzamides 101-102, potent and orally active.\(^\text{163}\) Novartis has studied the effect of 1,3-diaryl-(1H)-pyrazole-4-acetamides 103 on glucose-utilization in ob/ob mice:\(^\text{164}\) compounds such as 103a represent a potentially new class of agents for the treatment of diabetes.
In the field of hypolipidemic (also known as hypocholesterolemic and antihyperlipoproteinemic) agents, most publications deal with ACAT (acylCoA: cholesterol O-acyltransferase, EC 2.3.1.26) inhibitors. For instance, a number of 6,7-dihydro-4H-pyrazolo[1,5-a]pyrrolo[3,4-d] pyrimidine-5,8-diones 104, developed by Upjohn, were found to be potent modulators of serum lipoprotein levels in cholesterol-fed rats. Several other pharmaceutical companies, have explored ACAT inhibitors: Rhone-Poulenc Rorer 105 (RP 70676) and 106 (RP 73163), Parke Davis 107, DuPont Merck 108 (the presence of the dimethylamino groups caused a significant drop-off in potency compared with RP 70676) and Fujisawa 109 (FR 186054).

A more recent approach is that of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) inhibitors of the class of "statins". Researchers at Parke Davis prepared and evaluated a series of 1,3,5-trisubstituted pyrazolomevalonolactones, concluding that 110 is almost equipotent to compactin lactone. The same company has described 111, claimed to be as much more efficacious than lovastatin.

For the treatment of obesity, Henke from Glaxo Wellcome, has optimised a series of 3-(1H-indazol-3-ylmethyl)-1,5-benzodiazepines, potent and orally active CCK-A agonists derived from 112. Amongst a series of aminoguanidines and diaminoguanidines analogs of the antidiabetic/antiobesity agent 3-guanidopropionic acid, compound 113 is devoid of activity. Rimonabant, 44, is in clinical trials as an antiobesity drug.

4.3. Peptide and steroidal hormones

Steroidal pyrazoles have been known for a long time. Kirsche (ref. 3, p. 405) reported several of these compounds like cortivazol 114 (MI 2565, X-ray structure) and stanozolol 115 (MI 8873), both important and commonly used drugs. Cortivazol 114 is an anti-inflammatory glucocorticoid while stanozolol 115 is an anabolic steroid used as androgen. Nivazol 116 also belongs to the glucocorticoid class. As will be discussed in section 5.1., some steroidal pyrazoles have been proposed for the treatment of prostate cancer through inhibition of human cytochrome 17α-hydrolase-C17,20-lyase (P45017α).

Postmenopausal osteoporosis is caused by increased bone resorption following the loss of endogenous estrogens. Hormone replacement therapy with steroidal estrogens has been shown to prevent the onset of osteoporosis, however the observed increase in uterine cancer has limited its utility. The major inorganic component of bone is hydroxyapatite (HA), a hydrated form of calcium phosphate. In order to identify compounds for use as "bone targeting" agents, Wilson et al. decided to identify small molecules with HA affinity.
Amongst these compounds, 4-carboxy-3-hydroxypyrazoles 117 and 118, demonstrated good HA affinity which it is unaffected by the nature of the $N$-1 substituent. In a subsequent paper,\textsuperscript{179} they combined the bone targeting affinity of these pyrazoles with the non-steroidal estrogen hexestrol preparing compounds 119 ($n = 1$ or 4) which retained weak estrogenic activity \textit{in vitro}.

In a series of papers, Katzenellenbogen \textit{et al.}\textsuperscript{180-183} developed a series of 1,3,5-triaryl-4-alkylpyrazoles selective agonists for the estrogen $\alpha$-receptor (ER$\alpha$). The optimised core for high-affinity ER binding and agonist potency is represented by 120 ($X = H$, $OH$, $R = \text{alkyl}$). The most potent is $R = \text{Pr}$, $X = OH$ with an affinity ca. 50% that of estradiol. These compounds were the subject of considerable structural variation, changing the 1,3,5-triaryl-4-alkyl by the 1,3,4-triaryl-5-alkyl series with a decrease in affinity and, using basic side chains, developed a series of ER antagonists like 121.
Related to neurotensin [an endogenous tridecapeptide neurotransmitter (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Try-Ile-Leu-OH) that has been called the peptide for the next millennium,184] is SR 142948A 2-{[5-(2,6-dimethoxyphenyl)-1-(4-(N-(3-dimethylaminopropyl)-N-methylcarbamoyl)-2-isopropyl-phenyl)-1H-pyrazole-3-carbonyl]amino}adamantane-2-carboxylic acid, hydrochloride (122), a new and extremely potent neurotensin (NT) receptor antagonist.185

4.4. Liver alcohol dehydrogenase inhibitors

Liver alcohol dehydrogenase (EC 1.1.1.1) catalyses the first step in alcohol metabolism and is a rational target for inhibiting alcohol metabolism. Prevention of poisoning by methanol and damaging effects of ethanol metabolism are potential applications of inhibitors of alcohol dehydrogenase. From the pioneering work of Theorell186 it is known that pyrazole and some of its 4-substituted derivatives (methyl, iodo and bromo) are potent inhibitors of ethanol metabolism in vivo. Pyrazoles have been proposed as therapeutic agents for treatment of alcohol intoxication. Unfortunately, pyrazole is itself toxic and may not be useful for long-term treatment of humans.

Although some interesting efforts have been made, including X-ray studies and molecular modelling,187-190 4-methylpyrazole (fomepizol) continues to be the most efficient and less toxic of all the liver alcohol dehydrogenase inhibitors and inactivators. Note also, that pyrazole itself, an alcohol dehydrogenase inhibitor, has dual effects on N-methyl-D-aspartate (NMDA) receptors of hippocampal pyramidal cells, agonist and noncompetitive antagonist (see Section 2.1.).191

5. Chemotherapeutic agents

5.1. Anticancer drugs

Pyrazoloacridine, PZA, 123, 9-methoxy-N,N-dimethyl-5-nitro-pyrazolo[3,4,5-kl]acridine-2(6H)-propanamine (NSC 366140) is the first of a new class of rationally synthesised acridine derivatives to undergo clinical testing as an anticancer agent. Recent studies suggest that PZA might be a dual inhibitor of
DNA topoisomerases I and II and exerts its effects by diminishing the formation of topoisomerase-DNA adducts. PZA exhibits broad-spectrum antitumor activity in pre-clinical models in vivo and displays several remarkable properties including solid tumour selectivity, activity against hypoxic cells, and cytotoxicity in noncycling cells. PZA has been studied in phase I trials in adults and children, and is currently undergoing broad phase II trials. No significant antitumour activity has been seen in gastrointestinal malignancies and prostate cancer. Due to its unique properties, combination studies with other antineoplastic agents are in progress.\textsuperscript{192,193} 

Katayama et al.\textsuperscript{194,195} have demonstrated that some quaternary salts of pyrazolo[1,5-\textit{a}]indole derivatives 124-126 possess strong anticancer activities against cancer cells both in vitro and in vivo tests. These studies have also shown that quaternarization on the nitrogen of position 1 (pyrazolium salts) is essential for anticancer activity, since the free bases 127 lost most of their activity. Besides, the size and lipophilicity of the substituent at position 2 seem to be crucial for the in vitro activity, since in the case of small 2-alkyl substituents the anticancer activity is lower. These compounds also showed strong inhibitory activities against both DNA topoisomerase I and II, which could be the main course of their anticancer activity.

The alkylating agents represent one of the most efficient therapies in use for the treatment of several types of human tumours. These agents have in common the property of becoming strong electrophiles through the formation of carbonium ion intermediates or of transition complexes with the target molecules. These reactions result in the formation of irreversible covalent bonds with biomolecules (nucleic acids, enzymes, structural proteins, lipids or amino acids), by alkylating several of their nucleophilic moieties. Pyrazolysulfonlhydrazones 128 bearing electron-withdrawing substituents in the phenyl ring presented cytostatic activity against HeLa cells, being the \textit{p}-nitro derivatives the most effective ones.\textsuperscript{196} A quantitative structure-activity study of several binuclear pyrazoles 129-131 demonstrated that only those derived from the 4,4-\textit{bis}pyrazole ring 129 have shown interesting activity against HeLa cells, being 1,1'-dibenzyl-3,3',5,5-tetramethyl-4,4'-bispyrazole a powerful cytotoxic agent.\textsuperscript{197} 5-Benzamido-4-diazopyrazoles 132 have also shown moderate activity against a panel of human leukaemia, lymphoma and solid tumour cell lines,\textsuperscript{198} while pyrazolo[4,3-\textit{e}]pyrrolo[1,2-\textit{a}][1,4]diazepinones 133 revealed appreciable in vitro antitumor
activity on a L 1210 tumour cell line.\(^{199}\) Recently, some 2-pyrazoline-1,3,5-triazine derivatives \(^{134}\) possessing strong inhibition on various tumour panel cell lines derived from nine cancer types (leukaemia, lung, colon, brain, melanoma, ovarian, prostate, renal and breast) have been described.\(^{200}\)

The broad spectrum of biological properties of formycin 3 [1-C-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-1,4-anhydro-(1S)-D-ribitol, now called formycin A to differentiate it from its related derivative formycin B [1,4-dihydro-3-β-D-ribofuranosyl-7H-pyrazolo[4,3-d]pyrimidin-7-one] are related to its ability to replace an adenosine unit in a number of enzymatic reactions at the nucleotide level.\(^{201}\) The great importance of formycins A and B has led to the design and synthesis of new nucleoside analogues with modifications either in the carbohydrate or/and in the base. From a series of some substituted pyrazoles and pyrazolo[4,3-d]-1,2,3-triazin-4-one nucleosides and pyrazolo[3,4-d]oxazoles, Manfredini \textit{et al.}\(^{202-204}\) found that 135 presented moderate cytostatic activity against T-cells while 136 and 137 were potent and selective cytotoxic agents against T-lymphocytes. Certain pyrazole C-nucleosides 138 and 139 showed moderate cytotoxic effects against mouse neuroblastoma tumour cell lines, while the former showed also moderate activity against baby hamster kidney tumour cell lines.\(^{205}\) However, a study of structure-activity relationship of pyrazoles related to nucleosides, involving modifications of the glycosylic portion, showed that N-substituted pyrazoles 140 and 141 displayed no interesting cytotoxicity and antiproliferative activity on several leukaemia/lymphoma and solid tumour cell lines.\(^{206}\)

![Chemical Structures](image)

Certain pyrazolo[3,4-d][1,2,4]triazolo[2,3-a]pyrimidines 142 and 143 have shown high binding affinity for DNA. The presence of the 1,2,4-triazole nucleus seems to be crucial for this antitumor activity since the other pyrazolo[3,4-d]pyrimidines 144 and 145 presented lower affinity for DNA.\(^{207}\)

The binding affinity and specificity of pyrazoles to DNA was also demonstrated when they were incorporated in eight-ring hairpin polyamides, which specifically recognise predetermined sequences as...
side-by-side pairs in the minor groove of DNA. When they were incorporated at the N-terminus of the synthetic polyamides, the pair 3-pyrazole/pyrrole mimics the imidazole/pyrrole pair but with enhanced binding affinity and sequence specificity for guanidine-cytosine base pairs. The N-methylpyrazole/N-methylpyrrole pair, incorporated at the middle of these polyamides, specifies the adenine-thymine/thymine-adenine base pairs.

Anticancer drugs still have limited efficacy against numerous tumour types because cancer cells can develop mechanisms of resistance allowing them to evade chemotherapy. One type of multidrug resistance has been shown to be mediated by an energy dependent P-glycoprotein (PGP) which possesses low substrate specificity. A large number of actual used drugs are eliminated through PGP mediated efflux. In this context, the search for new drugs active towards such cells is of crucial interest for future cancer treatments. Pyrazolo[4,5-g]pyrido[1,2-a]benzimidazoles and exhibited significant in vitro cytotoxic activities against human leukaemia K562S and HL60S sensitive cell lines, but lower than the commercial drug doxorubicin. In the case of resistant cell lines (multidrug resistance +; K562R and HL60R) compounds and doxorubicin showed the same activity. These results indicate no resistance phenomena against these leukaemia cells.

In the search of new pharmacophores as antitumor agents, Ejima et al. discovered that the pyrazole hydrochloride derivatives and showed in vitro cytotoxic activity against P388 leukaemia cells and PC-6 human lung carcinoma cells. The most potent derivatives were those having a halogen atom at the o- and m-positions of the phenyl ring, which exhibited potent cytotoxic activity against some tumour cell lines including multidrug resistance cell lines due to the overexpression of P-glycoprotein. Among these compounds, the m-chloro derivative (R₁ = H, R₂ = m-Cl) was one of the most interesting.
Protein dependent kinases (PDK) play a key role in regulating the cell cycle machinery. An increasing body of evidence has shown a link between tumour development and PDK-related malfunctions and this has led to an intense search for small molecules of the PDK family as an approach to cancer chemotherapy. To date, only two compounds (flavopyridol and UCN-01) have entered into clinical trials as cancer chemotherapeutics based on cyclin dependent kinase (CDK) inhibition mechanism. Indenopyrazoles 150 were disclosed as a new structural class of cyclin dependent kinase inhibitors. These compounds are selective for the CDK related serine/threonine kinase family and are active in cell culture against a transformed human colon carcinoma cell line (HCT116). In addition, these compounds demonstrate in vivo activity by reducing tumour growth in a human xenograft mouse model in a dose dependent manner. 212

The epidermal growth factor receptor (EGF-R) is known to be overexpressed in a large percentage of clinical cancers of various types and to be associated with poor diagnosis. Inhibitors of the EGF-R PTK are therefore expected to have great therapeutic potential in the treatment of malignant and non-malignant epithelial diseases. Using a pharmacophore model for ATP-competitive inhibitors interacting with the active site of the EGF-R PTK, Traxler et al.213 developed a series of 4-(phenylamino)-1H-pyrazolo[3,4-d]pyrimidines 151 and 152 as highly potent inhibitors of the EGF-R tyrosine kinase, which also showed high selectivity toward a panel of nonreceptor PKCα and CDK1. Additionally, two of these compounds 152 (R1 = m-Cl, R2 = Cl or CH3, X = NH) showed satisfactory oral bioavailability in mice after oral administration and exhibited good in vivo efficacy in a nude mouse tumour model using xenografts of the EGF-R overexpressing A431 cell line. Denny et al.214 prepared a series of 5-[(3-bromophenyl)amino] pyrazolo[3,2-g]quinazolines and pyrrolo[3,2-g]quinazolines, 153 and 154, which also showed high potency for the inhibition of tyrosine kinase activity of the isolated EGF-R and of its autophosphorylation in EGF-stimulated A431 cells.

17-(1H-Pyrazol-1-yl)androstadiene 155 may be an alternative for the treatment of androgen-dependent diseases, namely prostate cancer, which is the second leading cause-related mortality in men in the USA and Europe. This compound is a moderate inhibitor of the human steroidal enzyme 17α-hydroxylase-C17,20-lyase (P45017α) a cytochrome P450 monooxygenase complex that catalyses the formation of androgens; its inhibition is an actual strategy in the treatment of patients with prostatic cancer. However, the actual drugs are not very potent inhibitors of P45017α and cause significant side effects, while 17-azolyl steroids, including 155, are specific inhibitors of this enzyme. 177
Although retinoids are thought to have great therapeutic potential, their toxic effects have so far limited their clinical use mainly to dermatological diseases and also some cancers, for which retinoids may have both therapeutic and chemopreventive applications. Recent research has focused on the synthesis and development of subtype-selective retinoids in order to reduce their toxicity. Nagai et al.\textsuperscript{215} synthesised a series of pyrazoles 156 as candidate retinoid acid receptor (RAR) agonists. These compounds have strong transactivation activities, but one of them, 4-[5-(1,5-diisopropyl)-1H-3-pyrazolyl]-1H-2-pyrrolyl]benzoic acid 156b, showed selective transactivation activity for the RAR\(_a\) receptor and had highly potent cell-differentiating activity on HL-60 cells.

Adenosine deaminase (ADA) is present in all mammalian cells and plays a central role in the differentiation and maturation of lymphoid system cells. Deficiency and abnormalities of this enzyme are reported in some leukaemia and immunodeficiency (including AIDS) diseases. It has been suggested that modulating ADA activity may be a target for chemotherapy. Among azole derivatives, pyrazoles were those presenting the lowest inhibitory activity on ADA.\textsuperscript{216}

In the 80s some authors studied the effects of pyrazole on animals treated with carcinogenic and mutagenic agents.\textsuperscript{217,218} Moriya et al. demonstrated that unsubstituted pyrazole is an effective inhibitor of the carcinogenicities of two large-bowel carcinogens, 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM), in rats when taken orally. They showed that this activity of pyrazole is due to its ability to inhibit at least two steps in the metabolism of DMH and AOM, preventing the formation of carcinogenic species.\textsuperscript{217,218}

5.2. Immunosuppressants and immunostimulants

Moyer et al. working at Pfizer discovered that pyrazolo[3,4-\(f\)]quinoline derivatives such as 157 are potent immunostimulants \textit{in vivo}.\textsuperscript{219,220} Scientists from Novartis, reported pyrazole bioisosters of leflunomide 158 (MI 5451) as B-cell immunosuppressants for xenotransplantation and chronic rejection with only compound 159 being equipotent with leflunomide.\textsuperscript{221}
5.3. Antiviral, antibacterial, antiparasitic, antiprotozoa and fungicides

5.3.1. Antiviral

The identification of HIV as the causative agent of AIDS has prompted an intense international research effort to find effective therapies for this disease. One of the prime targets of research has been the effort to find inhibitors of the essential aspartic protease (PR) of HIV. Several HIVPR (saquinavir, ritonavir, indinavir and nelfinavir) have been approved by the FDA and are being used in AIDS therapy in combination with reverse transcriptase (RT) inhibitors. However, the ability of the virus to generate resistant mutants suggests that there is an ongoing need for new, structurally diverse HIVPR inhibitors. Using the structural information gathered from the X-ray structures of various cyclic urea/HIVPR complexes, researchers from Dupont Merck Pharmaceutical company designed and synthesised many nonsymmetrical P2/P2'-substituted cyclic urea analogues 160. Their efforts have been concentrated on using an indazole as one of the P2 substituents since this group imparted enzyme potency as well as translation into excellent antiviral potency. The second P2 substituent was used to adjust the physical and chemical properties in order to maximise oral bioavailability. Using this approach several very potent and orally bioavailable compounds were discovered, 161 (R = H or 3-pyrazolyl) being the lead structures.\(^{222-225}\)

Some pyrazole nucleosides 136 and 162 inhibited the HIV-1 multiplication in acutely infected C8166 and Vero cells, and 136c showed a selective, although not potent, activity against the coxsackievirus,\(^{202,226}\) whereas compounds 132, 137, 140, 141 and 163 displayed no interesting antiviral activity, including HIV-1.\(^{198,203,206}\) The C-nucleoside antibiotics formycin A 3 and formycin B have also shown antiviral properties.\(^{201}\)

![Chemical structures](image)

Win 41258-3 164 \{4-[6-(2-chloro-4-methoxyphenoxy)hexyl]-3,5-diethyl-1H-pyrazole\}, a watersoluble pyrazole, showed \textit{in vitro} and \textit{in vivo} activity against herpes simplex virus types 1 and 2 (HSV-1 and -2). \textit{In vivo} it was effective against HSV-1 and -2 in mouse genital infection, after intravaginal administration, and also against guinea pig skin infection, produced by HSV-1, by topical application.\(^{227}\) Some pyrazolo[3,4-d]pyrimidines 143 and 144 also showed \textit{in vitro} activity against several types of virus, including the HSV-1.\(^{207,228}\)

Preliminary bioassays showed that some of the 3-methyl-1H-pyrazole-4-carboxylic ester derivatives 165-167 presented antiviral activity against TM Virus.\(^ {229}\)

The capacity of an organism to produce interferon in response to infection by viruses of certain protozoan parasites is thought to be an important non-specific defence mechanism. The interferon system is the earliest component of the host defence to become operative following virus infection and may also play a role in the later stages of recovery. It is now well established that, once evoked, interferon will inhibit the
replication of a wide variety of both RNA- and DNA-containing cytopathic and oncogenic viruses. An agent which stimulates release and/or in vivo synthesis of interferon has thus implications for the development of clinically useful broad-spectrum antiviral drugs. In a structure-activity study Crenshaw et al.\textsuperscript{230} found that pyrazolo[3,4-b]quinoline derivatives \textbf{168} are a new class of low-molecular-weight inducers of interferon.

On the basis of the antiviral activity of 1-adamantaneamine (amantadine) and in order to assess the possible pharmacodynamic effect of the adamantyl group, a highly lipophilic hydrocarbon moiety associated with the compact symmetrical architecture of the adamantane molecule, a series of N-adamantyl azoles and benzazoles have been tested against Semliki Forest Virus (SFV). Pyrazoles \textbf{169} protected cells from cytopathic effect at lower concentrations than amantadine, whereas they had equal or lower toxicity.\textsuperscript{231}

![Chemical structures](image)

\textbf{5.3.2. Antibacterial}

There are some natural antibiotics that contain a pyrazole ring, such as pyrazofurin or pyrazomycin \textbf{2} (an antibiotic isolated from the fermentation broth of \textit{Streptomyces candidus}) and formycin \textbf{3} (section 1.). Formycin has antiviral (section 5.3.1.) and antitumor properties (section 5.1.) and its total synthesis has been reported several times.\textsuperscript{201} Recently, Russian authors\textsuperscript{232} have described fifteen fluorescent pseudomonas, isolated from the rhizosphere of agricultural plants, which were similar in both their phenotypic properties and the chemical nature of produced pigments, to the previously described \textit{Pseudomonas fluorescens} var. \textit{pseudoiodinum}. DNA-DNA hybridization data showed their genetic similarity (but not identity) to different varieties of \textit{P. fluorescens}. A family of antibiotics-fluvios, belonging to pyrazolo[4,3-e]triazine derivatives, was isolated from studied strains; isolation, properties, antimicrobial and antitumor activity of \textit{fluvios} A \textbf{170}, B, C \textbf{171}, D \textbf{172}, and E \textbf{173} are described. Two other antibiotics APHE-1 and APHE-2 \textbf{174} have been isolated from the culture filtrate and mycelia of \textit{Streptoverticillium griseocarneum} NCIMB 40447 and their structure has been established as pyrazolo-isoquinolinone derivatives.\textsuperscript{233}
In the 80s a number of new parenteral cephalosporins with a broad spectrum of antibacterial activity and high stability against various β-lactamases have been marketed. They showed excellent activity against Gram-negative bacteria except *Pseudomonas aeruginosa* and moderate activity against Gram-positive bacteria, especially *Staphylococcus aureus*. Kawabata *et al.*\textsuperscript{234} prepared 3'-quaternary ammonium cephalosporins \textbf{175} which possess antibacterial activity superior to the marketed cephalosporins. For instance, 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-amino-2-methylpyrazolium) methyl-3-cephem-4-carboxylate showed extremely potent broad-spectrum activity against both Gram-positive bacteria, including *S. aureus*, and Gram-negative bacteria, including *P. aeruginosa*. Following the discovery of a non-natural 1β-methylcarbapenem antibiotic by a Merck Sharp & Dohme research group, Nagao *et al.*\textsuperscript{235} prepared a new derivative \textbf{176} bearing a σ-symmetric bicyclopyrazoliumthio group as a pendant moiety which exhibited excellent antibacterial activities against several strains.

β-Lactams exert their activity by acylation of several specific enzymes, the penicillin binding proteins (PBP’s), involved in bacterial cell wall biosynthesis. Jungheim *et al.*\textsuperscript{236-239} have prepared several
bicyclic pyrazolidinones 177-180 as \(\gamma\)-lactam analogues of the \(\beta\)-lactam antibiotics, assuming that these compounds might possess sufficient reactivity to react with the referred enzymes. Several of the synthesised compounds exhibited broad spectrum \textit{in vitro} antibacterial activity against a variety of Gram-positive and Gram-negative bacteria and one of the lead compounds 180 (LY186826) is indeed a bacterial cell wall synthesis inhibitor which acts on \(\beta\)-lactam target enzymes.

Mupirocin is the compound utilised by SmithKline Beecham for Bactroban ointment, which is a highly effective topical antibiotic for the treatment of skin infections and for the prevention of nasal carriage of multiple resistant \textit{S. aureus} in the hospital environment. The replacement of the metabolically sensitive alkoxycarbonyl moiety by a variety of heterocycles, yielded antibacterially active compounds in the case of oxazoles, while pyrazole analogues 181 were poorly active.\textsuperscript{240}

A structure-activity relationship study on the bacteriocidal and bacteriostatic ability of azasteroids 182-186 showed that they possess moderate \textit{in vitro} inhibitory activity against \textit{Bacillus subtilis} and \textit{Pseudomonas fluorescens}.\textsuperscript{241} Pyrazoles 187-189 were ineffective against standard strains of several bacteria\textsuperscript{242} while others like 189 showed inhibitory effect on the growth of \textit{S. aureus}.\textsuperscript{147} Some pyrazolo[1,5-\(a\)]pyrimidines (e.g. 190 and 191) showed \textit{in vitro} moderate antibacterial activity against some Gram-positive and Gram-negative bacteria\textsuperscript{243,244} and various pyrazolo-azaquinoline carboxylic acids 192 and 193 showed interesting activity against some Gram-positive bacteria but were ineffective against some Gram-negative bacteria.\textsuperscript{245} Some pyrazoloquinolines 194 and pyrimidoindazoles 195 showed potent antibacterial activity against \textit{S. aureus} and \textit{Streptococcus foecalis} and moderate activity against Gram-negative bacteria.\textsuperscript{246} 5-Benzamido-4-diazo-pyrazoles 132 have shown \textit{in vitro} inhibitory activity against Gram-positive bacteria, some of them being active at concentrations equal to that of streptomycin.\textsuperscript{198}

Apart from classical barbiturates, the pyrimidine ring is present in several pharmaceuticals, such as antimicrobial and antitumour agents. In the search of new, non-benzodiazipine anxiolytic drugs, Spanish researchers evaluated the action of bacteria \textit{Agrobacterium} sp. DSM 6136 and \textit{Rhodococcus erythropolis} DSM 6138 on a series of unexplored pyrazolylpyrimidines, including the anxiolytic lesopitron 22. They found that all their substrates were regioselectively oxidised, when free, at the C-2 and/or C-4 positions of the pyrimidine moiety, up to a maximum of two oxidations.\textsuperscript{247}

Multi-drug-resistant Gram-positive bacterial pathogens have become a serious problem in hospitals and the community being particularly alarming the emergence of staphylococcal strains with reduced susceptibility to vancomycin. More recently, a multinational team reported high rates of resistance among aerobic Gram-negative bacilli in European care units. Thus, the search for novel potent broad-spectrum antibacterial agents is being fervently pursued by pharmaceutical houses world-wide. A series of new nitrogen-carbon-linked (azolylphenyl)oxazolidinone antibacterial agents has been prepared in order to
expand the spectrum of activity of this class of antibiotics to include Gram-negative organisms. Some of these azolyl derivatives presented good antibacterial activity in vitro and in vivo against the fastidious Gram-negative organisms Haemophilus influenzae and Moraxella catarrhalis.

Helicobacter pylori is a causative agent of gastritis and gastric ulcers in humans and has also been associated with some types of gastric cancers. The widespread use of a battery of antibacterials for treatment of general infections has generated resistant strains of H. pylori in patient populations. Recently, it was reported a class of pyrazole-based compounds which are the first examples of H. pylori-specific antibacterial agents; in culture these compounds inhibit the growth of H. pylori selectively, showing no effect on other Gram-negative and Gram-positive bacteria or humans.

DNA gyrase (E.C. 5.99.1.3) is a well-established antibacterial target. It is an essential prokaryotic type II topoisomerase with no direct mammalian counterpart. It is involved in the vital processes of DNA replication, transcription and recombination. DNA gyrase catalyses the ATP-dependent introduction of negative supercoils into bacterial DNA as well as the decatenation and unknotting of DNA. In the search of novel inhibitors of DNA gyrase, Hoffmann-La Roche researchers developed a promising alternative approach to random screening which is based on the detailed 3D structural information of the targeted ATP
binding site. The 3D guided optimisation provided highly potent DNA gyrase inhibitors, e.g. indazole 198 is a tenfold more potent DNA gyrase inhibitor than the marketed drug novobiocin. 250

5.3.3. Antiparasitic and antiprotozoa

Malaria remains one of the most important infectious diseases in the world. A significant and increasing problem in malaria control is the resistance of malaria parasites to available chemotherapeutic agents. There is a pressing need to identify new antimalarial drugs. Charris et al. 251,252 reported the synthesis of 3-amino-9-phenylpyrazolo[3,4-b]-4-quinolones and 2,4-diamino-10-phenyl-pyrimido[4,5-b]-5-quinolones, which showed to be an interesting family of antimalarial agents in vitro. More recently this group showed that 3-amino-9-methyl-1H-pyrazolo[3,4-b]-4-quinolone 199 derivatives possess high antimalarial activity in vitro against a chloroquine-resistant strain of Plasmodium falciparum. 253 Nifurtimox (nfx) is the most important drug for the treatment of trypanosomiasis. However its use is limited due to its mutagenicity, side effects and non-curative action in certain cases. In these circumstances the development of new compounds alternative to the currently used nfx is a research area of great importance. In the search of new and more potent drugs against Trypanosoma cruzi, the aethiological agent of Chaga’s disease or American trypanosomiasis, some of us demonstrated that azole derivatives 200 and 201, structurally related to nfx, inhibited in vitro the growth of this protozoa. 254,255 Some of these compounds showed trypanocidal activity similar to that of nfx. However the in vivo assays indicated that they were not able to completely eradicate the infection in treated mice.

As pyrazolo[3,4-b]pyrazines have demonstrated important biological properties, recently El-Kashef et al. 256 synthesised several new derivatives and evaluated their antiparasitic activity against Trichomonas vaginalis and promastigotes of two Leishmania strains. Compound 202 displayed good in vitro activity against both parasites while compound 203 showed greater trichomonacidal than leishmanicidal activity; they also reported that pyrazole 204 has the same behaviour.

Benzimidazoles are the anthelmintic agents against the intestinal nematodes of sheep with the broadest known spectra of activity, but 1- and 2-carbamoylbenzotriazoles are also reported to have similar activity. However 1- and 2-acyl, alkoxy carbonyl- and carbamoylindazoles 205 and 206 showed some activity against Trichinella spiralis in mice but none of them demonstrated activity against sheep nematodes. 257
5.3.4. Fungicides

The field of antifungal azoles has been reviewed comprehensively by Zirngibl in 1998.\textsuperscript{258} It is apparent that the chemical basis of these drugs is dominated by imidazole and 1,2,4-triazole derivatives, other azoles, like pyrazole, playing a minor role. Although in our introduction we have pointed out that herbicidal and other agrochemical compounds will be excluded from this review, this is a difficult aspect in the present section because most fungus used in preliminary tests have no relevance in human medicine.

Aiello \textit{et al.}\textsuperscript{259} demonstrated that nitrosopyrazoles \textsuperscript{207} and \textsuperscript{208} displayed antifungal activity at non-cytotoxic concentrations. They showed that the lead compound (\textsuperscript{208}, R = CH\textsubscript{3}CH\textsubscript{2}) was 9 times more potent \textit{in vitro} than miconazole and 20 times more selective against \textit{Cryptococcus neoformans}, a pathogen for immunocompromised patients, and also 8- and 125-fold more potent than amphotericin and fluconazole, respectively. Activities higher than that of chlotrimazol \textsuperscript{209} were found for some \textit{N},\textit{N}-bis-azolylarylmethanes including pyrazole and indazole derivatives \textsuperscript{210}. A related approach was used by Menozzi \textit{et al.} but with another imidazole derivative, bifonazole \textsuperscript{211}, the resulting [\textit{a}-(1,5-disubstituted 1\textit{H}-pyrazol-4-yl)benzyl]azoles \textsuperscript{212} were tested \textit{in vitro} against \textit{Candida albicans} and other fungus with no significant results.\textsuperscript{261}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/figures.png}
\caption{Chemical structures of selected azole derivatives.}
\end{figure}

A series of pyrazolo[1,5-\textit{a}]pyrimidines were synthesised and tested as systemic fungicides, the parent compound \textsuperscript{213} was quite a potent inhibitor of mycelial growth.\textsuperscript{262} The pyrazolo[3,4-\textit{b}]pyrazines \textsuperscript{202} and \textsuperscript{203} and several other derivatives described in the paper of El-Kashef \textit{et al.}\textsuperscript{256} have also antifungal properties against \textit{Penicillium chrysogenum}, \textit{Fusarium latertium} and \textit{Rhizopus stolonifer} but were inactive against \textit{Aspergillus flavus}. Pyrazoles \textsuperscript{187} and \textsuperscript{188} (R\textsuperscript{1} = NO\textsubscript{2}) showed moderate activity against \textit{Candida Albicans},\textsuperscript{242} while preliminary assays showed that some of the 3-methyl-1\textit{H}-pyrazole-4-carboxylic ester derivatives \textsuperscript{165-167} presented fungicidal activity against wheat rust and phoma asparagus.\textsuperscript{229} A number of \textit{N}-pyrazolylsalicylamides, such as \textsuperscript{214}, show moderate antifungal activity.\textsuperscript{263} Garuti \textit{et al.} reported the lack of \textit{in vitro} activity of a series of 3-methoxypyrazole derivatives.\textsuperscript{264}

There are other reports showing that 5-benzamido-4-diazopyrazoles \textsuperscript{132},\textsuperscript{198} pyrazoles related nucleosides \textsuperscript{140} and \textsuperscript{141}\textsuperscript{206} and some pyrazolo[3,4-\textit{d}]oxazoles \textsuperscript{137}\textsuperscript{204} displayed no antifungal activity while other 5-alkylaminopyrazolo[3,4-\textit{d}]oxazoles\textsuperscript{265} possess only weak to moderate antifungal activity.
6. Conclusions: structure-biological activity relationships and modelling

On different occasions in the previous sections, different techniques to improve the properties of a drug have been reported. In this last section, we will summarise and classify these publications according to the methodologies used.

**SAR (pharmacophore), QSAR and CoMFA:** Qualitative structure-activity relationships (SAR), often related to establishing the topology of a receptor or the minimum structural characteristics of the pharmacophore, quantitative structure-activity relationships (QSAR) associated to Hansch, and the more recent comparative molecular field analysis (CoMFA) have been used to improve pyrazole-derived drugs. Leaving aside publications dealing with bioisosterism (for instance N/CH), most publications, including very recent ones, correspond to qualitative SAR discussions. In some cases, although the discussion remains qualitative, log $P$ and $pK_a$ values are reported. In the case of triphenyl-1$H$-pyrazole-1-nonanoic acid (62), based on a SAR approach, the authors have proposed a topological descriptor of a portion of the PGI$_2$ receptor occupied by pyrazole derivatives. QSAR studies are scarce and decreasing in interest: the multidrug resistance (MDR)-modulating activity of a series of 4-acylpyrazolones was studied using as descriptors the lipophilicity (calculated log $P$) and hydrogen bond acceptor strengths. The affinity for the benzodiazepine receptor of pyrazolo[4,3-$c$]quinolin-3-ones was optimized using Hansch approach while an example of application of the CoMFA to the field of dopamine D4 receptor antagonists can be found in ref. 39.

**Computational (molecular mechanics) and theoretical chemistry (semi-empirical and ab initio):** The size of the molecules described in this review is small enough to be calculated by high-level *ab initio* methods. A limitation occurs for molecules with many degrees of freedom (rotation about single bonds) because, then, the different minima may have very close energies and, consequently, be of little information value. In any case, these calculations correspond to isolated molecules (assumedly in the gas phase) that may have little resemblance to the real situation. A step further would be the inclusion of water molecules, but still far away to the interaction with the receptor. Using a combination of AM1 calculations to study the conformational properties of compound 21 and of model compounds, the authors were able to propose a model of the bioactive conformation adopted by neuropeptide receptor antagonists. A similar approach has been used in the case of compounds 74 and 52. Other authors have used, for similar purposes, molecular modelling with different force fields (amongst other, compounds 40, 57, 120, 153 and 154). One of the rare cases of *ab initio* 6-31G* calculations is reported in ref. 39.

**Acknowledgements**

Thanks are given to the Ministry of Science and Technology of Spain (SAF-00-114-C02-01), to the University of Aveiro and “Fundação para a Ciência e a Tecnologia” of Portugal for financial support. We gratefully acknowledge "Patro" for her help in searching bibliography.
References


PYRAZOLES AS DRUGS: FACTS AND FANTASIES

RECENT ADVANCES IN THE SYNTHESIS OF SATURATED NITROGEN HETEROCYCLES USING N-ACYLIMINIUM ION INTERMEDIATES

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Abstract. The reaction of N-acyliminium ions with carbon nucleophiles represents a powerful synthetic tool for the preparation of several nitrogen derivatives. This review reports some recent developments in the synthesis of saturated nitrogen heterocycles using N-acyliminium ions as reactive electrophilic intermediates.

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1. Introduction
Saturated nitrogen heterocycles are of paramount importance among the whole body of structurally defined substances endowed of biological and industrial interest. It is really difficult to browse whatever organic chemistry journal without to meet at least one article dealing with the synthesis and/or synthetic application of these heterocyclic derivatives. Beside simple ring systems containing few functional groups, many complex polycyclic structures are unceasingly discovered and this obviously represents a formidable challenge for every synthetic organic chemist. Furthermore, an increasing number of these compounds are needed in enantiopure form thus requiring the accomplishment of enantioselective processes. In this context, the availability of nitrogen containing chiral pools greatly facilitate the synthetic approach to these
heterocyclic systems.\textsuperscript{4,6} The addition of nucleophilic reagents to carbon-nitrogen double bonds is a common practice toward the synthesis of amino derivatives (Scheme 1).\textsuperscript{7-9}

\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle] (A) at (0,0) {$N$};
\node[draw,shape=circle] (B) at (1,0) {$R$};
\node[draw,shape=circle] (C) at (2,0) {$Nu$};
\node[draw,shape=circle] (D) at (3,0) {$N$};
\node[draw,shape=circle] (E) at (4,0) {$R$};
\node[draw,shape=circle] (F) at (5,0) {$Nu$};
\node[draw,shape=circle] (G) at (6,0) {$R$};
\node[draw,shape=circle] (H) at (7,0) {$Nu$};
\node[draw,shape=circle] (I) at (8,0) {$R$};
\node[draw,shape=circle] (J) at (9,0) {$Nu$};
\node[draw,shape=circle] (K) at (10,0) {$R$};
\node[draw,shape=circle] (L) at (11,0) {$Nu$};
\node[draw,shape=circle] (M) at (12,0) {$R$};
\node[draw,shape=circle] (N) at (13,0) {$Nu$};
\node[draw,shape=circle] (O) at (14,0) {$R$};
\node[draw,shape=circle] (P) at (15,0) {$Nu$};
\node[draw,shape=circle] (Q) at (16,0) {$R$};
\node[draw,shape=circle] (R) at (17,0) {$Nu$};
\node[draw,shape=circle] (S) at (18,0) {$R$};
\node[draw,shape=circle] (T) at (19,0) {$Nu$};
\node[draw,shape=circle] (U) at (20,0) {$R$};
\node[draw,shape=circle] (V) at (21,0) {$Nu$};
\node[draw,shape=circle] (W) at (22,0) {$R$};
\node[draw,shape=circle] (X) at (23,0) {$Nu$};
\node[draw,shape=circle] (Y) at (24,0) {$R$};
\node[draw,shape=circle] (Z) at (25,0) {$Nu$};
\node[draw,shape=circle] (aa) at (26,0) {$R$};
\node[draw,shape=circle] (bb) at (27,0) {$Nu$};
\node[draw,shape=circle] (cc) at (28,0) {$R$};
\node[draw,shape=circle] (dd) at (29,0) {$Nu$};
\node[draw,shape=circle] (ee) at (30,0) {$R$};
\node[draw,shape=circle] (ff) at (31,0) {$Nu$};
\node[draw,shape=circle] (gg) at (32,0) {$R$};
\node[draw,shape=circle] (hh) at (33,0) {$Nu$};
\node[draw,shape=circle] (ii) at (34,0) {$R$};
\node[draw,shape=circle] (jj) at (35,0) {$Nu$};
\node[draw,shape=circle] (kk) at (36,0) {$R$};
\node[draw,shape=circle] (ll) at (37,0) {$Nu$};
\node[draw,shape=circle] (mm) at (38,0) {$R$};
\node[draw,shape=circle] (nn) at (39,0) {$Nu$};\end{tikzpicture}
\end{center}

**Scheme 1**

Imines are usually poor electrophilic substrates for this purpose and therefore, strong nucleophilic reagents are required to carry out an efficient addition reaction. These carbanionic reagents in the presence of enolizable imines, frequently give deprotonation rather than addition products. Alternatively, the electrophilic character of the imino derivative can be suitably tuned by the appropriate choice of the nitrogen substituent. Nitrones are readily available starting materials for this purpose; they react with nucleophiles but can also be used as 1,3-dipoles in cycloaddition reactions.\textsuperscript{10-12} An enhanced reactivity toward nucleophiles is displayed by N-acylimines.\textsuperscript{13,14} These substrates can be prepared directly from aromatic or non-enolizable aldehydes, but must be generated \textit{in situ} from a suitable precursor when tautomerization to the more stable enamide is possible.\textsuperscript{15-18} A remarkable increase in the electrophilic character of carbon-nitrogen unsaturated substrates can be obtained moving to iminium ions that are able to react even with weak nucleophiles. The classical Mannich reaction, also referred as the aminoalkylation process of enols and enolates, is one of the most important carbon-carbon bond-forming reactions in organic synthesis.\textsuperscript{19,20} The vinylogous version of this process represents an important method for the preparation of several nitrogen heterocycles, including alkaloids, and has been recently reviewed.\textsuperscript{21,22} Among these electrophilic substrates N-acyliminium ions have deserved a special interest because of their availability and superior reactivity in comparison with N-alkyliminium ions toward nucleophilic systems.\textsuperscript{23-26}

This review reports some recent applications of these reactive intermediates towards the synthesis of saturated nitrogen heterocycles appeared in the literature during the period January 2000-August 2002. Emphasis is given to innovative synthetic approaches using N-acyliminium ion intermediates as well as significative extensions of previously known methods. The term “saturated” concerning the heterocycles examined in this review refers to the core structure of the molecule containing the nitrogen atom. Therefore, polycyclic structures containing unsaturations and aromatics in remote parts of the molecule are included.

### 2. N-Acyliminium ions

#### 2.1. General aspects

\textit{N}-Acyliminium ions are also referred as \textit{\alpha}-amidoalkylating cations and can be prepared according to Scheme 2.

The equilibrium in which the \textit{N}-acyliminium ion is involved is usually favored by acidic catalysts; the subsequent reaction with the nucleophile is an irreversible process and leads to the addition product. The nature of the acyl group greatly affects the ease of formation of the corresponding iminium ion. Recent studies of Eberlin and coworkers on the gas-phase electrophilic reactivity of cyclic \textit{N}-acyliminium ions with allyltrimethylsilane has allowed to establish the following order of intrinsic reactivity (Scheme 3).\textsuperscript{27,28}
It is worth noting that five-membered endocyclic iminium ions 4,6 are more reactive than their six-membered homologues 5,7, furthermore N-alkyl substitution (9) lowers the electrophilicity of the iminium group making it less reactive than protonated ions 4 and 5. Another interesting observation concerns the higher reactivity displayed by exocyclic N-acyl groups (6,7,8) compared with endocyclic system 9. This behavior could be ascribed to a better resonance effect involving the nitrogen lone pair in exocyclic derivatives. Finally, carbamate derivatives 6,7, are more reactive than amide 8, probably because a carbamate nitrogen lone pair is more effective in cation stabilization than an amide nitrogen.

A judicious choice of the leaving group X is also essential for the success of the procedure. In principle every group that can be easily removed through an elimination process is suitable for this purpose but, for practical reasons, only a limited number of them are used in synthesis.

2.2. Precursors of cyclic N-acyliminium ions

Different kind of cyclic N-acyliminium ions used for synthetic purposes are portrayed in Scheme 4.

Iminium derivatives 10 and 11 can be readily obtained by elimination from the corresponding α-hydroxy- or α-alkoxyamides/carbamates 14 that in turn can be prepared by selective reduction of cyclic imides 13 or lactams. Sometime, these α-oxygenated derivatives are more profitably converted into other α-substituted systems, as phenylsulfonyl derivative 15, in order to obtain different substrates that can be easily purified or are more reactive than their precursors (Scheme 5).

For ordinary ring systems (five or six) NaBH₄ is the reagent of choice, however, only DIBALH is able to reduce a wide range of medium and large ring lactams without any ring opening to the corresponding amino aldehydes.
Exocyclic iminium ions 12 are much less exploited mainly because their precursors are difficult to prepare using direct methods.\textsuperscript{32,33}

2.3. Acidic catalysts and nucleophiles

Lewis acids are commonly used as catalysts to obtain \(N\)-acyliminium ions from their precursors. A proper choice of the acid used is mandatory for the success of the synthetic protocol, since different activators can often lead to different results both in terms of efficiency and stereocontrol of the process. Of general use are Lewis acids as \(\text{TiCl}_4\), \(\text{SnCl}_4\), \(\text{BF}_3\ \text{Et}_2\text{O}\) and TMSOTf that is especially useful with \(\alpha\)-hydroxylated precursors. A wide range of nucleophiles are compatible with the use of these activators namely allylsilanes, enol ethers, (hetero)aromatics and even some organometallic reagents as organocuprates. For obvious reasons protic acids as TFA or formic acid find only a narrow application as promoters and their utilization is practically restricted to intramolecular processes in which simple alkenes or aromatic groups are involved as nucleophiles.\textsuperscript{23}

3. Synthesis of saturated nitrogen heterocycles

3.1. Pyrrolidines

The synthesis of substituted pyrrolidines can be accomplished by a suitable ring closure starting from open chain frameworks or by functionalization of commercially available pyrrolidinones, pyrrolines and other derivatives.\textsuperscript{34} Cyclic enecarbamates 17 can be functionalized at the double bond to afford 2-amido-3-iodo pyrrolidines 18. Aziridination-methanolation of the obtained adducts leads to the corresponding 2-methoxy-3-amido pyrrolidines 19 that via \(N\)-acyliminium ion intermediates are transformed into 2,3-disubstituted pyrrolidines 20-22 with a preference for \textit{trans} diastereomer (Scheme 6).\textsuperscript{35} The \textit{trans} diastereoselectivity can be substantially increased in the formation of ester derivatives 20 using titanium enolates of thiopyridyl esters as nucleophiles.\textsuperscript{36}

\(\alpha\)-Amino acid carbamates 23 react with (diacethoxyiodo)benzene (DIB) and iodine under irradiation with visible light giving a carboxyl radical that by loss of \(\text{CO}_2\) and further oxidation gives the corresponding \(N\)-acyliminium ion 24 (Scheme 7).\textsuperscript{37,38}

Iminium ion can be trapped with allyltrimethylsilane producing the allylated derivative 25 with high diastereoselectivity (10:1). Further radical allylation using allyltributiltin gives diallyl derivative 26 that by ring closing metathesis is transformed into the hexahydroindole 27. This procedure can be also extended to other carbon nucleophiles as silyl enol ethers and trimethylsilyloxyfuran.\textsuperscript{39,40}
Conventional electrochemical oxidation of N-protected pyrrolidines usually affords the corresponding α-alkoxy derivatives that can be isolated and converted into N-acyliminium ions by Lewis acid catalysts. This two-step method can be avoided exploiting a low temperature electrolysis of carbamate 28 that directly affords the N-acyliminium ion 29. By this way there is no need to use an acidic catalysis to generate the iminium ion and thus several organometallic reagents can be used as nucleophiles in this process (Scheme 8).

A silicon to carbon migration of aromatic rings is observed on optically active cyclic hemiaminals 31. Formation of the N-acyliminium ion is induced by a clay (montmorillonite K10) and release of the aromatic group is highly syn diastereoselective (Scheme 9).
The main problem associated with the application of solid phase synthesis to the chemistry of $N$-acyliminium ions concerns the stability of the linker under cationic reaction conditions and its efficient cleavage after the process has been completed. Hiemstra and coworkers have developed two interesting systems for this purpose, namely the 2-sulfonylethyl (SEC) and 2-thioethyl (TEC) carbamate linkers. A general strategy for the synthesis of 2,5-disubstituted pyrrolidines is portrayed in Scheme 10: carbonate 33 is
condensed with a suitable amine giving the corresponding carbamate 34. This acetal is treated with allyltrimethylsilane in the presence of BF₃·Et₂O giving the allylated product 36 in a tandem process involving α-ethoxypyrrolidine 35 as intermediate. Cleavage of the linker is realized under basic conditions using MeONa to afford trans-37 as main product.

The utilization of TEC as linker follows a similar synthetic pathway, but cleavage of the produced carbamate can be obtained directly under strong acidic conditions or oxidizing the sulfide moiety to a sulfonyl group and then using MeONa (Scheme 11).

**Scheme 11**

Generation and reaction of N-acyliminium ions are generally realized in anhydrous conditions, especially when strong Lewis acid are used as catalysts. Copper(I) bromide is able to promote the formation of N-acyliminium ion from α-methoxypyrrolidine 40 and to effect a coupling reaction with arylacetylene derivatives in water to afford the corresponding 2-propargyl pyrrolidines 41 (Scheme 12).

**Scheme 12**

Allylation of substituted α-alkoxy pyrrolidines usually occurs with moderate levels of diastereoselection. However, 2,3-O-isopropylidene pyrrolidine 42 reacts with allyltrimethylsilane in the presence of BF₃·Et₂O with exclusive formation of the 2,3-trans diastereomer 43 (Scheme 13).

The attack of the silane always occurs from the exo face of the bicyclic molecule and the stereochemical outcome is not affected by the relative position of other substituents. This probably means that no iminium ions are involved as reactive intermediates in this process. A consistent decrease in stereoselectivity is observed using a combination of BF₃·Et₂O and TMSOTf thus indicating that in these conditions the formation of N-acyliminium ions is more probable.
Functionalized 4-hydroxyproglutamates are important building blocks for the synthesis of many interesting biologically active heterocycles. \(^{(4R)}\) Hydroxyproline 44 is a cheap, commercially available compound that represents an ideal starting material for many syntheses leading to pyroglutamate derivatives. Fully protected proline 45 can be oxidized by RuO\(_2\)/NaIO\(_4\) in nearly quantitative yield to the corresponding pyrrolidinone 46. After Mitsunobu inversion in C-3, acetoxy derivative 47 is selectively reduced using LiBEt\(_3\)H and then allylated or cyanated using the corresponding silyl reagents to compound 49 (Scheme 14). \(^{48}\)

### 3.2. Pyrrolidinones

These heterocyclic systems are strictly related to pyrrolidines since the easy reduction of the carbonyl group represents an alternative method for their preparation. However, the importance of these lactam derivatives is not restricted to this synthetic opportunity since ring cleavage of pyrrolidinones provides a rapid and efficient entry to open chain derivatives. Functionalization of pyrrolidinones takes advantage from
their rigid structure that may allows the introduction of several functional groups in a stereoselective fashion.

Chiral pyrrolidinone 51 first introduced by Meyers et al.\textsuperscript{49} can be prepared starting from \((R)-(-)-\)phenylglycinol 50\textsuperscript{50} and used as precursor for \(N\)-acyliminium ions (Scheme 15).\textsuperscript{51}

\[ \text{PhNH}_2\text{OH} \rightarrow \text{PhN}^+\text{Ph} \]  

\[ \text{PhNH}^+\text{PhO} \rightarrow \text{PhN}^+\text{PhO} \]  

\[ \text{TiCl}_4 83\% \rightarrow \text{PhN}^+\text{PhO} \]  

\[ \text{TMSCHN TiCl}_4 89\% \rightarrow \text{PhN}^+\text{PhO} \]  

\[ \text{RCu BF}_3 \rightarrow \text{PhN}^+\text{PhO} \]  

\[ \text{THF, -78\degree C} 32\text{-}95\% \rightarrow \text{PhN}^+\text{PhO} \]  

Scheme 15

TiCl\(_4\) is used as promoter for allylations and cyanations while BF\(_3\) Et\(_2\)O is recommended for addition of low order cuprates. The diastereomeric excess never exceeds 80%.

Among the usual Lewis acid activators InCl\(_3\) represents a new option to convert \(\alpha\)-alkoxylactams into \(N\)-acyliminium ions.\textsuperscript{52} Only 0.6 equivalents of this acid are needed to promote the reaction.

A stereocontrolled addition of different nucleophiles to lactam 53 prepared from chiral lactone 52 has been studied by Smith III en route to the total synthesis of phosphatase inhibitors Calyculin A and B. Outstanding diastereoselection is observed using allyltrimethylsilane as well as silyl enol ethers, while TMSCN gives only modest results (Scheme 16).\textsuperscript{53}

\[ \text{52} \rightarrow \text{AcO} \rightarrow \text{Nu BF}_3 \text{Et}_2\text{O} \rightarrow \text{Nu} \]  

\[ \text{Scheme 16} \]

<table>
<thead>
<tr>
<th>reagent</th>
<th>(\alpha:\beta)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{SiMe}_3)</td>
<td>0:100</td>
<td>86%</td>
</tr>
<tr>
<td>TMSCHN</td>
<td>15:85</td>
<td>91%</td>
</tr>
<tr>
<td>OSiMe(_3)</td>
<td>0:100</td>
<td>81%</td>
</tr>
</tbody>
</table>

The addition product 55 obtained by reaction of 53 with enol ether of \(t\)-butylmethyl ketone is converted to alcohol 56 by ozonolysis of the corresponding silyl enol ether followed by reduction. A suitable
Manipulation of the protecting groups leads to the synthesis of pyrrolidinone 57 that is cleaved to compound 58 a key intermediate to the synthesis of Calyculin A (Scheme 17).

**Scheme 17**

Hydroxylated glutamic acids are potent ligands for glutamate receptors as NMDA, AMPA and KA. These open-chain derivatives can be conveniently prepared starting from L-tartaric acid that is converted into N-protected imide 59 and then to α-acetoxy pyrrolidinone 60 by a selective reduction-acetylation procedure (Scheme 18). Pyrrolidinone 60 upon reaction with Bu₃SnCN gives the corresponding cyano derivative 61 with satisfactory 4,5-cis-diastereoselectivity. Utilization of acetoxy derivative 60 is mandatory for the success of this procedure since neither hydroxylactam itself nor the corresponding methoxylactam are active toward the subsequent cyanation reaction. Cleavage of PMB-protecting group and acid hydrolysis of the cyano group completes the synthesis of 3,4-dihydroxy glutamic acid 62.

**Scheme 18**

Other nucleophiles as electron rich aromatics and propargylsilanes add to cyclic N-acyliminium ions and this constitute a synthetic route to enantiopure amidines, tetrahydroisoquinolines and other heterocycles.
3.3. Piperidines

The importance and synthetic applications of functionalized piperidines parallels that of their five membered homologs and several method for their stereoselective synthesis have been recently reviewed.\textsuperscript{58}

Leptophylline A is a bioactive extract of the Brazilian legume \textit{Cassia leptophylla} and with other compounds of similar structure represents the first example of an alkaloid lipid that shows interesting anticancer activity. A structurally related analogue of this alkaloid can be prepared starting from commercially available \(\text{D}-\text{glucal}\) that is transformed into trisubstituted piperidine \textit{64} (Scheme 19).\textsuperscript{59} This \(\alpha\)-ethoxy derivative is converted into \(N\)-tosyliminium ion using \(\text{TiCl}_4\) and is allylated stereoselectively from the less hindered \(\alpha\) side to give \textit{65} as the only diastereomer. Oxidative cleavage of the double bond affords the corresponding aldehyde \textit{66} that undergoes a Wittig reaction leading to chain elongated derivative \textit{67}. Removal of all protecting groups in \textit{67} completes the synthesis of alkaloid \textit{68} in 15\% overall yield from \(\text{D}-\text{glucal}.

\[ \text{D-Glucal} \rightarrow \textit{63} \rightarrow \textit{64} \rightarrow \textit{65} \rightarrow \textit{66} \rightarrow \textit{67} \rightarrow \textit{68} \]

Functionalization of six-membered ring enecarbamates represents a proper method to prepare suitable precursors of \(N\)-acyliminium ions. Dihydroxylation of chiral 1,4-ditosyltetrahydropyridines \textit{69} realized using \(\text{OsO}_4\) produces, after acetylation, \(\alpha\)-acetoxypiperidines \textit{70}.

A range of various nucleophiles was tested in order to evaluate the effect of different groups present in the structure on the stereochemical outcome of the addition product (Scheme 20).\textsuperscript{60}
Allylation shows no diastereoselection while reaction with silyl enol ethers gives opposite diastereofacial preference depending on the nature of R group.

Scheme 20

<table>
<thead>
<tr>
<th>reagent</th>
<th>yield</th>
<th>R</th>
<th>71</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂=CHSiMe₃</td>
<td>88%</td>
<td>i-Pr</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>CH₂=CHSiMe₃</td>
<td>90%</td>
<td>i-Pr</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>CH₂=CHSiMe₃</td>
<td>92%</td>
<td>i-Bu</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

Scheme 21

The success of synthetic procedures that employ chiral carbamates as precursors of N-acyliminium ions is often related to the availability of these unsaturated derivatives. Reduction of 3-hydroxypyridine 73 in the presence of benzyl chloroformate affords the corresponding enecarbamate 74 in racemic form (Scheme 21). This derivative can be resolved by a lipase-mediated kinetic resolution and (S)-3-hydroxycarbamate 76 is transformed into α-methoxycarbamate 78 and then allylated in satisfactory yield and diastereoselectivity.
An interesting process concerns 3-oxy derivative 79 that can be converted through simple protecting groups manipulation into 3-hydroxypiperidine 80. Upon mesylation, an intramolecular nucleophilic substitution leading to aziridinium salt 81 occurs, and by action of CsOAc in DMF this salt furnishes the ring-contracted product trans-5-allylprolinol acetate 82.

N-acylpyridinium salts have been used as precursors of a consistent number of piperidine alkaloids. Deoxoprosopinine 83 and other analogues have been isolated from the leaves of *Prosopis africana* and are endowed with antibiotic and anesthetic properties.

The strategy adopted by Comins *et al.* for the synthesis of these piperidine alkaloids utilizes chiral N-acylpyridinium salt 84 that reacts with high order cyanocuprate 85 to afford the corresponding addition product 86 in a regioselective fashion by the presence of triisopropylsilyl (TIPS) group (Scheme 22).64

Removal of the TIPS group produces 87 that is protected at nitrogen and then acylated using Pb(OAc)₄. Enone 88 needs to be converted into bicyclic derivative 89 that presents a more rigid structure
and ensures a better diastereoselectivity in the next synthetic steps. After selective 1,2-reduction and acetylation, diacetate derivative 90 is converted into conjugate N-acyliminium ion 91 that is attacked regio- and stereoselectively by allylsilane 92 to give the addition product 93 that is converted into (+)-deoxoprosopinine 83 by basic ethanolysis.

A detailed study on nucleophilic additions to N-acyliminium ions derived from 2-acyloxy-3-alkoxy piperidines has been recently carried out by Kobayashi and coworkers.65,66 Synthesis of 2,3-dioxy piperidines can be realized starting from enecarbamate 94 by oxidation with MCPBA or microencapsulated OsO₄ (Scheme 23).

\[
\begin{align*}
\text{Scheme 23}
\end{align*}
\]

Catalytic amounts of metal triflates are able to activate these dioxygenated derivatives 95, 96 towards the reaction with silyl enol ethers and silyl ketene acetics; in particular, Sc(OTf)₃ in dichloromethane is the most effective catalyst for this reaction.

The stereochemical outcome displayed by the process is affected by the nature of the substituent at C-3. Compound 95 usually affords the corresponding addition product 97 with cis-selectivity, while 3-acyloxy piperidines of type 96 provide the formation of the trans stereoisomers 98 as main products (Scheme 24).

\[
\begin{align*}
\text{Scheme 24}
\end{align*}
\]

Several factors as anomic effects, neighboring groups participation and steric bulkiness of the nucleophile play a crucial role in the stereoselectivity of the addition process on N-acyliminium ions.

All these effects have been studied during the work aimed to the enantioselective synthesis of febrifugine 99 an alkaloid found in Dichroa febrifuga, a chinese plant known for its antimalarial properties.

\[
\begin{align*}
\text{99}
\end{align*}
\]

Construction of the piperidine ring with a proper steroocenter at C-3 can be made starting from ester 100 that is converted into Weinreb amide 101 and then aminated following a modified Mitsunobu procedure using diphenylphosphoric azide (DPPA) (Scheme 25).
Reduction of the amide 102 follows a spontaneous cyclization to a lactol that is successively transformed to diacetoxy derivative 103. This diacete reacts with tin enolate 104 in the presence of Sc(OTf)₃ to afford addition product 105 in a trans/cis ratio of 80:20. Removal of Cbz and acetate protecting groups gives febrifugine 99.

A complementary strategy for the preparation of functionalized piperidines consists in the ring-opening allylation of N,O-acetals 106 catalyzed by Lewis acids. In this case, an open-chain compound 107
with syn stereoselectivity is obtained at first from the reaction as results of an acyclic N-acyliminium ion intermediate (Scheme 26).  

After suitable double bond functionalization to compound 108, the piperidine ring in 109 can be builted as illustrated in Scheme 27 for the synthesis of isofebrifugine 110.

A solid-phase synthesis of substituted piperidines has been realized by Hiemstra and coworkers as a logical extension of a previous procedure portrayed in Schemes 10 and 11. However, in this case the N-acyliminium ion precursor is isolated as 2-benzotriazolyl derivative and then made to react with allylsilanes in the presence of BF₃·Et₂O.  

3.4. Indolizidines

A consistent number of biologically active compounds endowed of indolizidine structure have recently emerged as potent glycosidase inhibitors (slaframine, lentiginosine, castanospermine etc.); other compounds as pumiliotoxin B are poisonous frog-alkaloids with interesting pharmacological activity.  

(-)-Coniceine 116 represents the simplest structure belonging to this class of derivatives and for its preparation Meyers and Groaning start from chiral bicyclic lactam 111 which is converted into the corresponding N-acyliminium ion 112 and then stereoselectively allylated to afford pyrrolidinone 113 (Scheme 28).

Scheme 28

Removal of the N-benzyl framework and N-allylation gives diallyl pyrrolidinone 114 that is treated with Grubbs’ catalyst for a metathesis process leading to bicyclic derivative 115. Full reduction of this unsaturated compound affords (-)-coniceine 116 in good overall yield.
Ring closing metathesis of diallylated pyrrolidines 118 has been also used for the synthesis of hydroxylated indolizidines starting from natural tartaric acid (Scheme 29). By this way a number of hydroxy derivatives including lentiginosine 119 can be prepared.

Piclavines have been found in the organic extract of the Bermudan tunicate Clavelina picta and are some of the few known indolizidines of marine origin. These compounds are antimicrobial and cytotoxic agents and the synthetic approach that leads to their preparation is depicted in Scheme 30.

Aldehyde 120 prepared from (S)-glutamic acid is made to react with sulfone 121 leading to pyrrolidinone 122 according with the method of Kocienski. Double bond reduction and transacetalization affords derivative 123 that by removal of the N-protection followed by cyclization gives enecarbamate 124. Methoxylation of 124 in the presence of camphorsulfonic acid (CSA) produces substrate 125 for the subsequent addition via N-acyliminium ion of silane 126 that occurs with high diastereofacial selectivity but with modest E/Z stereoselectivity to adduct 127. Reduction of the mixture of stereosomers provides piclavine A1 and A2.

Scheme 30

Since bicyclic derivative 125 has been recognized as a central intermediate for the synthesis of indolizidine systems, a different preparation of this indolizidinone has been reported using an asymmetric intramolecular Heck cyclization (Scheme 31). Vinyl bromide 128 reacts in the presence of a chiral
palladium complex giving indolizidinone 129 that suffers a chemoselective reduction of the conjugate double bond and a successive methoxylation of the enecarbamate system. By a similar procedure described in Scheme 30 product 125 can be converted into epiindolizidene 167B 130.

Functionalization of N-acyliminium ion derived from 125 invariably leads to epiindolizidines, however, addition reactions on monocylic iminium ions followed by ring closure can afford indolizidine rings.

When silane 131 is made to react with α-alkoxypyrrolidines the corresponding allylic alcohol 132 is obtained (Scheme 32). Oxidation of the hydroxy group and double bond reduction leads to ketone 133 that is not isolated but spontaneously cyclizes to the iminium ion and upon reduction of the C=N bond gives racemic indolizidine 167B 134 in satisfactory overall yield.

Scheme 32

A chiral tricyclic N-acyl-N,O-acetal incorporating (S)-2-(1-aminoethyl)phenol 137 has been introduced by Kibayashi et. al. as rigid system in order to obtain elevated diastereoselections in the addition of the corresponding N-acyliminium ion (Scheme 33). The origin of the diastereoselectivity in the
formation of 139 can be found in the chelation between titanium, carbonyl and phenolic oxygens that hinders one face of the iminium ion intermediate 138. Protection of the hydroxyl group and oxidative cleavage of the double bond affords aldehyde 140 that is converted into ketone 141 by a Horner-Wittig reaction followed by a reduction of the conjugate double bond. Pyrrolidinone 141 is then reduced to pyrrolidine 142 and finally catalytic hydrogenation leads to indolizidine 167B 134.

A similar strategy has been applied by the same group for the synthesis of (-)-adaline\textsuperscript{80} and (-)-stelletamide B 144, a cytotoxic metabolite isolated from marine sponges of the genus Stelletta (Scheme 34).\textsuperscript{81} In this case the enantiomer of adduct 138 has been used and the synthesis of key intermediate indolizidine 143 was achieved.

![Scheme 34](image)

An efficient synthesis of 1-aminomethyl indolizidine 143 has been accomplished exploiting the reaction of a chiral titanium enolate 145 with N-carbobenzoxy-\(\alpha\)-methoxypyrrolidine (Scheme 35).\textsuperscript{82} Removal of the Cbz group from adduct 146 occurs with a tandem cyclization to indolizidine 147 that is converted into desired amino derivative 143 by simple functional groups manipulation.

![Scheme 35](image)

The number of nucleophilic systems that can react with reactive iminium ions has been continuously increasing over recent years. Alkenylboronates are able to introduce an alkenyl fragment in the reaction with \(N\)-acyliminium ions that is amenable of further functionalization. This strategy has been applied to the stereoselective synthesis of 6-deoxycastanospermine 153 as illustrated in Scheme 36.\textsuperscript{83} Organoboronate 148 reacts with dihydroxypyrrolidine 149 to give in high yield and diastereoselectivity alkenyl derivative 150 that is dihydroxylated and then protected at the OH groups to compound 151. Hydrolysis of the acetate and oxidation with tetrabutyllumonium per ruthenate (TPAP) leads to aldehyde 152 that is converted into 6-deoxycastanospermine by usual procedures.

3.5. Quinolizidines

Intramolecular cyclization of alkynyltungsten complexes with \(N\)-acyliminium ions derived from \(\alpha\)-alkoxy piperidines is able to produce a quinolizidine skeleton. In this context the organometallic complex acts as an ester enolate equivalent (Scheme 37).\textsuperscript{84}
The alkynyltungsten specie is generated by reaction of a terminal alkyne 155 with CpW(CO)₃Cl and complex 156 is made to react with a Lewis acid following an aqueous work-up to afford in a
diastereoselective fashion quinolizidinone 157. Tungsten can be easily replaced by a benzyloxy group in 158 and by reduction of the carbonyl functions epilupinine 159 can be finally obtained.

Reaction of silyloxyfurans 160 with cyclic N-acyliminium ions gives butenolide systems in a vinylogous nucleophilic addition (Scheme 38). Compounds of type 161 can be reduced to lactones 162 and then converted into a quinolizidinone structure 163 that can be used to prepare several alkaloids as for instance homopumiliotoxin 223G 164.

Using a related strategy is also possible to prepare 5-hydroxy indolizidinones and quinolizidinones that are useful precursors of more complex heterocyclic systems.86,87

3.6. Other bicyclic systems

Several bicyclic systems containing saturated nitrogen heterocycles act as constrained peptidomimetics, a class of substances particularly useful for probing the biological relevance of a proposed peptide conformation.88 2-Alkenyl pyrrolidines have been recognized as pivotal intermediates for the synthesis of different peptidomimetics and an efficient method for their preparation has reported by Moeller et al. (Scheme 39).89-92 Anodic oxidation of pyrrolidine derivatives 165 is a very regioselective process that allows the preparation of suitable α-alkoxypyrrolidines 166. Reaction of these compounds with lithium alkenyl cuprates in the presence of BF₃Et₂O affords alkenylpyrrolidines 167 with high diastereoselectivity.

![Scheme 39](image)

With derivatives 168,171 in hand, different kind of peptidomimetics summarized in Scheme 40 can be prepared. For the synthesis of compound 170 a ring closing metathesis of diallyl derivative 169 using
Grubbs’ catalyst is the crucial step (eq. a),
while compound 173 is prepared using a classical ozonolysis of
the vinyl group in 172, followed by reduction of the spontaneously formed six-membered ring hemiaminal
(eq. b). Azaspirocycles constitute the core of many substances of practical interest. Azaspirocycle 174 is an
important intermediate toward the synthesis of pinnaic acid, a marine metabolite that shows anti-
inflammatory properties.

Danishefsky et al. have developed an interesting synthesis of this precursor starting from Meyers’
tricyclic lactam 175 that is allylated using standard conditions affording derivative 176 (Scheme 41). Successively, Boc protecting group is inserted and stereoselective methylation of the lactam 177 gives bicyclic derivative 178. Using a known chemistry compound 178 is cleaved to furnish cyclopentane 179 that is hydroborated at the double bond and then coupled with iododiene 181 in the presence of palladium catalyst. After removal of the Boc protection from derivative 182, the azaspiro system is
generated by intramolecular Michael addition of the nitrogen atom to dienyl ester appendage affording compound 183 that is transformed into desired intermediate 174 in few steps.

1-Azaspirocycles can be also prepared starting from cyclic N-acyl-N,O-acetals exploiting an intramolecular olefin-iminium cyclization. Ring closing metathesis has found a large application in the synthesis of cyclic derivatives and its utilization will probably increase even more in the future. Decahydroquinolines and other bicyclic derivatives can be prepared following the strategy depicted in Scheme 42. Allyl derivative 184 is further allylated using allyltributyltin to give the 2,3-trans-185 that undergoes a ring closure using Grubbs’ catalyst to bicyclic derivative 186. Reduction of the double bond and deprotection of the nitrogen give decahydroquinoline 187.

Scheme 42

Scheme 43
A related procedure using both ring closing metathesis or intramolecular Heck reaction allows the preparation of different bicyclic derivatives, and bridged azabicyclic structures. Glutarimide 188 is reduced to give \( \alpha \)-ethoxylactam 189 but every attempts to introduce the alkenyl side chain using organometallic reagents fails (Scheme 43). Converting 189 into the corresponding 2-phenylsulfonyl derivative 190 make the reaction with Grignard reagents successful to give alkenyl derivative 192. It is worth noting that this reaction occurs through a neutral \( N \)-acylimine derivative 191 that is formed by elimination of benzenesulfinic acid caused by the excess of Grignard reagent. Protection of the nitrogen atom and reduction of the carbonyl group gives piperidine 193 that is allylated to give predominantly the \( cis \)-stereoisomer 194. Ring closing metathesis affords bridged azabicycles 195 and after reduction, saturated compounds 196.

The *Gelsemium* alkaloids possess as a common feature a bridged polycyclic structure that can be assembled starting from a bridged azabicyclic building block. Ethoxylactam 197 is conveniently prepared from (S)-malic acid and upon reaction with formic acid in the presence of sodium iodide it is transformed into the corresponding \( N \)-acyliminium ion 198 that undergoes an intramolecular ring closure to azabicycle 199 (Scheme 44). This derivative is then converted into *ent*-gelsedine 200 by further synthetic transformations.

Cyclic \( \alpha \)-sulfonyl lactams present the advantage over common \( \alpha \)-alkoxy derivatives to be crystalline compounds easy to purify by crystallization. Therefore Hiemstra *et al.* decided to transform bicyclic \( \alpha \)-hydroxylactam 203, obtained by reductive desymmetrization of *meso*-imide 201 using chiral catalyst 202, into \( \alpha \)-sulfonyl lactam 204 (Scheme 45). This lactam can be obtained in 99% ee after repeated crystallizations and upon allylation gives product 205 that can be converted into chiral amidines.

Cyclic \( N \)-amidinyliminium ions present an interesting reactivity toward unsaturated derivatives as styrenes and 1,3-dienes. These reactive iminium ions 207 are prepared from thioaminal 206 by reaction with Cu(OTf)₂ (Scheme 46). Reaction of 207 with styrene occurs regio- and stereoselectively affording a
benzyl carbocation intermediate 208 that gives a cyclocondensed product 209 with d.r. 5:1. Reaction of 206 with \( \beta \)-dicarbonyl compounds affords unsaturated bicyclo derivatives arising from a Biginelli process.\(^{102}\)

\[
\begin{array}{c}
\text{HN-} & \text{H} & \text{HN} \\
\text{Cl} & \text{Cl} & \text{Cl}
\end{array}
\]

\[\text{Bn-} \quad \text{NH} \quad \text{NH}_2 \quad \text{SPh} \quad \text{HCl} \quad \text{206} \]

\[
\text{HN} \quad \text{NH}_2 \quad \text{HCl} \quad \text{207} \]

\[
\text{HN} \quad \text{NH}_2 \quad + \quad \text{Ph} \quad \text{HCl} \quad \text{208} \]

3.7. Tricyclic systems

Tricyclic pyrrolizidinone carboxylic acids harboring an angular methano group are mimics of carbapenems and carbapenams. Hanessian et al. have devised an interesting approach to these heterocyclic derivatives starting from lactam 210 that is alkylated using Me\(_3\)SnCH\(_2\)I giving a diastereomeric mixture of cis and trans adducts 211 (Scheme 47).\(^{103}\)

The major trans stereoisomer can be isomerized to the more stable cis isomer in basic conditions and is then made to react with allylmagnesium bromide to give the hemiaminal 212. Reaction with trifluoroacetic acid presumably forms the corresponding N-acyliminium ion 213 that favors a cyclopropyl ring closure to bicyclic derivative 214. Ozonization and Wittig olefination leads to compound 215 that is
reduced at the double bond and hydrolyzed to acid 216. Boc protecting group is finally removed and ring closure to lactam 217 completes this interesting synthetic procedure.

![Scheme 47](image)

Mitomycins belong to a family of antitumor agents as mitomycin C 218 which preparation has been the focus of many synthetic efforts.

A general approach to the mitomycin ring system developed by Coleman and Chen involves as crucial step the addition of silyl enol ether 219 with N-acyliminium ion derived from α-hydroxy pyrrolidine 220 (Scheme 48). Aldehyde 221 is formed in high yield as a sole stereoisomer and after reduction, the resulting alcoholic function is protected as triisopropylsilyl (TIPS) ether 222. Catalytic hydrogenation provides removal of the benzyl based protections and the phenolic hydroxyl group in 223 is converted into triflate ester 224. An intramolecular palladium-catalyzed coupling affords the tricyclic core of the mitomycin system 225 that can be further manipulated to obtain the desired derivatives of this important family of substances.

The pyrroloisoquinoline ring system is present in several molecules of the Erytrina alkaloids and the interest in this structural unit is witnessed by many synthetic approaches presented over recent years.
Bicyclic lactams are ideal substrates for the preparation of these tricyclic derivatives exploiting an intramolecular attack of the aromatic ring to the N-acyliminium ion intermediate (Scheme 49).\textsuperscript{106-108}

When unsubstituted lactam 226 is used the attack of the aromatic ring comes from the top \textit{re} side of the iminium ion 227 thus giving tricyclic derivative 228 as the exclusive stereoisomer. However the presence of a methyl group in 229 probably slows the reactivity of the intermediate iminium ion thus making possible a chelation by titanium as in 230. This offers an alternative pathway for the attack of the aromatic group from the \textit{si} side leading to 231 with modest diastereoselectivity. Similar results have been recently reported by Katritzky \textit{et al.} for the reaction of benzotriazolyl precursors of \textit{N}-acyliminium ions in the same process,\textsuperscript{109} and by Sotomayor \textit{et al.} for related structures containing a sulfur atom in the tricyclic ring.\textsuperscript{110-111}
Gathering several synthetic transformations in a sequential process is one of the major goals of the modern organic synthesis. The utilization of a domino sequence allows the preparation of complex structures in a single step with a considerable reduction in costs and environmental impact.

Recently Padwa and Waterson have developed a consecutive thionium/N-acyliminium ion cyclization sequence using dimethyl (methylthio)sulfonium tetrafluoroborate (DMTSF) 233 as promoter (Scheme 50).\(^{112}\)

DMTSF first acts as methylthiolating agent converting thioacetal 232 into alkylthiosulfonium salt 234 that by losses of methylalkyl sulfide is converted into thionium ion 235. Attack of nitrogen atom onto the cationic center gives α-phenylthiolactam 236 that reacting with excess of DMTSF affords N-acyliminium ion 237. This iminium ion cyclizes in the usual way to afford tricyclic derivative 238. Thionium salts can be also obtained starting from phenyl sulfoxides by reaction with silyl ketene acetals in the presence of ZnI\(_2\).\(^{113}\)

It is worth to note that this strategy although illustrated for the synthesis of tricyclic compound 238 is suitable for the preparation of many polycyclic derivatives.

Lepadiformine is a tricyclic alkaloid of marine origin (Clavelina lepadiformis) featured by a spirocyclo structure with moderate cytotoxic activity. Weinreb et al. have realized a very elegant total synthesis of the natural enantiomer of lepadiformine using iminium ion intermediates in two crucial steps of the synthesis (Scheme 51).\(^{114-115}\)

Reaction of organolithium 240 with chiral pyrrolidinone 239 gives addition product 241 that without isolation is transformed into N-acyliminium ion 242 using boron trifluoride-acetic acid complex. Attack of the allylsilane onto the less hindered side of the iminium ion 242 leads to spirocyclo derivative 243 in 52% overall yield. Compound 243 is then transformed into tricyclic derivative 244 and made to react with hexylmagnesium bromide in the presence of BF\(_3\)Et\(_2\)O assuming the formation of an iminium ion intermediate 245. Although the diastereoselectivity of this addition is not particularly high, derivative 246 which is in equilibrium with its conformer 247, after removal of the benzyl protecting group affords (-)-lepadiformine 248 in enantiopure form. A related approach has been used by Kibayashi et al. for the same synthesis exploiting a vinylogous intramolecular addition on a cyclic N-acyliminium ion.\(^ {116}\)
Phenylsulfonyl group can act as good leaving group in the formation of $N$-acyliminium ions, but it is also able to promote the formation of carbanions α to the sulfone moiety. This feature has been used by Lhommet et al. to prepare some azaspirocyclic derivatives as illustrated in Scheme 52. Enecarbamate 249 is transformed into sulfone 250 by addition of benzenesulfinic acid and then converted into the corresponding carbanion using LDA. Alkylation of this anion occurs with concomitant elimination of benzenesulfinic acid to afford substituted enecarbamate 251. This enecarbamate upon treatment with formic acid gives the $N$-acyliminium ion 252 that cyclizes to spiro derivative 253.

As discussed previously, synthesis of α-alkoxyamido derivatives starting from simple amides or carbamates often entails anodic oxidation of these nitrogen compounds. However, the apparatus required to
carry out such procedure is not always available in every laboratory. In this context diazotization of amides affords the same result using non-electrochemical conditions as illustrated in Scheme 53 for the synthesis of norsecurinine alkaloids.119-120

Bicyclic derivative 254 is treated with nitrous acid in the presence of CuCl to give α-methoxy derivative 255 that is allylated in the usual way to compound 256. Tricyclic system 257 is obtained after few steps while further synthetic manipulations leads to (-)-norsecurinine 258.

Some related strategies have been used in a stereocontrolled synthesis of the BCD ring of sparteine analogues,121 and in the preparation of azamide immunosuppressive drugs.122

Vinylsilanes of Z configurations and terminal alkynes tethered to a bicyclic structure are able to attack N-acyliminium ions giving a 6-endo ring closure. This approach allowed the preparation of quinolizidine alkaloid virgilidone (Scheme 54).123 Aldehyde 259 is converted into α-hydroxylactam 260 and then cyclization occurs in trifluoroacetic acid (TFA) to give 261 as single diastereomer. Product 261 is then reduced to virgilidone 262 in 65% yield.

3.8. Polycyclic systems

The chemistry of N-acyliminium ions has been often instrumental for the success of many synthetic procedures for the preparation of complex polycyclic molecules, especially when an elevated degree of diastereoselection is needed.
Since the synthesis of polycyclic derivatives usually requires a consistent number of steps to go to completion it is possible that these iminium ions intermediates are generated sequentially during the whole process as in the case of the synthesis of Cephalotaxine, an antileukemic alkaloid from *Cephalotaxus* specie (Scheme 55). Double bond hydroxylation of 263 with dimethyldioxirane gives methoxylated derivative 264 that is converted in tetrasubstituted *N*-acyliminium ion 265 using BF$_3$·Et$_2$O. Reactive iminium ion undergoes an intramolecular ring closure to give tetracyclic compound 266 and a subsequent ring expansion mediated by sulfuryl chloride affords compound 267. After simple synthetic manipulations, β-keto ester 268 thus obtained is reacted with *N*-iodosuccinimide that provides an electrophilic source of iodine generating a second *N*-acyliminium ion 269. This ion is attacked intramolecularly by the β-keto ester function allowing the assembling of the fifth ring of the pentacyclic structure 270. This intermediate is then converted into cephalotoxin 1 271 by means of few other synthetic steps.

![Scheme 55](image.png)

A related procedure has been used for the synthesis of some tetracyclic structures that includes aromatic and heteroaromatic rings in the terminal part of the molecular framework. The high reactivity of the furan ring toward electrophilic substitutions makes this heterocyclic ring a good candidate for the reaction with *N*-acyliminium ions as illustrated for the synthesis of the central tetracyclic core of nakadomarin A. Spirocycle 273, prepared from commercially available tetrahydropyridine 272 is coupled with boronic ester 274 in the presence of palladium complex (Scheme 56).
After reduction of the double bond of compound 275 the lactam and the ester groups are reduced with DIBALH and acetylated to give derivative 276. Simple treatment of 276 with \(\text{p-TsOH}\) in dichloromethane allows the intramolecular ring closure to give tetracyclic derivative 277. This last intermediate can be converted into nakadomarin A 278 after several synthetic steps.

\[
\begin{align*}
\text{272} & \quad \text{273} \\
\text{274} & \quad \text{275} \\
\text{276} & \quad \text{277} \quad \text{nakadomarin A}
\end{align*}
\]

**Scheme 56**

As previously described, 2-silyloxyfuran derivatives are syntetic equivalents of butenolide moieties in the reaction with electrophilic substrates. For the first total synthesis of stemonamide 282, a tetracyclic alkaloid, Kende et al. have used as crucial step for the assembling of the first two units, the addition of silyloxy derivative 280 to lactam 279 (Scheme 57).\(^{128}\) By this way it is possible to introduce in the molecular framework a densely functionalized structural entity.

\[
\begin{align*}
\text{279} & \quad \text{280} \\
\text{281} & \quad \text{282}
\end{align*}
\]

**Scheme 57**

More than a single cationic intermediate can be involved in cascade processes that permit the assembling of complex structural systems with high diastereoselectivity.\(^{129}\) For the total synthesis of jamtine 288, Padwa and Danca have exploited a Pummerer/thionium/N-acyliminium ion (Pictet-Spengler) cascade process that leads to the preparation of a tricyclic intermediate in a single step (Scheme 58).\(^{130}\) Heating sulfoxide 283 in the presence of camphorsulfonic acid (CSA) leads to thionium ion 284 via Pummerer
rearrangement followed by a ring closure that generated N-acyliminium ion 285. This reactive intermediate gives tricyclic derivative 286 by means of a Pictet-Spengler process\textsuperscript{131} and the fourth cycle is then introduced by a nucleophilic substitution of an enolate anion to afford product 287.

A Pictet-Spengler reaction also constitutes the key step in the synthesis of azapolycyclic derivatives starting from thioamides. Reaction of thioamide 289 with acid chloride 290 produces the corresponding thioimide 291 that undergoes an intramolecular nucleophilic substitution of bromide by the sulfur atom thus creating the N-acyliminium ion 292 (Scheme 59).\textsuperscript{132} Terminal double bond in 292 attacks the iminium ion and the resulting intermediate carbocation further cyclizes to polycyclic compound 294. Sulfur bridge and carbonyl group can be removed by reductive methods affording pentacyclic derivative 295.
4. Conclusions

An increasing number of synthetic procedures directed toward the preparation of saturated nitrogen heterocycles make use of N-acyliminium ions as reactive intermediates. The success of N-acyliminium ions in synthesis is mainly due to the ease of their preparation coupled with the high reactivity displayed in the reaction with a large variety of nucleophiles including alkenes and enol derivatives. Intermolecular formation of carbon-carbon bonds is an efficient process that occurs in good yields and with variable diastereoselectivity, depending on the nature of the stereodirecting group and by the nucleophile employed. Intramolecular processes usually display a better diastereoselectivity and are often used for the assembling of architecturally complex polycyclic molecules.

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References


Abstract. Different heterocycles (strained heterocycles and heterocycles with allylic and benzylic carbon-heteroatom bonds) can be opened reductively by treatment with lithium metal itself or in the presence of a stoichiometric or catalytic amount of an arene to give functionalised organolithium compounds which, by reaction with electrophiles lead to the formation of polyfunctionalised molecules in a direct manner.

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1. Introduction

Functionalised organolithium compounds\textsuperscript{1} are of interest in synthetic organic chemistry because polyfunctionalised molecules are obtained in only one step by reaction with electrophilic reagents.\textsuperscript{2} Due to the high reactivity of the organolithium compounds, these processes can be carried out under very mild reaction conditions. Functionalised organolithium compounds can be prepared by halogen-lithium exchange, metal-lithium exchange, direct deprotonation, addition of organolithium compounds to unsaturated systems,\textsuperscript{1,2} and probably one of the most elegant and direct strategies consists in the reductive opening of different appropriate oxygen-, nitrogen- and sulfur-containing heterocycles.\textsuperscript{3} Since most functionalised organolithium compounds are very unstable molecules, they have to be prepared at low temperature in order to avoid their decomposition.\textsuperscript{4} For that purpose, in the last few years a methodology consisting in the use of
an excess of lithium in the presence of a catalytic amount of an arene has been developed as lithiating agent,\(^6\) naphthalene and 4,4’-di-\textit{tert}-butylbiphenyl (DTBB) being the most commonly used.\(^7\) More recently, polymer supported naphthalene, biphenyl\(^8\) and also polyphenylene\(^9\) have been used as electron transfer reagents in these processes.\(^10\) Some requirements should be accomplished in order to get the reductive opening of a heterocycle: (a) Small heterocycles (three and four membered-rings) due to a release of strain energy\(^4\) and (b) heterocycles with activated bonds that can be reductively broken by means of the lithiating reagent, as in the case of compounds with allylic\(^11\) and benzylic\(^12\) carbon-heteroatom bonds as well as cyclic aryl ethers\(^13\) and thioethers.\(^14\) In this review, which updates our previous review,\(^4\) we will consider the reductive opening of different heterocycles and the synthetic application of the resulting functionalised organolithium compounds.

2. Reductive opening of strained heterocycles

The mechanism of strained heterocycles reductive opening with lithium metal, or other alkali metals, by stepwise electron transfer is less well understood than that of nucleophilic ring opening by means of a hydride ion.\(^15\) In the proposed mechanism an initial single-electron transfer (SET) from the metal to the heterocycle I takes place. The radical anion formed II suffers carbon-heteroatom bond scission to generate a new radical anion III. The late radical anion, which is very unstable, among other processes can be further reduced to a dianion IV (Scheme 1). In the case of non symmetrically substituted heterocycles, two possible reductive opening products could be obtained, in most cases being one of them predominant, playing an important role the nature of the alkali metal and the solvent.\(^16\)

![Scheme 1](image)

\(\text{Scheme 1}\)

2.1. Reductive opening of epoxides

Kaiser \textit{et al.} reported in 1971 that the treatment of aromatic epoxides with alkali metals in liquid ammonia led to isomerically pure less substituted alcohols.\(^17\) However, in the case of aliphatic epoxides, the most substituted alcohols were obtained by treatment with lithium in ethylenediamine.\(^18\)

![Scheme 2](image)

\(\text{Scheme 2}\)

In both cases, the reductive opening of epoxides takes place through the most stable of the two possible carbanions. In the case of styrene oxide (1a), reductive opening by treatment with two equivalents
of lithium in HMPA-diethyl ether followed by addition of deuterium oxide afforded 2-deuterio-2-phenylethanol (3a) (Scheme 2). This result is a proof of that β–functionalised organolithium compounds of type 2 are involved as reaction intermediates. These dianionic intermediates have also been prepared by deprotonation of β–hydroxymercurials followed by mercury–lithium transmetallation and by deprotonation of β–chlorohydrins followed by lithiation with lithium naphthalenide. In the case of using a chiral chlorohydrin, non-racemic β–functionalised organolithium compounds can be obtained.

In 1986 Bartmann developed a methodology which allowed the preparation and characterisation of dianions 2 in reasonable yields by reductive opening of epoxides, using lithium metal and a stoichiometric amount of an arene (biphenyl and naphthalene), and their reaction with electrophiles to explore the synthetic application of intermediates 2. The process did not take place with lithium itself at low temperature (around –90 °C) and it should be performed in the presence of an arene which acts as an electron carrier. Low temperature is necessary in order to prevent decomposition. Regarding the regioselectivity of the ring opening process for monosubstituted epoxides, in all cases only one regioisomer was detected after reaction with electrophiles. The most substituted carbanion is obtained when a phenyl or ester group is the substituent, but for alkyl substituents, the cleavage of the carbon–oxygen bond leading to the primary alkyl anion, which is more stable than a secondary one, takes place. These results can be explained either by assuming a stabilizing effect of the substituents during the formation of the carbanion or by considering the stability of the two possible radical anions initially formed after the ring opening. In all cases better yields were obtained by addition of lithium bromide (Scheme 3).

Starting epoxides can be prepared following different methodologies. The reaction of a carbonyl compound with in situ generated chloromethylolithium at –78 °C to room temperature yields after cyclisation the corresponding epoxides, which by reaction with lithium naphthalenide at –78 °C undergoes reductive opening. Reaction with different electrophiles followed by final acidic hydrolysis leads to functionalised alcohols 3h (Scheme 4).

Reductive opening of enantiomerically pure epoxides, which can be easily prepared from natural occurring hydroxy acids or by epoxidation of allylic alcohols, yields chiral dianions of type IV (X = O, n =...
0, Scheme 1). The latter strategy has been employed in one of the steps of the synthesis of calcitriol lactone,\textsuperscript{27} lithium di-\textit{tert}-butylbiphenylide being used as lithiating reagent of chiral epoxide 1i (Scheme 5).

![Scheme 4](image)

Scheme 4

![Scheme 5](image)

Scheme 5

Same reaction conditions have been applied to the synthesis of an advanced forskolin intermediate 3j. Reductive opening at \(-78 ^\circ\)C of an optically active epoxide 1j to give dianionic intermediate 2j and reaction with drimenal gives compound 3j after hydrolysis (Scheme 6).\textsuperscript{28}

![Scheme 6](image)

Scheme 6
The use of carbonyl compounds and carbon dioxide as electrophiles reacting with these chiral intermediates are of great interest because, 1,3-diols and β-hydroxy acids can be prepared in enantiomerically pure form. The reductive opening of commercially available (S)-1b or easily available chiral epoxides [1k, ent-1k, 1l, 1m] with an excess of lithium and a catalytic amount of DTBB at −78 °C gives the corresponding dianionic intermediates 2, which by reaction with several electrophiles followed by hydrolysis with water afford products 3 (Scheme 7). In the case of using prostereogenic carbonyl compounds as electrophiles, an almost 1:1 mixture of diasteromers is obtained, which could be easily separated by flash chromatography.

\[
\text{R}_2\text{O} \overset{\text{Li, DTBB (5%)}}{\longrightarrow} \text{OLi} \overset{1. E^+}{\longrightarrow} \text{OH} \overset{2. \text{H}_2\text{O}}{\longrightarrow} \text{R}_2\text{E}
\]

\[
\text{E}^+ = \text{H}_2\text{O}, \text{D}_2\text{O}, \text{CO}_2, \text{Bu'}\text{CHO}, \text{PhCHO}, \text{PhCOMe}, (\text{CH}_2)_3\text{CO}
\]

**Scheme 7**

The above mentioned methodology has been applied to the synthesis of branched-chain modified carbohydrates, which are glycosidic components of many antibiotics. Thus, DTBB-catalysed lithiation of epoxide 1n, easily prepared from D-glucose, yields intermediate 2n, which reacts with different electrophiles to give, after hydrolysis, compounds 3n. These compounds are 3-C-substituted D-allose derivatives (Scheme 8). Another epoxide 1o was also easily prepared from D-glucose and submitted to the same reaction conditions as for compound 1n, thus the expected products 3o, 6-C-substituted-3-deoxy-D-glucose derivatives, are isolated through the intermediate 2o (Scheme 8). For the D-fructose derivative 1p, a DTBB-catalysed lithiation followed by reaction with electrophiles and final hydrolysis yields 3-C-substituted-D-psicose derivatives 3p (Scheme 8). The reaction of intermediate 2p with ketone 4 (derived from D-fructose) affords C₂-symmetrical disaccharide 3pa in low yield (Figure 1). Methodologies to modify selectively the structure of steroids are also of interest and welcome because minor changes in their structure cause extensive changes in their biological activity. Reductive opening of epoxides derived from steroids, such as estrone derivative 1q and cholestanone derivative 1r, by a DTBB-catalysed lithiation followed by reaction with electrophiles and final hydrolysis gives 17α-
substituted-17β-estradiol derivatives 3q and 3β-substituted-3α-cholestanol derivatives 3r, respectively, through organolithium compounds 2q and 2r (Scheme 9).\textsuperscript{33,34}

![Scheme 8](image)

When keto sugars 4 (Figure 1) and 5 (D-glucose derivative, Figure 2) are used as electrophiles, in the case of the estrone derivative 1q, mixed products 3qa,b, having both a steroid and a sugar fragment, are obtained (Figure 2).\textsuperscript{34} Finally, the reaction of intermediate 2q with O-protected estrone 6 gave, after hydrolysis the expected C2-symmetrical steroid dimer 3qc (Figure 2).\textsuperscript{34}

### 2.2. Reductive opening of aziridines

Triphenyl aziridine 7a undergoes reductive opening by treatment with sodium in liquid ammonia to give N-(1,2-diphenylethyl)aniline (9a). However, a dianionic specie of type IV (Y = NPh, n = 0, Scheme 1), which is supposed to be the reaction intermediate, could neither be isolated nor used synthetically (Scheme 10).\textsuperscript{17}
Stamm and co-workers studied also the reductive opening of the so-called activated aziridines (\(N\)-carbonyl or \(N\)-sulphonyl derivatives), using anthracene hydride or the xanthenyl anion as reducing reagents. After a single electron transfer (SET) from the reducing reagent, a ketyl intermediate is formed, which undergoes ring cleavage (carbon-nitrogen bond) to generate a new radical anion. The latter radical anion decomposes mainly by both homo or cross combination leading to a mixture of reaction products. The metal accompanying the reducing reagents and the substituents in the aziridine rings plays an important role in the structure of the reaction products.\(^{35}\) Aziridine-2-carboxylate can be also reductively opened by means of a palladium catalyst. The process can be performed in a regioselective manner, thus the catalytic hydrogenation by \(\text{Pd/EtOH}\) leads to carbon(2)-nitrogen cleavage\(^{36}\) and the catalytic transfer hydrogenation with \(\text{Pd/HCO}_2\text{H/EtOH}\) leads to carbon(3)-nitrogen cleavage.\(^{37}\) More recently, Pak \textit{et al.} reported the regioselective reductive cleavage of aziridines substituted with an electron
acceptor group with magnesium in methanol, ketyl being the reaction intermediates, which undergo the cleavage. Functionalised organolithium intermediates, which are the targets of this review, are not involved as reaction intermediates in all these processes.

Scheme 10

Lithioarenes are not reactive enough to open reductively aziridines at low temperatures under the reaction conditions necessary to prevent decomposition of the dianionic resulting intermediates 8. However, the use of an excess of lithium in the presence of a catalytic amount of an arene is an effective lithiation mixture for these aziridines. Treatment of aziridines 7b-d under these reactions conditions at \(-78^\circ C\) gave intermediates 8, which reacted with different electrophiles and after final hydrolysis led to functionalised amines 9 (Scheme 11).

Scheme 11

Concerning the regiochemistry of the process for non symmetrically substituted aziridines (7c and 7d), the ring opening leads in general to the formation of the most stable \(\beta\)-nitrogenofunctionalised organolithium compound, such as primary carbanionic derivative 8c or benzylic dilithioderivative 8d (Scheme 11). In the case of \(N\)-phenyl-2-methylaziridine (7c), \(N\)-propylaniline was always a side-reaction product with less than 15% yield. This indicates that the other possible reductive opening process, leading to the less stable secondary dilithium derivative that abstracts a proton from the reaction medium took also place to a small extent.

Starting from chiral aziridines and applying the above mentioned procedure it is possible to prepare enantiomerically pure functionalised amines. Thus, when aziridines 7e and 7f are submitted to a naphthalene-catalysed lithiation followed by reaction with electrophiles and final hydrolysis with water, only one reaction product 9f is isolated, independently of the starting aziridine. These results can be rationalised
assuming that initially formed benzylic dianionic species \(8e\) from \(7e\), undergoes epimerization to the less-hindered intermediate \(8f\), which is the same that results for reductive opening of \(7f\) (Scheme 12). The starting aziridines \(7e\) and \(7f\) were easily prepared from (\(-\))-ephedrine by tandem chlorination-intramolecular cyclisation and using a Mitsunobu-type reaction, respectively.

\[
\begin{align*}
\text{Me} & \quad \text{Ph} \\
\text{Me} & \quad \text{Ph} \\
\uparrow & \\
\text{Li, C}_{10}\text{H}_8 (5\%) & \\
\text{Li} & \\
\text{Me} & \quad \text{Li} \quad \text{Ph} \\
\text{Me} & \quad \text{Li} \\
\uparrow & \\
\text{8e} & \\
\text{8f} & \\
\text{1. E}^+ & \\
\text{2. H}_2\text{O} & \\
\text{Me} & \quad \text{NH} \quad \text{E} \\
\text{Me} & \quad \text{E} \\
\end{align*}
\]

Scheme 12

Following with this systematic study on the reductive ring opening of three-membered heterocycles, reductive opening of thiiranes could not be applied to the preparation of \(\beta\)--thiofunctionalised organolithium compounds. Thiiranes are easily available from epoxides upon treatment with thiourea in chloroform.\(^{41}\)

\[
\begin{align*}
\text{Ph} & \quad \text{S} \\
\text{Li, DTBB (5\%)} & \\
\text{10} & \\
\text{Li} & \quad \text{SLi} \\
\text{Ph} & \quad \text{11} \\
\uparrow & \\
\text{1. E}^+ & \\
\text{2. H}_2\text{O} & \\
\text{Ph} & \\
\end{align*}
\]

Scheme 13

In the case of phenylthiirane (10), a DTBB-catalysed lithiation followed by reaction with electrophiles and final hydrolysis with water at \(-78^\circ\text{C}\), leads to ethyl benzene 13 as the major reaction product (Scheme 13). The lithiation can be performed also under Barbier-type conditions (lithiation in the presence of the electrophile) but the expected functionalised thiol has never been isolated.\(^{42}\) An explanation for these results is that the initially formed highly reactive dianionic derivative 11 undergoes \(\beta\)-elimination leading to styrene 12, even at \(-78^\circ\text{C}\) and, after hydrolysis in the reductive medium, the conjugate double bond is hydrogenated to ethylbenzene 13.

2.3. Reductive opening of oxetanes

Cohen et al. reported for the first time in 1989 on the reductive opening of oxetanes.\(^{43}\) Thus, treatment of oxetanes 14 with lithium and a stoichiometric amount of DTBB in THF at 0 °C gave dianionic species 15, which by reaction with electrophiles and final hydrolysis yielded functionalised alcohols 16 (Scheme 14). The main difference compared to oxiranes is the reaction temperature, because \(\beta\)--oxidofunctionalised organolithium compounds 2 should be prepared at \(-78^\circ\text{C}\) in order to avoid
decomposition, meanwhile the corresponding γ-functionalised ones 15 are stable even at room temperature. These species have also been prepared from γ-chlorohydrines through a chlorine-lithium exchange previous deprotonation. Regarding the regiochemistry of the process for unsymmetrical substituted oxetanes, reductive opening takes place always to give the most stable organolithium compound 15, which are the less substituted (such as 15c) or the benzyl substituted (15d) (Scheme 14).

![Scheme 14](image)

When reductive opening of unsymmetrical oxetanes takes place in the presence of a Lewis acid such as AlEt₃, the regiochemistry of the ring cleavage is the opposite as that commented above. In this case lithiation should be performed in the presence of a stoichiometric amount of DTBB in THF at −78 °C, this strategy being complementary to the former one (Scheme 15).

![Scheme 15](image)

The above shown methodology has found wide application in organic synthesis. For instance, the reaction of carbonyl compounds with intermediates 15 gives 1,4-diols which under acidic conditions undergo cyclisation leading to tetrahydrofurans.
In the case of using lactones as electrophiles in the presence of cerium trichloride, spiroketales are obtained after acidic work-up. Also cyclic Fischer-type chromium carbene complexes have been prepared when hexacarbonyl chromium was added first, followed by treatment with trimethyloxonium tetrafluoroborate (Scheme 16).

Enantiomerically pure functionalised alcohols are obtained from chiral oxetanes when the reductive opening is performed with lithium and a substoichiometric amount of DTBB in THF at 0 °C, followed by reaction with electrophiles and final hydrolysis with water (Scheme 17).

The reaction with prostereogenic carbonyl compounds as electrophiles gives an almost 1:1 mixture of diastereoisomers, which are easily separated by column chromatography, so enantiomerically pure diastereoisomers are obtained. Starting chiral oxetanes can be prepared from double methylenation of ketones or by methylenation of epoxides with trimethylsulfonium ylide. Oxetanes and were prepared from (-)- and (+)-menthone, respectively, and oxetane was prepared from commercially available (-)-glycidol.

\[
\begin{align*}
14 \xrightarrow{\text{Li, DTBB (5\%)}} & 15 \xrightarrow{1. E^+ \atop 2. \text{H}_2\text{O}} 16 \\
\text{[E}^+ = \text{D}_2\text{O, CO}_2, \text{Bu}^\text{iCHO, PhCHO, Me}_2\text{CO]} \\
\text{Scheme 17}
\end{align*}
\]

Recently Rama and Pasha found that lithium in the presence of biphenyl (catalytic amount) under refluxing THF is capable of inducing the oxetanes to undergo regiospecific ring opening leading exclusively to the formation of terminal alcohols, under aprotic conditions, in almost quantitative yield (Scheme 18). On the contrary internal alcohols are obtained when metallic hydrides are used as nucleophiles. In this process dianionic species of type (X = O, n = 1, Scheme 1) have been neither characterised nor proposed as reaction intermediates.

\[
\begin{align*}
14c; R^1-R^2 &= (\text{CH}_2)_5 \\
14d; R^1 &= \text{Ph}, R^2 = \text{H} \\
14m; R^1 &= \text{Me}, R^2 = \text{Ph} \\
14n; R^1 = R^2 &= \text{Ph} \\
16 \xrightarrow{1. \text{Li, Ph}_2 \text{ (cat.)} \atop 2. \text{H}_2\text{O}} & \\
\text{[Scheme 18]}
\end{align*}
\]
The reductive cleavage of 2-methyleneoxetanes has been studied by Howell and Hashemzadeh. In the case of 3,3-dimethyl-2-methylene-4-phenyloxetane (14o), it undergoes reductive opening with lithium and a catalytic amount of DTBB at temperatures ranging from −78 to 0 °C to give the dianionic intermediate (15o), which reacts regioselectively with aldehydes and ketones to give aldol adducts (18) in variable yields (Scheme 19).

However, under the same reaction conditions, 2-methylene-3-phenyloxetane (14p) gave unexpected lactone (19) with 84% yield (Scheme 19). It is postulated that (19) arises from a coupling of a radical enolate derived from (14p) and the enolate of acetaldehyde, a product of THF decomposition under the reaction conditions.

![Scheme 19](image)

### 2.4. Reductive opening of azetidines

Azetidines (20) are less reactive than aziridines (7) toward the reductive opening with excess of lithium and a catalytic amount of DTBB, mainly due to the decrease in ring strain. For that reason, the process should be performed at higher temperatures, that is −15 °C, compared to −78 °C for aziridines (see above). Dianionic intermediates (21) are obtained in the lithiation of azetidines which upon reaction with electrophiles and hydrolysis with water lead to regioselectively functionalised amines (22) (Scheme 20). A phenyl substituent (aryl, in general) is necessary at 1- or 2-position for the reductive opening to take place. For instance, N-cyclohexylazetidine does not undergo reductive cleavage with the mentioned lithiating mixture even at room temperature. Concerning the regiochemistry of the process for unsymmetrically substituted azetidines, in the case of 2-phenylsubstituted heterocycle (20b), the most stable benzylic organolithium derivative (21b) is formed instead of the primary one. However, for 2-methyl-1-phenylazetidine (20c), after reductive opening and reaction with deuterium oxide as electrophile, a 2:1 mixture of compounds (22c) and (22"c) is surprisingly obtained. Compound (22c) comes from the less stable secondary organolithium derivative (21c), which decomposes by proton abstraction prior to react with deuterium oxide, whereas deuterated compound (22"c) results from the more stable dianion (21"c), which remains stable under the reaction conditions until the addition of deuterium oxide (Scheme 20).

Alternatives to the reductive opening of azetidines for the synthesis of γ-aminofunctionalised organolithium compounds (21) are deprotonation of amines, chlorine-lithium exchange in N-benzyoyl-γ-chloramines and addition of alkyl lithium reagents to allylic amines.
3. Reductive opening of cyclic allyl and benzylic ethers, amines and thioethers

Allylic and benzylic carbon-heteroatom bonds can be reductively cleaved by means of alkali metals through a SET process in the same way as for strained heterocycles (see above). In the case of cyclic allylic and benzylic systems, a reductive ring opening takes place, leading to functionalised dianionic compounds.

In the proposed mechanism, a radical anion VI is initially formed after electron transfer from the metal to the heterocyclic substrate V. This highly unstable radical anion undergoes cleavage of the activated allylic or benzylic carbon-heteroatom bond to generate a new and more stable radical anion VII where the negative charge is placed on the heteroatom, which is newly reduced to the dianionic intermediate VIII (Scheme 21).

3.1. Reductive opening of cyclic allyl ethers, amines and related thioethers

In sharp contrast to the behaviour of epoxides and oxetanes, tetrahydrofuran (23a) as well as tetrahydropyran do not undergo reductive opening by means of lithium metal itself and in the presence of arenes as electron carriers at low temperatures. An explanation for that could be the difference in ring strain among these heterocycles. However tetrahydrofuran (23a) can undergo reductive opening when treated with lithium biphenylide at 66 °C, but the resulting dianion decomposes under these conditions before reacting with electrophiles. It is possible also to carry out this process at low temperature but
necessarily in the presence of boron trifluoride etherate. Thus, treatment of the complex resulting from 23a and the Lewis acid with lithium and DTBB in a stoichiometric ratio at −78 °C leads to δ-oxygenofunctionalised organolithium compound 24a which after reaction with electrophiles and final hydrolysis gives functionalised alcohols 25a (Scheme 22). The same process can be performed using an excess of lithium and a catalytic amount of naphthalene as lithiating mixture (Scheme 22). In the case of 2-methyltetrahydrofuran (23b), reductive ring opening leads to the formation of the more substituted organolithium derivative 24b in a similar way as for oxetanes (see above) (Scheme 22).

\[
\begin{align*}
\text{Li, ArH, BF}_3\cdot\text{OEt}_2 & \quad \text{Li}^+ \quad \text{1. E}^+ \quad \text{2. H}_2\text{O} \\
& \quad \text{25} \\
\text{23a; } R = \text{H} & \quad \text{23b; } R = \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{ArH} & = \text{DTBB, C}_{10}\text{H}_8 (4\%) \\
\text{E}^+ & = \text{Pr}^\text{t\text{r}}\text{CHO, Bu}^\text{t\text{r}}\text{CHO, Bu}^\text{t\text{r}}\text{CHO, PhCHO, p-MeOC}_6\text{H}_4\text{CHO, Et}_2\text{CO, MeCOBu}^\text{t\text{r}}, \text{MeCOPh} \\
\end{align*}
\]

Scheme 22

However, tetrahydrofuran and tetrahydropyran derivatives with a vinyl (alkenyl, in general) substituent at the 2-position 23c,d are easily opened reductively with lithium in the presence of DTBB at 0 °C (Scheme 23). In this case it is not necessary the presence of a Lewis acid for carbon-oxygen bond activation due probably to the stability of the resulting allylic dianions 26. The reaction of these dilithium derivatives with electrophiles leads to a mixture of regio- and stereoisomers 27-27” (Scheme 23).

\[
\begin{align*}
\text{Li, DTBB} & \quad \text{Li}^+ \quad \text{1. E}^+ \quad \text{2. H}_2\text{O} \\
& \quad \text{26} \\
\text{23c; } n = 1 & \quad \text{23d; } n = 2 \\
\end{align*}
\]

\[
\begin{align*}
\text{[E}^+ & = \text{H}_2\text{O, Pr}^\text{t\text{r}}\text{CHO-CeCl}_2, \text{Pr}^\text{t\text{r}}\text{CHO-Ti(OP}^\text{t\text{r}})\text{d}] \\
\end{align*}
\]

Scheme 23

Ketalisation of α,β-unsaturated carbonyl compounds with 1,2-ethanodiol leads to a special kind of allyl ethers, which are able to undergo reductive opening. In the case of the 2-cyclopentenone derivative 28, lithiation under Barbier-type conditions (lithiation in the presence of the electrophile) with lithium and a catalytic amount of DTBB leads first to the formation of dianion 29. This intermediate can be considered a masked homoenoate and reacts with the electrophile which is present in the reaction medium to give 30. Final acidic hydrolysis leads to 3-substituted cyclopentenone 31 (Scheme 24). The whole process represents the conjugate addition of an electrophile to an α,β-unsaturated carbonyl compound and is analogous to an unpoled Michael reaction.

The reductive opening of a 3,4-dihydro-2H-oxepine ring has been reported by Hirama et al. as a undesired side reaction in the last step of the convergent synthesis of ciguatoxin CTX3C, which along with brevetoxins are structurally classified as ladderlike polyethers. The lithium DTBB-mediated reduction of 28-
tribenzyl ciguatoxin CTX3C derivative 32 at −78 °C is accompanied by reductive cleavage of the A ring allylic ether to give 33 (Scheme 25). This problem has been overcome by using sodium in a mixture of ammonium, ethanol and THF as solvents at −90 °C.62

\[
\text{O}_2\text{Li} \quad \text{DTBB (2.5%), } E^{+} \quad \begin{cases} \text{O}_2\text{Li} \\ \text{O}_2\text{Li} \end{cases} \xrightarrow{\text{H}_2\text{O}^{+}} \text{O}_2\text{E} \\
{28} \quad \text{[} E^{+} = \text{Bu}^{+}\text{CHO, Me}_2\text{CO, Et}_2\text{CO, Pr}_2\text{CO, (CH}_2\text{)}_3\text{CO]} \\
\text{Scheme 24}
\]

It is known that strained nitrogenated heterocycles such as N-phenylaziridines and N-phenylazetidines undergo reductive opening upon treatment with lithium in the presence of an arene but, N-phenylpyrrolidine remains unchanged under the same reaction conditions even after three days at room temperature because of the lack of ring strain and of instability of the resulting dianionic species.63 However, N-phenylpyrroline 34 gives a stable allylic dianion 35 when treated with an excess of lithium in the presence of a catalytic amount of DTBB at 20 °C. The reaction of 35 with different electrophiles followed by hydrolysis gives a mixture of regioisomeric functionalised amines 36a,b (Scheme 26). The ratio of isomeric amines 36 depends strongly on the electrophiles. Thus, in the case of using H\textsubscript{2}O or D\textsubscript{2}O as electrophiles, 36a was obtained exclusively, and for carbonyl compounds and CO\textsubscript{2}, mixtures of 36a and 36b were obtained, the latter being always more abundant (Scheme 26).63
Gleason and Manthorpe have reported on the reductive opening of bicyclic thioglycolate lactams 37, by using lithium DTBB as reducing reagent at −78 °C. The mentioned process takes place by formation of a relatively stable dianion enolate derivative 38 through a carbon-sulfur bond cleavage at the α-position with respect to the carbonyl group.

![Scheme 26](image)

These dianion enolates 38 are trapped by addition of trimethylsilyl chloride to give silyl ketene aminals 39. In the case of α,α-disubstituted amide enolates, the reaction with unactivated alkyl iodides leads to a stereoselective formation of quaternary carbon centres in compounds 40 (Scheme 27).

![Scheme 27](image)

### 3.2. Reductive opening of cyclic benzyl ethers

As previously commented, benzylic carbon-oxygen bonds are susceptible of suffering reductive cleavage by means of lithium metal to generate benzylic organolithium compounds. In the case of cyclic benzyl ethers, oxygenofunctionalised organolithium compounds are the reaction intermediates. The treatment of 2-phenyl-1,3-dioxolanes 41 (easily available by ketalisation of the corresponding carbonyl compounds) with an excess of lithium and a catalytic amount of naphthalene at −40 °C affords dianions 42. The reaction of these intermediates with different electrophiles leads to compounds 43 and after hydrolysis to polyfunctionalised compounds 44 (Scheme 28). When after addition of the first electrophile, the reaction mixture is allowed to reach room temperature, a second benzylic carbon-oxygen bond reductive cleavage
takes place to give intermediate 45, which after reaction with a second electrophile and final hydrolysis gives compounds 46 (Scheme 28).66

\[
\begin{align*}
41a: R &= H \\
41b: R &= Me \\
41c: R &= Ph
\end{align*}
\]

\[
\begin{align*}
42 & \xrightarrow{\text{Li, } C_{10}H_8 (4\%)} 43 & \xrightarrow{\text{H}_2\text{O}} 44 \\
& \xrightarrow{\text{E}_1^+} 43 & \xrightarrow{\text{H}_2\text{O}} 44
\end{align*}
\]

(Scheme 28)

The reaction of intermediates 48, resulting from the reductive opening of starting dioxanes 47, with electrophiles, followed by hydrolysis, gives 3-substituted-3-phenylpropan-1-ols 49 in good yields. The reaction works well in the case of methylene derivatives 47a-c, the process being synthetically no useful for acetone derivatives 47d (Scheme 29).67

\[
\begin{align*}
47a: R^1 &= H, R^2 = H \\
47b: R^1 &= H, R^2 = Me \\
47c: R^1 &= H, R^2 = Ph \\
47d: R^1 &= Me, R^2 = Ph
\end{align*}
\]

\[
\begin{align*}
47 & \xrightarrow{\text{Li, } C_{10}H_8 (2.5\%)} 48 & \xrightarrow{\text{E}^+} 49
\end{align*}
\]

(Scheme 29)

The reductive lithiation of diastereomeric mixtures of 4-aryl-5-alkyl-1,3-dioxanes 47e-g with lithium in the presence of a catalytic amount of naphthalene at −78 °C occurs with epimerisation at the benzylic centre to give intermediates 48, which by reaction with alkyl halides or carbon dioxide affords 2-alkyl-3-substituted-3-arylpropan-1-ols 49, or the corresponding lactones with satisfactory to high diastereoselectivities (Scheme 30).68

1,3-Oxazolidines 50 are the mononitrogenated derivatives related to 1,3-dioxolanes 41 and they can also undergo reductive cleavage by means of lithium metal in the presence of a catalytic amount of
naphthalene at −20 °C to generate α-N,N-dialkylaminosubstituted benzyllithium derivatives 51, which are of great interest in synthetic organic chemistry because by reaction with electrophiles, functionalised aminoalcohols 52 are obtained in satisfactory yields (Scheme 31). Starting oxazolidines are readily available by reaction of the corresponding aromatic aldehydes with 2-(N-methyl)aminoethanol.

![Chemical reaction](image)

**Scheme 30**

![Chemical reaction](image)

**Scheme 31**

This process has been studied for diastereomeric bicyclic 2-phenyloxazolidine 53, derived from 2-hydroxymethylpiperidine and benzaldehyde upon acid-catalysed cyclisation. In this case a 92:8 mixture of racemic diastereoisomers is obtained and the stereochemistry of the major stereoisomer is shown on Scheme 32. Reductive metallation of 53 with lithium in the presence of a substoichiometric amount of naphthalene at −20 °C occurs with epimerisation at the benzylic carbon atom. Reaction of dianionic intermediates 54 with alkyl halides affords substituted amino alcohols 55 in a highly syn-selective fashion. Observed diastereoselectivities are rationalised in terms of rapid equilibration of epimeric intermediate organolithiums 54, one of which reacts preferentially under appropriate reaction conditions. Deuteration of the same intermediates usually leads to deuterated amino alcohols with low diastereoselectivities, unless the resulting mixture is allowed to equilibrate before deuteration (Scheme 32).
Phthalan (56a) and isochroman (56b) are a special kind of cyclic benzyl ethers. In this case, 56a and 56b are benzocondensed cyclic ethers and there is not a phenyl group as substituent. These heterocycles are opened reductively with lithium and a catalytic amount of DTBB at 0 °C to afford dianions 57 which have shown a wide use in organic synthesis, giving by reaction with electrophiles at −78 °C and final hydrolysis products 59 (Scheme 33).72,73

In addition, the lithiation of 56a can be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. After addition of the first electrophile, the resulting alcalate 58a is stirred in the presence of the excess of lithiating mixture at room temperature for four additional hours to give a new organolithium intermediate 60a, which finally reacts with a second electrophile to yield difunctionalised products 61a (Scheme 33).72

Diols 59a and 59b, derived from the reaction of intermediates 57 with carbonyl compounds \((E_1^+ = R^1R^2\text{CO})\), are easily cyclised under acidic conditions to give the corresponding six- and seven-membered benzocondensed cyclic ethers 62 (Figure 3).72,73 Using N-silylaldimines as electrophiles, aminoalcohols 59' are obtained as reaction products, which after chlorination followed by cyclisation under basic conditions lead to the formation of tetrahydroisoquinolines and benzazepines 62', interesting units in many naturally occurring compounds (Figure 3).74 When ketones derived from D-fructose 4 (Figure 1) and D-glucose 5 (Figure 2), as well as O-ethoxymethylsubstituted estrone 6 (Figure 2) and cholestanone [precursor of the epoxides 1r (Scheme 9)] are used as electrophiles, diols 59aa-ad and 59ba-bd32,34 are obtained as reaction products. Cholestanone derivatives 59ad,bd are obtained as an almost 1:1 diastereomeric mixture due to the lack of diastereoselectivity in the nucleophilic addition to the carbonyl group. The transformation of these compounds into the expected heterocyclic products 62aa-ac and 62ba-bc is easily achieved under typical Mitsunobu reaction conditions (Figure 3).31,33

Dianionic intermediates 57 behave as typical organolithium compounds, so they react with common electrophiles. However, reactions like acylation, dimerisation or specially conjugate addition to electrophilic
olefins are problematic because the high reactivity of the intermediates leads to many side-reactions. Exchanging lithium by another metal it is possible to modulate the mentioned reactivity.

Figure 3

Thus, the reaction of organolithium intermediates 57 with electrophilic olefins in the presence of copper(I) salts and HMPA in THF at −78 °C leads, after hydrolysis with a saturated solution of ammonium chloride, to products 63, resulting from a conjugate addition (Scheme 34). The same process but using an acyl chloride instead of electrophilic olefins affords the expected ketones 64 from an acylation process (Scheme 34). Compounds 63 are also obtained when the reaction between 57 and olefins was carried out in the presence of Lewis acids \([ZnX_2 (X=Cl, Br, I), AlCl_3, FeCl_3, BF_3]\) instead of CuI (Scheme 34). By contrast, intermediates 57 undergo dimerisation in the presence of copper(II) chloride to yield dimers 65 (Scheme 34). Working in the presence of triisopropoxytitanium chloride, functionalised organolithium compounds 57 could discriminate between aldehydes and ketones, the process being selective for aldehydes
at room temperature.\textsuperscript{78} Another synthetically useful finding is that the reaction of intermediates 57 with an equimolecular amount of zinc bromide and copper cyanide, followed by treatment with different allylic chlorides or bromides, leads, after hydrolysis, almost exclusively to the corresponding alcohols 66 resulting from a $S_N2'$ displacement, the process being highly regioselective (Scheme 34).\textsuperscript{79}

![Scheme 34](image)

The palladium-catalysed Negishi cross-coupling reaction can be applied also to in situ generated functionalised organozinc reagents, which are easily prepared from functionalised organolithium compounds 57 by a lithium-zinc transmetallation process with zinc bromide. This reaction is not possible without the help of both the zinc and palladium components. The process works well for arylic and vinylic bromides, as well as with iodides, compounds 67 being generally obtained in good yields (Scheme 35).\textsuperscript{80,81}

![Scheme 35](image)
Azzena et al. studied also the DTBB-catalysed reductive opening lithiation of several substituted phthalans 56c-h. The regiochemistry of the reductive opening process always takes place to lead to the most stable of the two possible dilithium intermediates 57,57' after arylmethyl carbon-oxygen bond cleavage, and it depends on the substituents. So aryl substituents stabilise anionic species and by contrast alkyl substituents do the opposite (Scheme 36).82

![Scheme 36]

Heterocyclic compounds such as the polycyclic ether 56i and the naphthalene derivative 56j undergo also reductive ring opening to give the corresponding dilithiated intermediates 57i and 57j under the same reaction conditions (Figure 4). In the first case after reaction with D₂O a quantitative yield was obtained. However, in the case of 56j the reaction products resulting for one or two reductive carbon-oxygen bond cleavage were obtained depending mainly on the relative amount of lithium used for the lithiation.82b

Biphenyl derivative 68 and naphthalene derivative 71 are symmetrical cyclic diarylmethyl ethers and after treatment with lithium and a catalytic amount of naphthalene give intermediates 69 and 72 respectively. The reaction of these dianionic species with electrophiles followed by hydrolysis with water allows the access to unsymmetrically 2,2'-disubstituted-1,1'-biphenyl and 1,8-disubstituted naphthalene derivatives 70 and 73, respectively (Scheme 37).83

Treatment of benzo[c]-1,3-dioxane and 1,3-oxathiane derivatives 74, with excess of lithium and a catalytic amount of DTBB at 20 °C (for dioxanes 74a-g) or at −78 °C (for oxathianes 74h-n) followed by hydrolysis, leads to the formation of 2-substituted homobenzylic alcohols 75.

Cyclisation of these alcohols either under acidic conditions in refluxing toluene or under Mitsunobu-type reaction conditions gives 2,3-dihydro-2-substituted benzofurans or thiophenes 76.
[E\(^+\) = H\(_2\)O, D\(_2\)O, Pr\(^i\)Br, Bu\(^n\)Br, Me\(_3\)SiCl, Me\(_2\)CO]

Scheme 37

Scheme 38
Starting heterocycles 74 are easily prepared by ketalisation of carbonyl compounds with \(\alpha\)-(hydroxymethyl)phenol or \(\alpha\)-(hydroxymethyl)thiophenol 77 (Scheme 38). In this process, a benzylic carbon-oxygen bond cleavage takes place first leading to dianionic alcohates 78, which undergo \(\beta\)-elimination giving benzylic dianions 79 together with the carbonyl compound used for the preparation of the starting heterocycles 74. These species react immediately to give 80, which after hydrolysis with hydrochloric acid, lead to final compounds 75 (Scheme 38). 86

### 3.3. Reductive opening of cyclic benzyl amines

As commented above, strained \(N\)-phenylsubstituted nitrogenated heterocycles undergo reductive opening by an arene-catalysed lithiation, \(N\)-phenylpyrrolidine remaining unchanged under the same reaction conditions. However, \(N\)-isopropyl-2-phenylpyrrolidine (81) gives the dianion 82 when treated with an excess of lithium in the presence of a catalytic amount of DTBB at 20 °C for 30 min. In this case reductive opening takes place due to the stability of resulting benzylic intermediate 82, which after reaction with different electrophiles and final hydrolysis with water, gives functionalised amines 83 (Scheme 39). 83

\[
\begin{align*}
\text{Ph} & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Ph} & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Ph} & \quad \text{Li, DTBB (2.5 \%)} \\
81 & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Li, DTBB (2.5 \%)} \\
\text{Pr}^i & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Li, DTBB (2.5 \%)} & \quad \text{Li, DTBB (2.5 \%)} \\
82 & \quad \text{1. E}^+ & \quad \text{1. E}^+ & \quad \text{1. E}^+ & \quad \text{1. E}^+ \\
& \quad \text{2. H}_2\text{O} & \quad \text{2. H}_2\text{O} & \quad \text{2. H}_2\text{O} & \quad \text{2. H}_2\text{O} \\
83 & \quad \text{(28-85\%)} & \quad \text{(28-85\%)} & \quad \text{(28-85\%)} & \quad \text{(28-85\%)} \\
\end{align*}
\]

\[E^+ = \text{H}_2\text{O}, \text{D}_2\text{O}, \text{MeI}, \text{Bu}^i\text{CHO}, \text{PhCHO}, \text{Me}_2\text{CO}, (\text{CH}_2)_4\text{CO}, (\text{CH}_2)_5\text{CO}, \text{CO}_2\]

**Scheme 39**

Other types of cyclic benzyl amines are isoindoline and tetrahydroisoquinoline derivatives 84, which are the analogous nitrogenated compounds of oxygen-containing heterocycles phthalan (56a) and isochroman (56b). Treatment of \(N\)-phenylisoindoline (84a) or \(N\)-phenyltetrahydroisoquinoline (84b) with an excess of lithium and a catalytic amount of DTBB at 20 °C followed by addition of an electrophile at low temperature and final hydrolysis with water gives functionalised amines 86, benzylic dianionic intermediates 85 resulting from the reductive ring opening being involved in the process (Scheme 40). 86

\[
\begin{align*}
\text{84a; } n = 1 & \quad \text{Li, DTBB (4.5\%)} & \quad \text{84a; } n = 1 & \quad \text{Li, DTBB (4.5\%)} & \quad \text{84a; } n = 1 & \quad \text{Li, DTBB (4.5\%)} \\
\text{84b; } n = 2 & \quad \text{Li, DTBB (4.5\%)} & \quad \text{84b; } n = 2 & \quad \text{Li, DTBB (4.5\%)} & \quad \text{84b; } n = 2 & \quad \text{Li, DTBB (4.5\%)} \\
\text{Li} & \quad \text{Li} & \quad \text{Li} & \quad \text{Li} & \quad \text{Li} \\
85 & \quad \text{1. E}^+ & \quad \text{1. E}^+ & \quad \text{1. E}^+ & \quad \text{1. E}^+ \\
& \quad \text{2. H}_2\text{O} & \quad \text{2. H}_2\text{O} & \quad \text{2. H}_2\text{O} & \quad \text{2. H}_2\text{O} \\
86 & \quad \text{(32-89\%)} & \quad \text{(32-89\%)} & \quad \text{(32-89\%)} & \quad \text{(32-89\%)} \\
\end{align*}
\]

\[E^+ = \text{H}_2\text{O}, \text{D}_2\text{O}, \text{CH}_2=\text{CHCH}_2\text{Br}, \text{CO}_2, \text{Pr}^i\text{CHO}, \text{Bu}^i\text{CHO}, \text{PhCHO}, \text{Me}_2\text{CO}, \text{Pr}^i\text{COMe}, (\text{CH}_2)_4\text{CO}, \text{PhCOMe}\]

**Scheme 40**

159
In the same way as for symmetrical cyclic diarylmethyl ethers 68 and 71 (Scheme 37), the corresponding N-methylamino biphenyl derivative 89 and the naphthalene derivative 92 give under the same reaction conditions the unsymmetrically 2,2'-disubstituted-1,1'-biphenyl and 1,8-disubstituted naphthalene derivatives 91 and 94, respectively, benzylic dianions 90 and 93 being in this case the reaction intermediates, respectively (Scheme 41).83

![Diagram](image)

Scheme 41

3.4. Reductive opening of cyclic benzyl thioethers

Oxetanes 14 and azetidines 20 (see above) undergo reductive opening by means of alkali metals in the presence of an arene, but thietane itself or alkyl substituted thietanes are stable compounds towards the same reductive reagents because they are less strained heterocycles due to the longer carbon-heteroatom bond distances. However, 2-phenylthietane (95a) can be reductively opened with lithium in the presence of a catalytic amount of DTBB at low temperature. In this case a phenyl group at 2-position is necessary for the reductive opening to take place in order to stabilise the \( \gamma \)-thiofunctionalised organolithium compound 96a, intermediate which has also been prepared through a halogen-lithium exchange85 as well as the corresponding functionalised radicals from iodinated precursors.86

![Diagram](image)

Scheme 42

The same methodology has also been applied to the reductive opening of 2-phenyltetrahydrothiophene (95b) and 2-phenylthiane (95c). The reaction of the resulting dianionic intermediates 96 with electrophiles, followed by hydrolysis with hydrochloric acid, leads to the formation of regioselective functionalised thiols 97 (Scheme 42).87
As it could be expected by considering the reactivity of phthalan (56a) and isochroman (56b), thiophthalan (98a) and thioisochromans 98b,c are reductively opened with lithium and a catalytic amount of DTBB at −78 °C (instead of 0 °C for 56) in order to avoid undesired side reactions.

\[
\begin{align*}
\text{Scheme 43} \\
\text{The reaction of the resulting dianionic intermediates 99 with different electrophiles leads to compounds 101, after acidic hydrolysis (Scheme 43).}^{88}
\end{align*}
\]

In a similar manner to phthalan (56a) (see Scheme 33), in the case of thiophthalan (98a), two electrophilic fragments can be introduced at both benzylic positions if after reductive opening and reaction with the first electrophile, the resulting intermediate 100a is

\[
\begin{align*}
\text{Scheme 44} \\
\end{align*}
\]
allowed to react at room temperature, leading to organolithium compounds 60a, which after reaction with a second electrophile and hydrolysis with water yields o-xylene derivatives 61a (Scheme 43).

Applying the same strategy as for phthalan (56a) and thiophthalan (98a), the lithiation of 2,7-dihyrodibenzothiepin (102) can be directed either to the formation of sulfanyl alcohols 105 or to the introduction of two different electrophiles at both benzylic positions in a sequential manner, to yield difunctionalised biphenyls 107. Thus, the treatment of compound 102 with an excess of lithium and a catalytic amount of DTBB at −78 °C leads to intermediate 103, which reacts with carbonyl compounds to give alkoxides 104, and after acidic hydrolysis to the afore mentioned sulfanyl alcohols 105. However, when alkoxides 104 are stirred at room temperature in the presence of the excess of the lithiating mixture, the remaining benzylic carbon-sulfur bond is cleaved leading to new intermediates 106, which after reaction with a second electrophile and final hydrolysis with water lead to polyfunctionalised compounds 107 (Scheme 44).89

4. Reductive opening of cyclic aryl ethers and thioethers
4.1. Reductive opening of cyclic aryl ethers

Alkyl aryl ethers, in general, and the corresponding cyclic alkyl aryl ethers IX, in particular, have not been used extensively for the generation of organolithium compounds by means of lithium metal itself or in the presence of an arene, because of the competition of two different bond cleavages:13a alkyl-oxygen bond cleavage leading to alkyllithium phenolates X (dealkylation process) and aryl-oxygen bond cleavage leading to aryllithium alcoholates XI (dearylation process) (Scheme 45). There are many factors which control this reductive cleavage, among them (a) the electronic effect of the metallic cation resulting after the electron transfer to the substrate when using alkali metals as reducing reagents,13b (b) the presence of other contraions,13c (c) the conformation of the substrate13b and (d) the polarity of the solvent.13d,e

The reductive ring opening of dibenzofuran (108a) was initially investigated by Gilman and Esmay,90 further developments of the reaction with the aim of synthetic applications having been made by Keumi and collaborators.91 They found that 2-hydroxybiphenyls 110 are obtained in high yields in the reaction of three equivalents of lithium in dioxane with cyclic diaryl ethers 108 under reflux and after final acidic hydrolysis. For alkyl substituted dibenzofurans 108b-g, non-substituted aryl-oxygen bond is cleaved selectively to give dianionic intermediates 109 (Scheme 46).

The synthesis of 2'-phosphanyl-1,1'-biphenyl- and 2'-phosphanyl-1,1'-binaphthyl-2-ols and their silyl ethers 110a and 113, respectively, has been developed by a DTBB-catalysed lithiation of dibenzofuran (108a) and dinaphthofuran (111) in THF at room temperature to give intermediates 109a and 112, respectively, after subsequent reaction with chlorophosphanes (and work-up with acetic acid) or trimethylchlorosilane. When the reaction is performed in ether, in the absence of arene and with sonication at ether reflux, reaction times are considerably longer (Scheme 47).92
could be generated after a carbon-aromatic lithiation,\textsuperscript{114} with an excess of lithium in the presence of a catalytic amount of DTBB in THF at 0 °C gives the functionalised organolithium compounds.

It has recently been reported the preparation of alkyllithiums from alkyl phenyl ethers through an arene catalysed lithiation,\textsuperscript{115} so in the case of cyclic alkyl aryl ethers functionalised organolithium compounds could be generated after a carbon-oxygen bond cleavage. Thus, the treatment of 2,3-dihydrobenzofuran (114) with an excess of lithium in the presence of a catalytic amount of DTBB in THF at 0 °C gives the functionalised organolithium compounds.
dianion 115, which after reaction with different carbonyl compounds and final hydrolysis with water leads to compounds 116 (Scheme 48).  \(^{93,94}\)

Dehydration under acidic conditions of diols 116 leads to chromans 117, homologous heterocycles of starting 2,3-dihydrobenzofuran (114). In some cases diols 119 are also isolated as side reaction products in less than 18% yield (Figure 5). An explanation for this result is that dealkylation leading to intermediate 115 is the predominant process and dearylation to 118 (Figure 5) occurs in a minor extension.

**Figure 5**

Chroman (120) [homologous heterocycle of 2,3-dihydrobenzofuran (114)] undergoes DTBB-catalysed lithiation, but reaction conditions are different than for compound 114. In this case, the process should be performed at room temperature instead of 0 °C and for a longer reaction time (3 h instead of 1.5 h). After addition of different carbonyl compounds as electrophiles, followed by acidic hydrolysis, a mixture of regioisomeric alcohols 123 and 124 is surprisingly obtained, indicating that dianions 121 and 122 are involved as reaction intermediates. These results can be explained assuming that dearylation leading to intermediate 121 is in this case the only process, but under the reaction conditions used (room temperature and long reaction time), the initially formed dianion 121 is in equilibrium with the apparently more stable benzylic dianion 122 through an inter- or intra-molecular deprotonation process (Scheme 49).  \(^{94}\)

**Scheme 49**

In the case of 2,3-benzofuran (125), a stereoselective ring opening lithiation takes place under the same reaction conditions as for 2,3-dihydrobenzofuran (114) shown on Scheme 48, yielding the (Z)-organolithium intermediate 126 which, by reaction with different electrophiles and final acidic hydrolysis,
gives the expected (Z)-products 127. Cyclisation of the products obtained by reaction with carbonyl compounds, under acidic conditions, affords the expected substituted 2H-chromenes 128 (Scheme 50), including deoxycordiachromene 128h (Figure 6).  

![Scheme 50](image)

Finally, when 4H-chromene (129) is submitted to the same lithiation mixture as above, at 20 °C, followed by acidic hydrolysis, a mixture of 3-phenylpropanal (132) and 2-allylphenol (133) in a 2:1 ratio, is respectively obtained in 95% overall yield, intermediates 130 (through dearylation) and 131 (through dealklylation) being probably involved in the process. In this case dearylation is predominant over dealklylation, the use of carbonyl compounds as electrophiles leading to a complex mixture of reaction products (Scheme 51).  

![Scheme 51](image)

### 4.2. Reductive opening of cyclic aryl thioethers

In the case of the polyaromatic sulfur-containing heterocycle flavophen 134, a reduction with potassium metal yields a stable dianion 135, whereas under identical reaction conditions with lithium or sodium the reduction does not proceed beyond the radical anion.

Sulfur extrusion from this dianion proceeds upon further contact with the reducing metal: the extrusion begins with the introduction of a third electron in the polycyclic ring system 135 to give a radical trianion 136, weakening one the carbon-sulfur bonds giving after scission the carbanion sulfur radical 137. Proton (or deuterium) abstraction by 137 results in the radical dianion 138. Transfer of another electron yields radical trianion 139 and the second carbon-sulfur bond is cleaved giving atomic sulfur and carbanion 140, which abstracts another proton (or deuterium) to give compound 141 (Scheme 52).
Screttas and Micha-Screttas\textsuperscript{14a,b} developed a methodology for the preparation of organolithium compounds starting from phenylthioethers, being an alternative to the use of chlorinated materials as precursors of this intermediates. Since then, the cleavage of the carbon-sulfur bond in phenylthioethers using either the stoichiometric\textsuperscript{14c} or the catalytic version of the arene-mediated lithiation\textsuperscript{97} has been extensively used to generate organolithium compounds by sulfur-lithium exchange. Applying this methodology, sulfur-containing heterocycles, such as dihydrobenzothiophene (142a)\textsuperscript{98} 3,4-dihydro-2H-benzothiane (142b)\textsuperscript{98} and trimethylbenzo-1,3-thiazolidine (142c)\textsuperscript{98b,99} in which the sulfur atom is attached to a fused aromatic ring, have been reductively opened by the mixture lithium-DTBB at 0 °C to give dianions 143. The reaction of these dianionic intermediates with electrophiles followed by acidic hydrolysis gives functionalised thiophenols 144 (Scheme 53).

Scheme 52

\[
\begin{align*}
134 & \xrightarrow{2 \text{e}^-} 135 & 136 & \xrightarrow{+\text{e}^-} 137 \\
138 & \xrightarrow{(D)H} 139 & 140 & \xrightarrow{H^+ \text{ or } D^+} + S_8
\end{align*}
\]

Scheme 53

The DTBB-catalyzed lithiation of 4-hetero-substituted dibenzothiins 145 [phenoxathiin (145a), phenothiazine (145b), and thianthrene (145c)] at low temperature gives the corresponding functionalised
organolithium intermediates 146, which by reaction with different electrophiles afford the expected functionalised thiols 148, after hydrolysis.

![Scheme 54](image)

The cyclization of some carbonyl compound derivatives under acidic conditions gives the corresponding homologous seven-membered dibenzo heterocycles 149 (Scheme 54).\textsuperscript{100} From a synthetic point of view, the whole process 145 • 149 represents a homologation of the starting materials 145. In the case of thianthrene (145c), all the reactions should be performed at \(-90^\circ\text{C}\) in order to avoid undesired side processes. However, when after the addition of a carbonyl compound as the first electrophile, the resulting intermediate 147c is allowed to react with the excess of the lithiation mixture present in the reaction medium, a new intermediate 150 is formed. The addition of a second electrophile, and final hydrolysis with water, yields 1,2-difunctionalised benzene derivatives 151 (Scheme 54).\textsuperscript{101}

Acidic cyclization of diols 151, resulting from the use of two carbonyl compounds as electrophiles, gives substituted phthalans 152 practically in quantitative yields (Figure 7). Specially interesting is the use of carbon dioxide as the second electrophile because after acidic work-up, substituted ftalides 153 are obtained (Figure 7). Through this methodology, thianthrene 145c acts as a dianionic synthon of type XII (Figure 7) but making possible to discriminate between both carbanionic centers, so two different (or equal) electrophiles can be used.\textsuperscript{101}
5. Conclusions

The reductive opening of heterocycles with lithium metal itself or in the presence of a stoichiometric or catalytic amount of an arene has proved to be a direct and easy way to achieve the preparation of functionalised organolithium compounds in only one single step starting, in general, from readily available materials. The reaction of these intermediates with electrophiles gives polyfunctionalised reaction products in only one step. In the case of using carbonyl compounds as electrophiles, the resulting functionalised alcohols can undergo dehydration to give a new heterocyclic systems, representing the whole process a homologation of the starting heterocycles. Finally, enantiomerically pure reaction products can be obtained when starting from chiral heterocycles.

References
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Abstract. The chemistry of 4,5-mono- and/or di-substituted monocyclic furan-2,3-diones is surveyed covering a ten-years period from 1991–2001. Besides methods of preparation particular emphasis is directed towards thermolysis reactions which afford highly reactive α-oxoketenes, either as neat compounds or “in situ”, and their behaviour in cycloaddition reactions ([4+2] versus[2+2] processes) as well as reactions with nucleophiles. Furan-2,3-diones themselves undergo thermally as well as photochemically initiated cycloaddition reactions, in particular 4-acyl derivatives serve as oxa-1,3-diene systems in hetero-Diels-Alder reactions, mostly accompanied by unexpected novel rearrangements, which were investigated with aid of isotopic labelling. Applying several mono-or bis-nucleophiles as reagents various novel heterocyclic systems including some deeply coloured dyes were obtained too.

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1. Introduction

This review on the chemistry of functionalized furan-2,3-diones covers the literature of a 10-years period starting from 1991. It should be regarded as a continuation of a preceding report on a similar topic covering the literature up to 1991. Furthermore, some results dating back before 1991 are also enclosed, since they have now become accessible.

In order to get a concise and convenient view on that kind of compounds some general restrictions have to be made first:

a) Monocyclic 2,3-dihydro-furandiones (4,5-unsaturated) are under discussion exclusively, fully saturated or fused systems are a priori excluded (Chart 1).

b) The furandiones are further subdivided into separate sections depending on the substitution pattern on C-4,5. In particular, derivatives having carbonyl functionalities at C-4 offer specific reactivities towards nucleophiles as well as cycloaddition processes.

2. Synthesis and preparation

Cyclocondensation reactions of 1,3-H-active substrates with oxalyl chloride still looks to be the most convenient and widely used procedure to generally prepare 4,5-substituted furan-2,3-diones (Scheme 1). \(^2-10\) In particular, applying MgCl\(_2\) as catalyst, established by Saalfrank et al., \(^4,5\) the scope of that methodology has been significantly expanded:

\[
\begin{align*}
R^1 \text{CH}_2 \text{CH}_2 & \quad \text{R}^1 \text{CH}_2 \text{CH}_2 \quad \text{R}^1 \text{CH}_2 \text{CH}_2 \\
R^2 & \quad \text{R}^2 \quad \text{R}^2
\end{align*}
\]

\[
\text{Scheme 1}
\]
It is interesting to note, that the product obtained from acetone dicarboxylic ester ($R_2=\text{CH}_2\text{COOR}$) in solution predominantly is found in its tautomeric form exhibiting an exocyclic C=C-bond (Scheme 2).\(^5\)

In a suitable variation of that general methodology the enolic form of the substrate before reacting with oxalyl chloride may first be converted into a silyl ether derivative (Scheme 3).\(^2,6\)

![Scheme 3](image1)

Surprisingly, from reaction of acetophenone and oxalyl chloride instead of the expected furan-2,3-dione a bis-furanone derivative is obtained in very low yield (16%), obviously the result of an unusual dimerization process (Scheme 4).\(^11\)

![Scheme 4](image2)

A totally different approach makes use of intramolecular cyclocondensation of acylpyruvic acid derivatives in the presence of polyphosphoric acid or better trifluoroacetic anhydride/KOH affording the corresponding furandiones in good yields (60–70%) (Scheme 5).\(^12,13\) For preparing 5-alkylfuran-2,3-diones this clean and efficient method seems far superior to the previously reported cyclocondensation reactions of silyl enol ethers with oxalyl chloride.\(^2,6\)

![Scheme 5](image3)

In a very specific case, starting from thiazolidinediones and alkylamines pyrrolinethiones were obtained, which in alkaline medium rearrange into the corresponding functionalised furan-2,3-diones (Scheme 6).\(^14\)

![Scheme 6](image4)
3. Thermolysis

3.1. Formation of neat α-oxoketenes

Furan-2,3-diones in general are suitable precursors for the formation of highly reactive α-oxoketenes, which, depending on their specific substitution pattern, may be trapped as reactive intermediates only or generated and characterized as stable species (Scheme 7).\(^{15}\)

\[
\begin{array}{c}
\text{Furan-2,3-dione} \\
\xrightarrow{\Delta T, \text{CO}} \\
\text{α-oxoketene}
\end{array}
\]

**Scheme 7**

Stabilization may be achieved either electronically\(^ {16}\) or sterically,\(^ {17}\) e.g. ketene carboxylic esters are well known as rather stable molecules since the nineteen twenties,\(^ {16a}\) and the bulky \(t\)-butyl group also dramatically enhances the stability of the α-oxoketene moiety (Scheme 8).\(^ {17}\)

\[
\begin{array}{c}
\text{R}-\text{C}=\text{O} \\
\text{R}-\text{O} \\
\text{R}-\text{C}=\text{O} \\
\text{R}-\text{O}
\end{array}
\]

**Scheme 8**

Very recently, methoxycarbonyl-pivaloylketene\(^ 8\) has been prepared as neat compound from flash vacuum pyrolysis (FVP) of 5-\(t\)-butyl-4-methoxycarbonyl-2,3-dihydrofuran-2,3-dione in 80% yield (Scheme 9). This α-oxoketene combines both stabilizing effects within the molecule, represented by the ester as well as the \(t\)-butyl group.

\[
\begin{array}{c}
\text{MeOOC} \\
\text{FVP (400 °C, 10² mbar)} \\
\text{CO} \\
\text{MeOC}
\end{array}
\]

**Scheme 9**

3.2. In situ-generation of α-oxoketenes

Several 5-aryl substituted furan-2,3-diones eliminate carbon monoxide upon refluxing in toluene to generate the corresponding α-oxoketene as reactive intermediate.\(^ {18-21}\) This also stands for 4-\(N\)-phenylcarbamoyl-5-phenylfuran-2,3-diones (Scheme 10).\(^ 3\) Evidence for the in situ formation of the oxoketene was taken from various trapping reactions only (see 3.3. and 3.4.\) since direct observation was not possible.

3. 3. α-Oxoketenes–Chemical reactions

3.3.1. Dimerization
It is well known that in the absence of any other reactant α-oxoketenes generated *in situ* have a strong tendency to undergo [4+2] cyclodimerization usually affording α-pyrone derivatives (Scheme 11).\(^\text{15}\) Thus, one molecule represents the oxa-1,3-diene system while the C=C of the second ketene acts as dienophile.

Scheme 10

\[
\begin{align*}
\text{Ar} & \xrightarrow{\text{toluene, 1h}} \text{HCO}_2
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = \text{Ph; } & o,p-\text{ClPh; } o,p-\text{NO}_2\text{Ph;} \\
p-\text{MePh; } p-\text{MeOPh; } p-\text{FPh; } 2-\text{Furyl}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{toluene, 3h}} \text{PhN} \xrightarrow{\text{CO}_2} \text{Ar}
\end{align*}
\]

\[
\text{Ph} = \text{Ph; Et}
\]

Scheme 11

\[
\begin{align*}
\text{O} & + \text{O} \xrightarrow{\text{[4+2] Dim.}} \text{O}
\end{align*}
\]

Scheme 12

\[
\begin{align*}
\text{Ar} = \text{Ph; } o,p-\text{ClPh; } o,p-\text{NO}_2\text{Ph; } p-\text{MePh; } p-\text{MeOPh; } p-\text{FPh; } 2-\text{Furyl}
\end{align*}
\]

stable with \( R = \text{N(CH}_3)_2 \)
However, while ketene carboxylic esters are highly reluctant to form any dimerization products,\textsuperscript{15} sterically stabilized neat \(\alpha\)-oxoketenes follow different routes. Obviously due to severe steric hinderance coming from the bulky \(t\)-butyl groups dimerization of neat dipivaloylketene at room temperature takes place involving a ketene C=O as dienophile and leads to different 1,3-dioxinones (A and B, Scheme 12) depending on the specific reaction conditions,\textsuperscript{17a,b} e.g. the presence of pyridines causes exclusive formation of dimer B.\textsuperscript{17b} The reason for that behaviour was seen in the formation of a zwitterionic intermediate generated by nucleophilic attack of the pyridine nitrogen at the central ketene carbon. The existence of such highly reactive zwitterions (C, Scheme 12) could recently be verified applying 4-dimethylamino-pyridine (Steglich base) as pyridine derivative.\textsuperscript{22}

Similarly, methoxycarbonyl-pivaloylketene (see Scheme 9) exclusively undergoes dimerization across the ketene C=O irrespective of any reaction conditions applied (Scheme 13).\textsuperscript{8}

The exact structural approval of the dimer regarding \(E/Z\) isomerism was achieved with aid of extensive \(^{13}\)C NMR experiments.\textsuperscript{8}

![Scheme 13](image)

When dipivaloylketene and methoxycarbonyl-pivaloylketene are generated simultaneously by FVP of an equimolar mixture of both precursors, namely the corresponding furan-2,3-diones, after warm-up of the cold finger besides small amounts of homo-dimers a mixed dimer is obtained as the main reaction product (Scheme 14).\textsuperscript{23} Its exact structural approval is based on a single crystal X-ray analysis indicating that dipivaloylketene has served as the dienophile.\textsuperscript{23}

![Scheme 14](image)

This overall experimental findings on the different dimerization behaviour of monomeric \(\alpha\)-oxoketenes depending on their specific substitution pattern has also be confirmed with aid of semiempirical (AM1) calculations on the substituent effect in such dimerization reactions comparing dibenzoylketene and dipivaloylketene, respectively.
In good agreement with the experimental results it clearly came out, that in case of the latter dimerization across both the carbonyl groups (A and B, Scheme 12) should be favourd because of its lower activation energy.24

3.3.2. Electrocyclization

Furan-2,3-diones bearing a N-phenylcarbamoyl side-chain at C-4 on heating in toluene afford a 3-benzoyl-4-hydroxy-2-quinolone ring system as a result of a 6\(\pi\)-electrocyclization of the corresponding \(\alpha\)-oxoketene intermediate (Scheme 15).3

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{R} & \quad \text{Ph}
\end{align*}
\]

- CO
\[\Delta T\]

\[
\begin{align*}
\text{[CO]} & \quad \text{6}\pi\text{-electrocyclization}
\end{align*}
\]

Scheme 15

3.3.3. Cycloadditions

As observed with the dimerization reactions (see 3.3.1.) cycloadditions of \(\alpha\)-oxoketenes, irrespective whether generated in situ or as neat compounds, usually proceed regioselectively as [4+2] processes15 mainly of the inverse- or hetero-Diels-Alder type, where the oxoketene represents the electron-deficient oxo-1,3-diene reactant.8,18,19

Therefore, electron withdrawing substituents in the aroyl group facilitate these cycloaddition reactions.19 Examples are given in Scheme 16.

\[
\begin{align*}
\text{Ar}^1 & \quad \text{Toluene, 100°C} & \quad \text{CO} \\
\text{Ar}^2 & \quad \text{CH}_2 \\
\text{TMSO} & \quad \text{Ar}^2
\end{align*}
\]

\[
\begin{align*}
\text{Ar}^1 & \quad \text{Ph, NO}_2\text{Ph, ClPh, MeOPh} \\
\text{Ar}^2 & \quad \text{Ph, MePh, MeOPh, FPh, NO}_2\text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{Ar}^1 & \quad \text{Ar}^2 \\
\text{Ar}^2 & \quad \text{Ar}^1 \\
\text{Ar}^1 & \quad \text{Ar}^2
\end{align*}
\]

Scheme 16

Depending on the substitution pattern of the aryl groups in diene and dienophile, the primarily formed cycloadduct stabilizes predominantly either affording a 4-pyrone derivative or an open-chain 1,3,5-triketone.19
In a similar way neat methoxycarbonyl-pivaloylketene, generated \textit{in situ} by thermolysis of the corresponding furan-2,3-dione, serves as electron deficient oxa-1,3-diene adding different kinds of dienophiles, \textit{e.g.} carbodiimides, Schiff bases, alkenes (Scheme 17).\textsuperscript{40}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme17}
\end{center}

Scheme 17

Surprisingly, in case of the reaction of methoxycarbonyl-pivaloylketene with diphenylketen-$N$-arylimine, instead of the pivaloyl-carbonyl the less active ester carbonyl group is involved in the cycloaddition process (Scheme 18).\textsuperscript{8} The reason for that unexpected behaviour can be seen in the strong steric hinderance of the bulky $t$-butyl group in the s-$Z$ conformation required and the diphenylmethylene unit of the keteneimine during the approach of the reactants forming the transition state. But, if the ester C=O participates in the oxadiene system the steric interaction is minimized.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme18}
\end{center}

Scheme 18

Quite different results are obtained applying remarkably stable dimeric $\alpha$-oxoketenes described in Schemes 12 and 14, respectively, in cycloaddition reactions. Both molecules are rather reluctant to undergo reactions with different types of dienophiles. In case of dialkylcarbodiimides only reaction products were isolated in low to moderate yields, but, as evidenced by X-ray structure analyses, instead of $[4+2]$ adducts obviously $[2+2]$ cycloaddition reactions across the ketene moiety leading to spiro-$\beta$-lactams must have occurred (Scheme 19).\textsuperscript{17b,23} This behaviour is well known from simple ketenes,\textsuperscript{15b,16} but has never been observed with $\alpha$-oxoketenes so far. With aid of \textit{ab initio} as well as semiempirical (AM1, PM3) calculations on $\alpha$-oxoketenes in general it came clear, that sterically crowded derivatives, as the two dimeric oxoketenes presented in Schemes 12, 14 and 19, are found to exist solely as $s$-$E$ conformers. The rotational barrier to adopt the $s$-$Z$ conformation essential for generating $[4+2]$ adducts would be approximately 15 Kcal/mol.\textsuperscript{25}
3.3.4. Reactions with nucleophiles

One of the most common reactions of α-oxoketenes - as with ketenes in general - is the addition of nucleophiles which leads to β-ketoacid derivatives following a reaction pathway outlined in Scheme 20. Preparative,21 structural and stereochemical,27,28 mechanistic27,29 and theoretical30 aspects have been thoroughly investigated.15,26

![Scheme 19](image)

Some more recent examples are presented in Schemes 21 and 22: dipivaloylketene adds C-nucleophiles with subsequent ring closure to pyrono-compounds,31 while functionalised NH₂-nucleophiles afford dipivaloyl acetic acid amide derivatives, which in some case may be cyclized to pyrimidines.32

In a similar way, methoxycarbonyl-pivaloylketene adds primary amines to afford pivaloyl-malonlic ester amide derivatives (Scheme 23),8 which by no means could be cyclized as successfully done with dipivaloyl acetic acid derivatives (Schemes 21 and 22). Furthermore, it is interesting to note, that all primary adducts depicted in Schemes 21–23 unequivocally prefer the non-enolized tautomeric conformation in solution, evidenced by the presence of the corresponding C-H signals in ¹H as well ¹³C nmr spectra, although the enolic species should considerably be stabilized by hydrogen bridges. These rather surprising experimental findings were supported by semiempirical calculations on the keto-enol tautomerism of diacylacetic acid derivatives in general.33

More exciting results were obtained from reactions of neat dimeric α-oxoketenes and e.g. electron rich aromatic primary amines.34,35 The dioxinonyl-oxoketene ring is transformed into a mono-functionalized bridged bisdioxide derivative, exhibiting axial chirality. This rather rare heterocyclic system is further converted into the 2,4,6,8-tetraoxadamantane skeleton by simple acidic hydrolysis (Scheme 24).36
Scheme 21

Scheme 22

Scheme 23
This reaction sequence could be extended to oximes and mono-substituted hydrazines\textsuperscript{37} and furthermore, from reaction with OH-nucleophiles bis acid-functionalized bisdioxine molecules are obtained (Scheme 25).\textsuperscript{35}

Due to their specific geometry the bifunctionalized derivatives, in particular the bisacid chloride, are suitable to serve as novel chiral spacer units in macrocyclic systems of different sizes, which are currently tested as new host-systems in several host-guest interactions (Scheme 26).\textsuperscript{38,39}
4. Cycloaddition Reactions

Due to their different chemical behaviour in cycloaddition reactions in general, the furan-2,3-diones have to be divided into two groups: a) furan-2,3-diones without any functionality at C-4 (4.1.); b) 4-acylfuran-2,3-diones (4.2.).

4.1. 5-Aryl-furan-2,3-diones

5-Aryl-furan-2,3-diones have been reported to undergo Wittig reactions\(^1\) with acylmethylene-triphenylphosphoranes affording regioselectively 2-acylmethylene-5-aryl-3(2H)-furanones in good yields (40–90%).\(^2\) These reactions in general might be regarded as 2+2 cycloaddition processes\(^3\) to give oxaphosphetanes as intermediates,\(^4\) followed by the corresponding 2+2 cycloreversions (Scheme 27).

\[
\text{Ar} = \text{CO}_2
\]

\[
(\text{Ph})_3\text{P}\text{Me}
\]

\[
\text{Wittig reaction}\]

\[
40-90\%
\]

\[
\text{CO}_2\text{Me}
\]

\[
(\text{Ph})_3\text{P} = \text{O}
\]

\[
\text{Scheme 27}
\]

On the other hand, when 5-aryl-furan-2,3-diones were treated with diphenylketene, generated \textit{in situ} by thermolysis of benzoyl-phenyldiazomethane, 2+2 cycloaddition of the ketene with subsequent
cycloreversion occurred across the carbonyl at C-3, thus ending up with 2(3H)furanone derivatives (Scheme 28). A quite similar behaviour was also observed reacting 4-acylfuran-2,3-diones with diphenylketene (see also 4.2). The [2+2] photocycloaddition reaction of 5-arylfuran-2,3-diones to trimethylsilyloxyethylenes proceeds with excellent stereoselectivity to form cis-fused cyclobutano-4,5-dihydrofuran-2,3-diones in moderate to high yields (Scheme 29).

\[
\begin{align*}
\text{Ar} & \quad \text{CH}_2 \\
\text{OTMS, hv (> 300nm)} & \rightarrow \\
\text{DME, 0 °C, 40-99%} & \rightarrow \\
\text{TMSO} & \text{Ar}
\end{align*}
\]

Scheme 29

4.2. 4-Acyl-furan-2,3-diones
4.2.1. Thermal cycloaddition reactions

The oxa-1,3-diene moiety in those furan-2,3-diones, formed from the carbonyl group at C-4 and the endocyclic C=C-bond, is capable to add several dienophiles via 4+2 (or 4+1, with isocyanides) cycloaddition processes, in most cases accompanied by surprising novel molecular rearrangements (Scheme 30).

\[
\begin{align*}
\text{X=Ph, Y=Z} & \quad \text{Ph} \\
\text{Ph} & \quad \text{1/2} \\
\text{1/2} & \rightarrow \\
\text{Ph} & \quad \text{1/2}
\end{align*}
\]

Scheme 30

The basic experimental findings with 4-benzoyl-5-phenylfuran-2,3-dione as suitable educt, outlined in Scheme 30, describing reactions of isocyanates, carbodiimides, ketenes, ketenimines, isocyanides and imines, as well as the mechanistic investigation of the molecular rearrangements with aid of O-labelling, have already been reported in a previous review. A closer look to the outcome of the reaction of 4-benzoyl-5-phenylfuran-2,3-dione with carbodiimides made obvious, that, depending on the specific substitution pattern of the carbodiimide, different heterocyclic systems were obtained (Scheme 31). With aid of O-labeling studies, by comparison of the distribution of the label within starting materials and various products applying O-NMR spectroscopy, again an unusual furandione-furandione rearrangement was disclosed (Scheme 30). This
rearrangement can be regarded as a peculiar variation of the well known nucleophilic substitution at a vinylic carbon.\textsuperscript{55}

\[ \text{Scheme 31} \]

On the first view, the experimental results of reactions of 4-benzoyl-5-phenylfuran-2,3-dione with S-heterocumulenes (N-sulfnylamines, sulfur diimides) looked rather simple since either the corresponding pyrrol-2,3-diones or iminobenzyl-furan-2,3-diones were obtained (Scheme 32).\textsuperscript{56}

But, based upon \textsuperscript{17}O-labeling experiments, again evidence was found for all reactions to proceed via several molecular rearrangements of the furandione-furandione type accompanied also by long-range Dimroth rearrangements.\textsuperscript{56,57}

\[ \text{Scheme 32} \]
In addition, in order to get some more insight into these rather complex reaction sequences several semiempirical as well as density functional calculations were performed. In particular, this was successfully done with the reaction of 4-benzoyl-5-phenylfuran-2,3-dione and ketenimines, where, depending on the substituents of the ketenimine, either furo[3,2-e]1,3-oxazines or furo[3,2-c]pyridines were obtained (Scheme 33). 59, 60

The overall outcome of these calculations was in nice accordance with all sometimes divergent experimental findings and brought about a final confirmation for these novel rearrangements. 58, 59, 60

Exchange of the aroyl- against an ester group at C-4 of the furandione obviously changes the chemical reactivity significantly. The ester carbonyl is not sufficiently active to serve as part of the heterodiene unit essential for hetero Diels-Alder reactions. Alternatively, the heterocumulene is inserted into the furandione ring forming a seven-membered ring system, which is stable in case of the carbodiimide, while decarboxylates in case of the isocyanate (Scheme 34). 61
It was further reported that nitrons undergo a 1,3-dipolar cycloaddition regioselectively across the C=C bond of the furandione (Scheme 34).

### 4.2.2. Photocycloaddition reactions

Photocyclization of 4-benzoyl-5-phenylfuran-2,3-dione with electron rich alkenes and phenylethyne afford regio- and stereoselectively the corresponding [2+2] adducts in low to moderate yields. On heating the phenylethyne adduct after decarbonylation may form a cyclobuta[b]oxetanone intermediate which undergoes electrocyclic ring opening to afford a α-pyrono derivative (Scheme 35).

![Scheme 35](image)

### 5. Reactions with nucleophiles

#### 5.1. 5-Aryl-furan-2,3-diones

Due to their specific structural feature the 5-aryl-furan-2,3-diones offer several positions to be attacked by nucleophiles: a lactone moiety at C-2, a carbonyl group at C-3 and an endocyclic enol ester carbon at C-5. However, all experimental results reported indicate an attack of the corresponding nucleophile at the lactone carbonyl with subsequent ring opening (see the following paragraphs).

#### 5.1.1. NH-Nucleophiles

Primary amines bearing a great variety of substituents (e.g. R=H, alkyl, aryl, hetaryl) and 5-arylfuran-2,3-diones react in a general mode with ring opening to afford open-chain multi-carbonyl compounds (Scheme 36).

![Scheme 36](image)

In addition, the so formed 1,3-dicarbonyl units in many cases were then cyclized to 1,2-diazoles by reaction with hydrazine hydrate and/or, depending on the specific functionalization of the amine originally...
applied, further heterocyclization was achieved.\textsuperscript{66,67} Some selected examples are presented in Schemes 37 and 38.

\begin{equation}
\text{Ar}-\text{CO}-\text{NH}-\text{R} \xrightarrow{\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}} \text{65-90\%} \quad \text{Ar}-\text{CO}-\text{NH}-\text{R}
\end{equation}

\( R = -\text{CH}_2\text{-CH}_2\text{-NH-Ac} \)

\( -\text{N}=\text{Ar} \)

\( -\text{NH-C-aryl (hetaryl)} \)

**Scheme 37**

\begin{equation}
\text{Ar}-\text{CO} \xrightarrow{\text{rt}, 60-80\%} \text{Ar}-\text{CO}-\text{N} \equiv \text{S}
\end{equation}

\( X = \text{Cl, Br} \)

**Scheme 38**

\begin{equation}
\text{Ar-NH}_2 \quad 88-100\% \quad \text{70-94\%} \quad \text{R-NH}_2 \quad 90-96\% \quad \text{R-NH-NH}_2
\end{equation}

**Scheme 39**
4,5-Diphenylfuran-2,3-dione and arylamines gave the aroylpyruvic acid amides as expected, with alkylamines, obviously due to their stronger basicity, recyclization to pyrrole derivatives occurs. A similar behaviour is also observed applying alkylhydrazines which afford 1,2-diazinones (Scheme 39).
When bis-amines\textsuperscript{69} or hydroxy-amines\textsuperscript{70} were applied, the primary ring-opened product immediately underwent cyclocondensation to the corresponding heterocyclic system as the final reaction product (Schemes 40 and 41).

5.1.2. OH–Nucleophiles

Several oximes and bis-oximes have been reacted at 25–60 °C with 5-arylfurandiones providing O-arylpyruvoyloximes in nearly quantitative yields. In boiling toluene (110 °C) O-arylacetyloximes were formed due to decarbonylation reactions (Scheme 42). Most of these compounds exhibit marked bacteriostatic and anti-inflammatory effects.\textsuperscript{71}

\[
\begin{align*}
\text{Ar} & \overset{\Delta T}{\longrightarrow} \text{Ar} \quad \text{Ar} \quad \text{Ar} \\
& \overset{\Delta T}{\longrightarrow} \text{Ar} \\
& \overset{\Delta T}{\longrightarrow} \text{Ar}
\end{align*}
\]

\textbf{Scheme 42}

In a similar way, with bis-oximes the corresponding bis\((O,O’\)-arylpyruvoyl\()-) and bis\((O,O’\)-arylacetyl\)-1,2-dioximes were obtained in high yields. These compounds possess moderate to high analgesic activities.\textsuperscript{72}

5.1.3. C-Nucleophiles

CH-acidic compounds are also capable to add to the lactone carbonyl in furan-2,3-diones either with, in order to generate a carbanion intermediate,\textsuperscript{73} or without\textsuperscript{74} basic catalysis, thus affording 2-hydroxy-furan-2-ones or open-chain tetracarbonyl compounds, occasionally in oxo-cyclo tautomerism with their cyclized forms (Schemes 43 and 44).\textsuperscript{75}

The course in the reaction of furan-2,3-diones with diazoalkanes is shown to strongly depend on the nature of the diazo compound employed. Whilst with diazomethane a 2-spirocyclopropane-3-oxofuran is obtained, the reaction with diphenyldiazomethane takes place at C-3 to afford a 3-oxiranyl-furan-2-one.

The diazoethane also attacks C-2 but obviously induces a ring enlargement reaction inserting the CH thus forming a 4-pyran-4-one system (Scheme 45).\textsuperscript{76}
Scheme 43

Scheme 44

Scheme 45
5.2. 5-Acyl-furan-2,3-diones

5.2.1. NH$_2$-Nucleophiles

In continuation of previous investigations on reactions of 4-benzoyl-5-phenyl-furan-2,3-dione with hydrazines$^{77}$ which afforded the corresponding pyrazole-3-carboxylic acid, a further cyclization to a pyrazolo[3,4-d]pyridazine system was achieved by cyclocondensation with phenylhydrazine or hydrazine, respectively (Scheme 46)$^{78}$.

![Scheme 46](image)

Several deeply coloured compounds representing poly-fused tetraaza heterocyclic skeletons as chromophores were obtained from cyclocondensation reactions of 4-benzoyl-5-phenyl-furan-2,3-dione with 1,2-diaminoquinolinium, or 1,2-diaminoisquinolinium perchlorates and subsequent treatment of the so formed furo[2,3-e]quinolino(isoquinolino)[1,2-b]-as-triazinium perchlorate with ammonia or hydrazines (e.g. Scheme 47)$^{79}$.

![Scheme 47](image)

5.2.2. Miscellaneous

A novel isoindigoide dye$^{80}$ has been prepared from reaction of 4-benzoyl-5-phenyl-furan-2,3-dione with Lawesson reagent$^{81}$ via sulfurization of the carbonyl at C-3, dimerization across the C=S bond and
extrusion of sulfur (Scheme 48). This dye can thermally be isomerised into a pyrano[4,3-c]pyrane, accompanied by a significant hypsochromic shift.

![Scheme 48](image)

Deeply violet crystals, obtained from reaction of 4-benzoyl-5-phenylfuran-2,3-dione with methylenetriphenylphosphorane according to a known procedure, were disclosed as a resonance stabilized cyclic acyldienetriphenylphosphorane as the result of a transylidation process (Scheme 49). In a similar reaction, 5-aryl-furan-2,3-dione and triphenylphosphoranylidenepyruvate afforded a deeply coloured cyclic oxalyl ylide.

![Scheme 49](image)

References


METAL-CATALYZED CYCLOCARBOXYLATION REACTIONS
FOR THE SYNTHESIS OF LACTONES AND LACTAMS

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Abstract. The preparation of a variety of heterocyclic compounds such as lactones, lactams, pyrrolidinones, and others can be achieved by cyclocarbonylation reactions catalysed by various metal complexes. Palladium salts with the combination of phosphine ligands have resulted effective catalyst systems for the cyclization reactions. New synthetic strategies and novel approaches devoted to the preparation of such compounds having different ring size still remain a stimulating area of academic and industrial research.

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References
1. Introduction

This review is mainly focused on the catalytic preparation of different heterocyclic compounds in particular lactones and lactams having 4, 5, 6 or 7-membered (indicated also as β, γ, δ, ε lactones and lactams) (Figure 1), and in larger rings by pursuing innovative routes that consist mainly in the incorporation of carbonyl moiety (C=O) into an organic molecule and subsequent formation of carbonyl compounds.\(^1\)

The studies of Falbe and Korte, pioneers of the carbonylation chemistry, have opened the way to this metal catalyzed chemistry for the preparation of a variety of cyclic compounds (lactams, succinimide derivatives, etc.).\(^2\) Today, there are different new methods available for cyclocarbonylation reactions.

The methods reported in the literature are mainly identified with different names and among the most important cited are carbonylative ring formation (that is carbon monoxide insertion reactions into suitable functional groups) and ring expansion reactions (that is insertion of carbon monoxide into a previously formed heterocycles).

These processes have been usually accomplished by metal catalysed carbonylation and palladium based catalysts were among the most efficient for the preparation of a variety of mono-, bis-lactones and lactams.

![Figure 1](image_url)

This review is mainly focused to describe recent results on the preparation of those heterocycles containing both saturated and unsaturated five, and larger rings through metal catalysed cyclocarbonylation reactions. It is important to note that there is a great interest to develop new selective processes for the synthesis of these compounds because of their use in building up biologically active compounds\(^3\) with pharmacologically activity (fungicidal, antitumoral and anti-inflammatory)\(^4\) and undergo easily ring opening for the synthesis of polyesters.\(^5\)

2. Cyclocarbonylation reactions

2.1. General features on cyclocarbonylation reactions

Different synthetic approaches for the construction of targeted heterocyclic compounds have been reported. Also, various mechanisms have been proposed based on the reactivity of different functional groups present in the substrate (double bond, triple bond, amine group etc.). For example, the accepted mechanism of the carbonylation reaction of alkenes or alkynes catalysed by transition-metal complex is shown in the Scheme 1.

Double or triple bond of unsaturated substrates, bearing an adjacent functional group X (such as hydroxyl, amino, formyl, and ester), could be initially coordinates to the metal to give the intermediate A. Then, there is an intramolecular interactions of the metal with the functional groups X and formation of metallocycle intermediate B. Successive step is the coordination of carbon monoxide leading to the
formation of the intermediate C. Elimination of the metal followed by ring closure affords cyclic carbonyl compounds D.

Scheme 1

In the case of halo-alcohol or halo-amine compounds, a different pathway is proposed (Scheme 2).

Scheme 2

The insertion of the metal M into the C-Hal bond (oxidative addition) would give the intermediate A which contains the functional group X such as -OH or -NH₂ adjacent to the C-halide bond. The successive coordination and insertion of carbon monoxide forms the intermediate B. The subsequent elimination of the metal produces the carbonyl compound D.

Scheme 3
A different mechanism is proposed for the ring expansion. This can be explained through insertion of CO in the ring (Scheme 3) in which the driving force of the process is the strain small cycle (oxirane, aziridine, etc.) which usually favours the formation of a larger cycle.

Recent papers reported another possible alternative mechanism (Scheme 4) in which a bi-metal catalyst is the intermediate key of the process.

![Scheme 4]

Although these mechanisms are not exhaustive because they depend on the metals and ligands involved, however, they resume possible pathways through which it is possible to describe the formation of the cyclic compounds.

2.2. Synthesis of lactones

2.2.1. Synthesis of four-membered lactones (β-lactones)

β-Lactones represent an important class of naturally occurring compounds. Cyclocarbonylation reaction catalysed by transition metal is a useful methodology for their synthesis. However, only a limited number of papers have been reported in the literature for their synthesis. β-Lactones were usually obtained by cyclisation of β-halo derivatives or β-hydroxy acid derivatives or by addition of ketene to carbonyl compounds.

Palladium-catalysed reactions provided an important route for clean preparation of such compounds. For example, the oxidative carbonylation of alkenes 1, 3 in the presence of water (Schemes 5 and 6) is a direct way for the preparation of β-lactones 2, 4.6

![Scheme 5]

![Scheme 6]
The carbonylation of the saturated and unsaturated the halogen-alcohols 5 and 7 has been also used to synthesize the four membered ring compounds 6 and 8 (Schemes 7 and 8).\(^7\)

\[
\text{Ph} \quad \text{Br} \quad \text{OH} \quad + \quad \text{CO} \quad \xrightarrow{\text{Pd}(\text{PPh}_3)_2\text{Cl}_2} \quad \text{Ph} \quad \text{O} \\
\text{5} \quad \text{6 (63%)}
\]

**Scheme 7**

\[
\text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{OH} \quad + \quad \text{CO} \quad \xrightarrow{\text{Pd}(\text{PPh}_3)_2\text{Cl}_2} \quad \text{CO} \\
\text{7} \quad \text{8 (52%)}
\]

**Scheme 8**

Recently, Qing and co-workers have reported a successful synthesis of 3-(2,2,2-trifluoroethylidene)-2-oxetanones (β-lactones) in the presence of palladium (0) complex as a catalyst (Scheme 9).\(^8\)

\[
\text{R}^1, \text{R}^2= \text{alkyl (4 examples)} \quad \xrightarrow{\text{CO, Pd}(\text{PPh}_3)_4, \text{Ag}_2\text{CO}_3 / \text{Et}_3\text{N}} \quad \text{F}_3\text{C} \quad \text{I} \quad \text{R}^1 \quad \text{R}^2 \quad \text{O} \\
\text{Scheme 9}
\]

On the contrary, the cyclocarbonylation reaction of Z-3-iodo-3-trifluoromethyl allylic alcohols, in the presence of a catalytic amount of Pd(Ph$_3$)$_4$ produced five member ring lactones such as 3-trifluoromethyl-2-(5$H$)-furanones (Scheme 10).\(^9\)

\[
\text{R}^1, \text{R}^2= \text{alkyl or aryl (5 examples)} \quad \xrightarrow{\text{CO, Pd}(\text{PPh}_3)_4, \text{Ag}_2\text{CO}_3 / \text{Et}_3\text{N}} \quad \text{F}_3\text{C} \quad \text{I} \quad \text{R}^1 \quad \text{R}^2 \quad \text{O} \\
\text{Scheme 10}
\]

Some of these products were also obtained by cyclocarbonylation reaction of trifluoromethyl propargylic alcohols in the presence of a catalytic amount of Pd(OAc)$_2$ and PPh$_3$.\(^{10}\)

Recently, Matsuda and co-workers have reported a new method for the preparation of novel four membered ring compounds by cyclocarbonylation reaction of alkynes bearing a trialkyl silyl group, catalysed by rhodium complexes. (Scheme 11).\(^{11}\)

These examples represent a particular cases of rhodium-catalysed reactions in which the alkynes, bearing a trialkyl silyl group on the $sp$-carbon, smoothly incorporate carbon monoxide to form the four
membered ring lactone. The propensity to form $\beta$-lactone depends on both steric and electronic factors. The authors have reported that a better selectivity for $\beta$-lactone was obtained in the case of bulkier silyl group, such as Bu'Me$_2$Si and by using a stronger base such as DBU (DBU=1,8-diazabicyclo[5.4.0]undec-7-ene). The method was also valid for the preparation of spiro type $\beta$-lactones.

![Scheme 11](image)

Matsuda and co-workers reported successively, one-pot synthesis of silyl-3-2-(5H)-furanones by reacting 1-substituted-3-silylpropyn-1-ols CO and H$_2$ in the presence of a catalytic amount of Rh$_4$(CO)$_{12}$ (Scheme 12). Hydroformylation compounds were also obtained as by-product.

![Scheme 12](image)

The authors have also reported that lower selectivity was obtained in the case of other molecules where a mixture of five, six and seven membered ring heterocycles was produced (Scheme 13).

![Scheme 13](image)

(Z)-$\alpha$-(Alkoxycarbonyl)methylene-$\beta$- and $\gamma$-lactones were also obtained in good yields by PdI$_2$/KI catalysed carbonylation reactions of propynyl alcohols and but-3yn-1ols respectively (Schemes 14 and 15).
The insertion of carbon monoxide in an epoxide and aziridine rings represents an alternative way to β-lactones and lactams,\textsuperscript{14,15,16} precursors for the synthesis of polymers\textsuperscript{17} and polypeptides.\textsuperscript{18} However, various transition metal complexes have been used to catalyze the CO insertion in these small rings,\textsuperscript{19,20} and very few catalysts were able to promote such transformation selectively and with high yields.\textsuperscript{21}

Dicobalt octacarbonyl in the presence of hydroxy-substituted pyridines has been used for the carbonylation reactions of a variety of epoxides (such as ethylene and propylene oxide). A mixture of lactones and polyester oligomers were obtained and their ratio was dependent on reaction condition.\textsuperscript{20d,21a,22} Yield and selectivity in such reactions were typically low.\textsuperscript{23}
Recently Coates and co-workers have reported a novel catalytic synthesis of β-lactones (Scheme 16) catalyzed by the complex [(salph)Al(THF)₂][Co(CO)₄] 15 (Figure 2).²⁴

Catalyst 15 was able to carbonylate selectively a variety of epoxides; such as propylene oxide and epichlorhydrin and the conversion was 95% and 73% respectively. In the case of carbonylation of isobutylene oxide the corresponding lactone was obtained, as a mixture of the two possible regioisomers, with conversion of about 90% after 1h.

The authors elucidated the mechanisms of the formation of the lactones according to two different hypothesised pathways: the first one is related to a nucleophilic attack by the anionic Co(CO)₄⁻ to the epoxide related to give the substituted lactone; the second is an electrophilic attack to the epoxide ring by Lewis-acidic complex [(salph)Al]⁺ successively trapped by Co(CO)₄⁻ leading to the corresponding lactone. Relatively high yields and good selectivity were also obtained using [Cp₂Ti(thf)₂][Co(CO)₄] as catalyst.²¹b

2.2.2. Synthesis of five-membered lactones

2.2.2.1. Synthesis of five-membered unsaturated lactones (furanones)

Furanones are unsaturated lactones and represent an important class of heterocyclic compounds due to their biological activity (Figure 3).

![Furanones](image)

The synthesis of these compounds was achieved catalytically and more easily than β-lactones. Mixture of furanones 2-, 2(3H)-, and 2(5H)-furanones, for example, were catalytically obtained in 61-93% yields by reacting α-keto alkynes with CO and H₂ in the presence of a catalytic amount of the zwitterionic rhodium complex (η⁶-C₆H₅BPh₃)Rh⁺(1,5-COD) 16, (Figure 4) and triphenyl phosphite as a ligand (Scheme 17).²⁵

![Rh complex](image)

The complex 16 was reported to be a very active catalyst for the cyclohydrocarbonylation reaction of a variety of substrates containing different alkyl, aryl, vinyl, and alkoxy groups attached to the acetylenic moiety. The steric and electronic properties present in the molecules influence the chemo- and regioselectivity of the reaction. For example, when the substituent R₂ is an alkyl chain, 2(3H)-furanones were selectively obtained in high yields; and when R₂ is an aromatic group, 2(5H)-furanones were instead
formed. 3(2H)-Furanones were obtained by reacting alkynols, carbon monoxide and halogens in the presence of transition metals complexes.\textsuperscript{25}

\[
\begin{align*}
\text{[Rh\textsuperscript{+}], (PhO)\textsubscript{3}P} & \quad \text{CO/H\textsubscript{2}} \quad 20-40 \text{ atm.} \\
\text{CH\textsubscript{2}Cl\textsubscript{2},} & \quad \Delta, 24-48 \text{ h} \\
\end{align*}
\]

23 examples

\[
\begin{align*}
\text{Scheme 17}
\end{align*}
\]

The synthesis of 3(2H)-furanones was explained by the authors considering a possible mechanism in which there is catalytic intermolecular cyclocarbonylation of iodoarenes with alkynes or alkynols, or considering that there is intramolecular cyclocarbonylation of alkynols.

Palladium bis(dibenzylideneacetone) [Pd(dba)\textsubscript{2}] in the presence of 1,4-bis(diphenylphosphino)butane (dppb) in 1,2-dimethoxyethane (DME) was able to promote intramolecular carbonylative cyclisation of alkynols affording to the corresponding 2(5H)-furanones (Scheme 18).\textsuperscript{26}

\[
\begin{align*}
\text{Pd(dba)\textsubscript{2}, dppb} & \quad \text{CO} \\
\text{DME, 20 atm.} & \quad 150 \text{ °C, 48 h} \\
\text{8 examples} & \quad 62-80\%
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 18}
\end{align*}
\]

The ruthenium complex Ru\textsubscript{3}(CO)\textsubscript{12} in the presence of Et\textsubscript{3}N was also an effective catalyst for the cyclocarbonylation of different allenyl alcohols producing a mixture of γ- and δ-lactones.

Similarly, the cyclocarbonylation of 3,4-pentadien-1-ol and 2-methyl-4,5-hexadien-2-ol, in the presence of Ru\textsubscript{3}(CO)\textsubscript{12}/Et\textsubscript{3}N as a catalytic system, produced δ-lactones, 5,6-dihydro-3-methyl-2H-pyran-2-one, and 5,6-dihydro-6,6-dimethyl-3-methyl-2H-pyran-2-one, respectively, in quantitative yield (Scheme 19).\textsuperscript{27}

\[
\begin{align*}
\text{Scheme 19}
\end{align*}
\]

It was observed that the presence of a heteroatom in the molecule may influence the rate and the chemoselectivity of the reaction.
Gabriele and co-workers reported the synthesis of 3-alkyl or 3-aryl substituted 2(5H)-furanones by reductive carbonylation of alk-1-ynes in the presence of KI and water and catalytic amounts of palladium iodide.28

2.2.2. Synthesis of five- and six-membered saturated lactones

The preparation of five-membered ring saturated lactones have been achieved by homogeneous catalyst via the direct insertion of carbon monoxide into four-membered cyclic or, in phase transfer catalysis, by lactonisation of various allylic alcohols.

For example, primary allylic alcohols with CO in the presence of the catalytic system PdCl₂-CuCl₂, hydrochloric acid and oxygen, gave the corresponding five membered lactones in good yields.29 Differently substituted five-membered ring saturated lactones were also obtained reacting secondary and tertiary allylic alcohols with CO/H₂ mixture in the presence of palladium based catalysts (Scheme 20).26

![Scheme 20](image)

Palladium complexes were also used as catalysts for the cyclocarbonylation of 3-butyne-1-ol 17 to give α-methylene lactone 18 in good yield (Scheme 21).30

![Scheme 21](image)

Inoue and co-workers reported the cyclocarbonylation of 3-butyne-1-ols catalysed by cationic palladium-phosphine complexes affording selectively six- or five-membered ring lactones (Scheme 22).31

![Scheme 22](image)

Other additional methods for the preparation of five membered γ-lactones have been reported.
Differently, very few examples on the carbonylative route to six-membered δ-lactone rings are reported.

For example, 5-hydroxy-1-pentyne 19 in the presence of 1 equivalent of benzenethiol and 1 mol % of platinum (0) catalyst was carbonylated to α-[(phenylthio)methyl]-δ-lactone 20 with high selectively and good yield. The same reaction was performed with 0.1 equiv. of benzenethiol, led to α-methylene γ-lactone 21 as a major product (Scheme 23).32

\[
\begin{align*}
\text{HO} & \equiv + \text{PhSH} \quad \text{1 equiv.} \quad \text{MeCN, 120 °C, 4 h} & \text{CO (30 atm)} & \begin{array}{c}
\text{O} \\
\text{SPh}
\end{array} + \begin{array}{c}
\text{O} \\
\text{Ph}
\end{array} \quad \text{20 (73 %)} + \text{21 (0 %)}
\end{align*}
\]

Scheme 23

2.2.3. Synthesis of five-, six- and seven-membered fused to aromatic rings lactones and bis-lactones

Another important class of lactones is the five-, six-, and seven-membered fused to aromatic ring lactones.

As a general method, palladium-catalysts promoted carbonylation reactions of a variety of substrates for the preparation of fused aromatic ring lactones. For an example, the benzylic alcohol 22 bearing an halogeno (or halogenomethyl) substituent in orto-position was cyclocarbonylated easily to five-membered ring lactone 23 using a catalytic amount of Pd(PPh₃)₂Cl₂ and tertiary amine (Scheme 24).7

\[
\begin{align*}
\text{I} & \equiv \text{OH} \quad \text{DMF, 60 °C, 72h} & \begin{array}{c}
\text{O} \\
\text{Ph}
\end{array} \\
\text{22} & \quad \text{CO (1-4 atm)} & \begin{array}{c}
\text{O} \\
\text{PdL₃}
\end{array} + \begin{array}{c}
\text{O} \\
\text{Cl}
\end{array} \quad \text{23 (100%)}
\end{align*}
\]

Scheme 24

Cyclocarbonylation of o-allylbenzyl chloride 24 in the presence of a palladium catalyst and triethylamine provided an efficient route to benzoannulated enol lactone 27 in high yield (Scheme 25).
Product 27 is considered a useful intermediate for the synthesis of antiulcer agent U-68,215. The authors reported 25 and 26 as intermediates in the reaction.

Cyclocarbonylation of the trifluoro-methanesulfonic acid 5-methoxy-2-propionyl-phenyl ester 28 in the presence of Pd(OAc)$_2$, dppp [1,3-bis(diphenylphosphino)propane] and triethylamine afforded five-membered ring lactone 29 in good yield (Scheme 26).

\[
\text{CH}_3\text{O} \begin{array}{c} \text{OTf} \\ \text{Pd(OAc)}_2 \text{- dppp} \end{array} \xrightarrow{\text{Et}_3\text{N, DMF, 60 °C}} \text{CH}_3\text{O} \xrightarrow{\text{CO (1atm)}} \text{29 (85%)}
\]

Scheme 26

\[
\text{CO (40 atm)} \xrightarrow{\text{5%Cl}_2\text{Pd(PPh}_{3}\text{) \text{- Et}_3\text{N (2 equiv)}}} \xrightarrow{\text{MeCN, benzene 100 °C, 20h}} \xrightarrow{\text{31 (90 % Z/E=92/8)}} \text{32 (3 %)}
\]

Scheme 27

\[
\text{CO (40 atm)} \xrightarrow{\text{5%Cl}_2\text{Pd(PPh}_{3}\text{) \text{- Et}_3\text{N (2 equiv)}}} \xrightarrow{\text{benzene 100 °C, 20h}} \xrightarrow{\text{33}} \text{34 (36% trans/cis=82/18)} \xrightarrow{\text{35 (31%)}}
\]

Scheme 28

\[
\text{CO (1atm), Pd(PPh}_{3}\text{)_{14} \text{- TIOAc, CH}_{3}\text{CN, 80 °C}} \xrightarrow{\text{37}} \text{38 (65%)} \xrightarrow{\text{36 \text{- 22 \text{- CO (1atm), Pd(PPh}_{3}\text{)_{14} \text{- TIOAc, CH}_{3}\text{CN, 80 °C}}}}} \text{39 (65%)}
\]

Scheme 29

Palladium-catalyzed carbonylation reaction of 30 produced 31 in 90 % yields (Z/E isomers were in the ratio 92:8) and trace amount of 32 (Scheme 27). Carbonylation of 33 in benzene produced also a mixture of lactones 34 (trans/cis = 82/18) and 35 in 36 and 31 % yields respectively (Scheme 28).
Cyclocarbonylation of norbornene 36 in the presence of palladium catalysts and aryl iodide compounds, such as 37 or 22, produced six- and seven-membered ring lactones 38 and 39 (Scheme 29). With few exceptions, these palladium catalyzed carbonylation reaction exhibits preference for five- or six-membered rings.

Recently, the cyclocarbonylation of 2-allyl phenol derivatives, using Pd(OAc)$_2$ and dppb system affording a mixture of five-, six- and seven-membered rings lactones has been reported (Scheme 30).

It was observed that, when the reaction was carried out using toluene as a solvent and CO/H$_2$ in the molar ratio 1/1, the seven-membered ring lactone was produced as the major product; and, when the reaction was conducted in dichloromethane and using CO/H$_2$ in the molar ratio 1/5, the five-membered ring lactone was the major product.

The homogeneous catalytic system Pd(OAc)$_2$ - dppb was demonstrated to be active catalyst also for double cyclocarbonylation reactions of bis-allyl phenols to the corresponding bis-lactones.

For example, 3,6-bis allyl catechol 40 reacted with CO and H$_2$ in the presence of a catalytic amount of Pd(OAc)$_2$ and dppb in toluene to give selectively in one-pot synthesis, 7-membered ring bis-lactone 41 in 79% isolated yield (Scheme 31).

The synthesis of bis-lactones can be achieved in two steps reaction. For example, the mono allyl hydroquinone 42 was first cyclocarbonylated in toluene to give 43 in 92% yield. This latter, after further allylation and Claisen rearrangement, was converted into the isomers 44 and 45 which were successively cyclocarbonylated to be transformed into the corresponding bis-lactones 46 and 47 (Scheme 32).

Using different reaction conditions, it was possible to obtain bis-lactones having two different ring sizes (7-6, 7-5, 6-6). For example, 42 can be carbonylated in CH$_2$Cl$_2$ to give a mixture of 5-, 6-, 7-membered ring mono-lactones 43, 48, 49 (Scheme 33).

Compounds 43, 48, 49, after allylation and Claisen rearrangement, were successively cyclocarbonylated to bis-lactones containing 7-5, 7-6, 7-7 or 6-7, 6-6, 6-5 or 5-7, 5-6, 5-5 rings. Other bis-lactones, 50-59, were also prepared (Figure 5).
Scheme 32

Scheme 33

Figure 5

Bis-lactones synthesized by cyclocarbonylation reactions
2.3. Synthesis of lactams and pyrrolidinones

Heterocyclic compounds containing amido group in the ring are counted among many important natural products, such as vitamins, hormones, antibiotics, as well as pharmaceuticals and herbicides.

Carbon monoxide insertion and/or addition to allylic precursors may lead to the formation of both linear and cyclic carbonyl compounds. In these transformation, rhodium, platinum, palladium and nickel based catalysts have represented the most active catalysts for the synthesis of γ-butyrolactam and N-alkyl-pyrrolidinones.

2.3.1. Synthesis of four-membered lactams (β-lactams)

The preparation of four-membered ring lactams (β-lactams) was achieved by ring expansion of aziridines usually obtained by inserting catalytically carbon monoxide molecule in the aziridine ring.\(^{19b,20a-j}\)

For instance, \(N\)-alkyl phenylaziridines undergo CO insertion in the presence of \([\text{Rh(CO)}_2\text{Cl}]_2\) as a catalyst to give in quantitative yields the corresponding β-lactams with regiospecific insertion of the CO into the most substituted ring carbon-nitrogen bond.\(^{20h}\)

However, this method was limited to aziridines bearing an activating group such as a phenyl or vinyl in the 2-position of the aziridine ring.

Interestingly, in the presence of excess of \(\text{Ni(CO)}_4\) as a catalyst the CO insertion occurred into the less substituted C-N bond of the ring with the retention of configuration.\(^{19b}\)

In the case of \(N\)-alkylaziridines by using \(\text{Co}_2(\text{CO})_8\) as a catalyst very high yields were obtained.\(^ {20a}\) According to the authors, the CO insertion occurred into the less substituted carbon-nitrogen bond by a \(\text{SN}_2\) like mechanism with the inversion of configuration. It was observed that \(\text{Co}_2(\text{CO})_8\) was the active catalyst also for the preparation of various β-lactams bearing different functionalities (2-alkoxycarbonyl, silyl, 2-hydroxymethyl) and for the preparation of optically active β-lactams.\(^ {41}\)

Very few examples of synthesis of β-lactams obtained by direct cyclocarbonylation have been reported in literature. Salerno and co-workers reported one of these peculiar cases as an extension of the synthesis for the analogous β-lactones systems (Scheme 34).\(^ {42,13a,13b}\)

\[\begin{align*}
\text{H} & + 2\ \text{CO} + \text{R}^3\text{OH} + \frac{1}{2}\ \text{O}_2 & \text{PdI}_2-\text{Kl} & \text{-H}_2\text{O} \\
\text{R}^2\text{R}^1\text{NH}-\text{R} & & & 78-95\%
\end{align*}\]

\[\text{Scheme 34}\]

2.3.2. Synthesis of five-membered unsaturated and saturated lactams

2.3.2.1. Synthesis of five-membered unsaturated lactams

The cyclocarbonylation of methylacrylamide 60 catalyzed by rhodium-phosphine complex gave the unsaturated five membered ring lactam 61 in good yields (Scheme 35).

As reported by Negishi and co-workers, the method was used as a general route to prepare unsaturated 5-membered ring lactams.\(^ {43,44}\)
Recently, another group has reported the carbonylation of imines in the presence of Ru$_3$(CO)$_{12}$ elucidating the role of the ruthenium catalyst, Ru$_3$(CO)$_{12}$ (Scheme 36).\(^{44}\)

\[
\begin{align*}
\text{CH}_3\text{NH}_2 + \text{CO} / \text{H}_2 & \xrightarrow{[\text{Rh}-(\text{CO})_2\text{Cl}]_2, \text{PPh}_3} \text{CH}_3 \\
60 & \xrightarrow{\text{Toluene, NEt}_3} \xrightarrow{80 \text{ atm}, 120 \ ^\circ\text{C}} 61 (45) \\
\end{align*}
\]

Scheme 35

The catalyst induces firstly the catalytic C-C coupling of $\alpha,\beta$-unsaturated imines with CO to yield an imine-aldehyde in $\beta$ position with respect to the C-N double bond; the intramolecular cyclization reaction takes place via the nucleophilic attack of the nitrogen towards the carbonyl carbon atom forming a pyrrolidinone system. A second ruthenium complex catalysed C-C coupling reaction leads to the formal insertion of one molecule of ethylene into a C-H bond of the pyrrol-2-one in ortho position with respect to the keto group. By this selective reaction 1,3-dihydro-pyrrol-2-one derivatives can be easily prepared.

\[
\begin{align*}
\text{R}-\text{N}R^1 & \xrightarrow{\text{CO} / \text{C}_2\text{H}_4} \text{R} \xrightarrow{\text{C}_2\text{H}_4} \text{R}^1 \xrightarrow{\text{CO} / \text{C}_2\text{H}_4} \xrightarrow{\text{Ru}_3(\text{CO})_{12}} \text{Et} \\
6 \text{ examples} & \xrightarrow{\text{Ru}_3(\text{CO})_{12}} \xrightarrow{\text{Ru}_3(\text{CO})_{12}} (15-95\%) \\
\end{align*}
\]

Scheme 36

Analogously, the carbonylation of $\beta$-naphthylaldimines produced ethyl-4-propionyl-2,9b-dihydrobenzo[e]isoindol-1-one derivatives (Scheme 37).\(^{45}\)

\[
\begin{align*}
\text{R} & \xrightarrow{\text{CO} / \text{C}_2\text{H}_4} \text{Et} \\
2 \text{ examples} & \xrightarrow{\text{Rh}_3(\text{CO})_{12}} \\
\end{align*}
\]

Scheme 37

2.3.2.2. Synthesis of five-membered saturated lactams (pyrrolidinones)

$N$-Alkyl-2-pyrrolidinones, mainly obtained via the carbonylation of $N$-alkylamines, are important compounds widely used as extractants in the petrochemical industry and as monomers for the production of synthetic fibres. Cobalt complexes were the most employed catalysts for the preparation of saturated five-membered ring lactams or their homologous (Scheme 38); but, these processes required drastic reaction conditions and exhibited poor selectivity (e.g. temperature high than 280 °C) favouring also competing allylic isomerization and polymerisation.\(^{46,47}\)

Rhodium based catalysts showed much better catalytic activity. For example, in the presence of carbon monoxide and ammonia, rhodium catalysts promoted the cyclocarbonylation reaction of allylic chloride 62 affording the corresponding $\gamma$-butyrolactam 63 with good yield and high selectivity (Scheme 39).\(^{48}\)
In a similar manner, the carbonylation of allylic halides in the presence of primary alkylamines catalysed by rhodium complexes led to \( N \)-alkyl substituted-2-pyrrolidinones (Scheme 40).\(^{48}\)

These reactions were catalyzed by different rhodium complexes such as \( \text{Rh(acac)}_3 \) and \( \text{RhCl(PPh)}_3 \), producing the \( N \)-alkyl-2 pyrrolidones in high yields and good selectivity. Cobalt catalysts were totally ineffective for these transformations.

In 1997 Jegorov and co-workers have reported cyclocarbonylation reactions of a variety of substrates using different Rh-phosphine complexes and confirmed that the mixture of \( \text{CO/H}_2 \) in the molar ratio 1:1 promoted better than pure carbon monoxide under milder conditions. They observed also a minor selectivity in the case of monodentate phosphine ligands and hypothesized the formation of Rh (0) clusters in the catalytic process.\(^{49}\)

The Zwitterionic complex \( \eta^6-\text{C}_6\text{H}_6\text{BPh}_3\text{Rh(COD)}^+ \), in the presence of sodium borohydride showed to be an active catalyst for the carbonylation reactions of \( N \)-allylic arylamines (Scheme 41) but with relatively lower yield when \( R^1=\text{C}_6\text{H}_{11} \) and \( R^2=\text{H} \).

The addition of dichlorotricarbonylruthenium as a co-catalyst in the reaction increased the yields to 59%. \( \text{Ru(CO)}_3\text{Cl}_2 \), dppb in the presence of syn-gas was also active catalyst in these transformations.\(^{50}\)
Rh$_4$(CO)$_{12}$ in the presence of syn-gas (CO/H$_2$) promoted also the carbonylation of 1-phenyl allylamine 64 and 3-phenyl allylamine 66 to 5-phenyl-2-pyrrolidinone 65 and 3-phenyl-2-pyrrolidinone 67 respectively in relative good yield (Scheme 42).  

Interestingly, 2-pyrrolidinones were obtained also via Wacker–type reaction by the conversion of $N$-carbamoyl or acetyl-4-trimethylsilyl-3-alkyn-1-amines. This catalysis has been extended to the carbonylation of certain vinylic (and propargyl) congeners.

In spite of various methodologies for the synthesis of $N$-allyl or $N$-benzyl 2-pyrrolidinones, very few examples of other $N$-aryl-2-pyrrolidinones have been reported. These interesting compounds have been prepared recently by the carbonylation of 2-aminophenol 68 or 2-aminothiophenol 69 in the presence of a stoichiometric amount of allyl halides derivatives 70-72 and catalyzed by Pd(OAc)$_2$ and dppb (Scheme 43).

2.3.3. Synthesis of six-membered unsaturated lactams

Few examples on the synthesis of six-membered ring unsaturated lactams are reported in the literature. They have been usually prepared by cyclocarbonylation reactions catalyzed by metal-complexes.
The cyclocarbonylation of α-or β-allenic sulfonamides, for example, in the presence of Ru$_3$(CO)$_{12}$ and Et$_3$N under CO atmosphere in dioxane produced heterocyclic γ and δ-unsaturated lactams in good yields (Scheme 44).

\[
\text{CO (20 atm)} \quad \text{Ru$_3$(CO)$_{12}$ (1 mol %)} \quad \text{Et$_3$N (1.5 equiv), dioxane} \quad \text{54-95%}
\]

\[
\begin{aligned}
&\text{R}^1 \equiv \text{alkyl, aryl} \\
&\text{R}^2 \equiv \text{Ts, Mts, Bn}
\end{aligned}
\]

**Scheme 44**

A cycloaddition [5+1] involving the ring-opening of cyclopropane has represented a great potential way for the construction of six-membered carbonyl compounds. Wender and co-workers have reported the catalytic cycloaddition reactions which involve the opening of a cyclopropane ring. Murai and coworkers reported another example in which cyclopropyl imines behaved as an assembling unit. Some other examples include Ru$_3$(CO)$_{12}$-catalyzed carbonylative [5+1] mode of cycloaddition reactions of cyclopropyl imines leading to six-membered unsaturated lactams (Scheme 45) have been reported.

\[
\text{CO (2 atm)} \quad \text{Ru$_3$(CO)$_{12}$ (2 mol %)} \quad \text{Toluene} \quad \text{10-76%}
\]

**Scheme 45**

The reaction of the cyclopropyl imine 73 (anti/syn = 3.3/1, 1 mmol) in toluene in the presence of a catalytic amount of Ru$_3$(CO)$_{12}$ under CO atmosphere at 160 °C gave 3,4-dihydro-1-(1,1-dimethylethyl)-6-phenyl-2(1H)-pyridinone 74 in good yield. When the reaction was carried out at 140 or 180 °C, only trace amount of 74 was formed. This reaction was substituent dependent. In fact, the use of PhCH$_2$, p-MeOC$_6$H$_4$, or OMe as R substituent on the imine nitrogen gave no product of the reaction. The use of a cyclohexyl group as the N-substituent, such as in 75, gave a comparable yield (61%) of the corresponding γ-lactam 76 (Scheme 46).

\[
\begin{aligned}
&\text{CO (2 atm)} \quad \text{Ru$_3$(CO)$_{12}$ (2 mol %)} \quad \text{Toluene} \quad \text{74-76 (75-61%)}
\end{aligned}
\]

**Scheme 46**
2.3.4. Synthesis of five- and six-membered fused to aromatic rings lactams

In 1995, Takahashi and co-workers have described the rhodium-catalysed cyclocarbonylation of 2-alkylaniline 77 to five membered ring lactam; once again it was possible to control the selectivity of 78 or 79 acting on the reaction condition (Scheme 47).\(^5\)

More recently, Gabriele and co-workers reported the palladium oxidative carbonylation reactions of 2-ethynylaniline derivatives in methanol and PdI\(_2\)/KI as the catalytic system under a 4:1 CO/air mixture at 25 °C for the synthesis of (E)-3-(methoxycabonyl)methylene-1,3-dihydroindol-2-ones.\(^5\)

Controlling the reaction conditions it is possible to have good selectivity in the palladium acetate-phosphine cyclocarbonylation reaction of 2-aminostyrenes to five- and six–membered lactams (Scheme 48) and 2-allylanilines to five, six and seven membered lactams (Scheme 49).\(^3\)

2.2. The Pauson-Khand reaction

Pauson-Khand reaction is one of the most important carbon skeleton-forming reactions by transition metal where a carbonylative coupling of alkene-alkyne or alkyne-alkyne occurs.

These transformations take place in the presence of Co\(_2(CO)_8\) where alkyne and alkene functionalities present in the same molecule react with carbon monoxide in a formal [2+2+1] cycloaddition to form cyclopentenones (Scheme 50).\(^5\)
The interest for this class of reactions is due to the capability of transition metals to assemble simple molecules and carbon monoxide in a convergent manner. However, the limit of this reaction is represented by the requirement of stoichiometric amount of transition complex. Only recently the reactions were performed catalytically in concomitance with the development of the titanocene and oxa-titanocene chemistry.59

The intramolecular Pauson-Khand reaction mediated by Cp₂Ti(PMe₃)₂ has been also reported for molecules in which one of the alkyne or the alkene group is replaced by a carbonyl group and in this case γ-butyrolactones or fused butenolides are the products of the reaction (Scheme 51). The process, in this case, is known as "Hetero Pauson-Khand" reaction.

![Scheme 51](image)

A similar approach has been successfully employed for the construction of five-membered ring carbocycles, but not for heterocycle synthesis.

In 1996, Crowe and Vu reported a titanium-mediated synthesis of γ-butyrolactones which proceeds, under mild conditions, through coupling-carbonylation-reductive elimination. The procedure has been successfully applied to molecules containing aldehyde or ketone groups and a terminal olefinic group forming bicyclic γ–butyrolactone (Scheme 52).60

Buchwald and co-workers have reported the carbonylation reaction of o-allyl aryl ketones into γ–butyrolactones catalysed by Cp₂Ti(PMe₃)₂ or Cp₂Ti(CO)₂. The reaction proceeded via the carbonylation of an oxatitanacycle followed by thermally-induced reductive elimination and formation of the γ–butyrolactone.61 The authors have suggested that the key step in the catalytic cycle is the formation of a charge transfer complex or the reversible electron transfer between the catalyst and the substrate.

![Scheme 52](image)

Interestingly, a general catalytic procedure for the asymmetric intramolecular Hetero-Pauson-Khand cyclization of various substrates catalyzed by a chiral titanocene complex was successively developed (Scheme 53).62
Several nickel-complexes were able to promote such carbocyclization reactions but only in stoichiometric way. Dienes and enynes bearing allylic acetate or an allylic halide moiety; such as for example the compound 80, undergo nickel-catalyzed reactions affording monocyclization or bicyclization products 81, 82 and the conversion was 68%. The authors reported that the reaction proceeds via olefin insertion into an initially formed allylnickel complex, followed by hydride elimination (Scheme 54).

Allyldipropargylamine 83 reacted with a triethylsilane under CO atmosphere in the presence of rhodium complexes via silylcarbocyclization reaction involving only 1,6-diyne moiety to give exomethylene-4-piperidinone 84 in high yield (Scheme 55). The same reaction catalyzed by (t-BuNC)₄RhCo(CO)₄ in toluene produced 85 as the predominant product together to a small amount of 84.

3. Trends in cyclocarbonylation reactions
3.1. Cyclocarbonylation of steroids and other natural substrates
Steroids are a biologically important class of compounds because of the large range of applications in the pharmaceutical industry. Steroids bearing different functionalities can represent an important new class of compounds. For example, new estrone derivatives having contemporary lactone and epoxide functionality can improve their biological activity.

Recently, it has been reported that palladium acetate and dppb catalyze the regioselective lactonization of allyl steroids forming exclusively 7-membered ring lactones with excellent isolated yields (98%).

Very interestingly, the addition of one epoxide function in the seven-membered ring lactone steroid was obtained by coupling of the carbonyl group of the cyclopentanone ring with 2-benzothiazolylchloromethylitum survive to the transformation (Scheme 56).65

Scheme 56

Lenoble and co-workers reported that the cyclocarbonylation of (1R, 2S, 5R) isopulegol 96 using PdCl2(PPh3)2-SnCl2 the catalytic system produced two compounds 97 and 98 with a diasteroisomeric excess up to 60% (Scheme 57).
Interestingly, the enantiodifferentiation took place also by using non-chiral conventional ligand and could be attributed to the chiral starting material itself.\textsuperscript{66}

\begin{align*}
\text{Scheme 57} \\
Pd_2(dba)_3 \text{ catalized cyclocarbonylation reaction of the highly enantiomerically enriched (R)-1-p-tolyl 1-pentyn-3-ol 99 producing (R)-incrustoporin (R)-100 (Scheme 58), an important antibiotic isolated from } \text{Incrustoporia Carneola, with retention of configuration.}\textsuperscript{67}
\end{align*}

\begin{align*}
\text{Scheme 58} \\
\text{Some coumarin derivatives have been obtained by palladium catalyzed reaction (Scheme 59).}\textsuperscript{68,69} \\
The authors explained that the role of carbon monoxide in this case was important just to form the catalyst.
\end{align*}

\begin{align*}
\text{Scheme 59} \\
\text{Rhodium-catalysed carbonylation of 2-alkynylphenol derivatives under water-gas shift reaction conditions gives benzofuranone derivatives and coumarin derivatives in high yield (up to 96%, 2:3 = 65:35), in which the hydroxy group adjacent to the carbon-carbon triple bond participates in the cyclic carbonylation (Scheme 60).}\textsuperscript{70}
\end{align*}

\begin{align*}
\text{Scheme 60} \\
\text{6 examples} \\
11-52\% \\
20-47\%
\end{align*}
A variety of substituted coumarins has been prepared in good yields by palladium-catalyzed coupling of \( o \)-iodophenols with alkynes and 1 atm of carbon monoxide.\(^{71}\) Recently “Cardanol” derivatives have been transformed into the corresponding lactones through cyclocarbonylation reactions.

Cardanol, which can be considered a renewable organic source, is simply obtained by vacuum distillation of “Cashew Nut Shell Liquid” (CNSL), the international name of the alkylphenolic oil contained in the spongy mesocarp of the cashew nut shell and derived as by-product of cashew industry.\(^{72}\) Its production in the world (Africa, Asia, and South America are the main producer countries) is estimated to be about 500,000 tons per year and for that could represent a very interesting renewable organic source.\(^{73}\)

Cardanol is considered a mixture of 3-\( n \)-pentadecylphenol and its unsaturated derivatives having respectively one, two or three conjugated double bonds on the alkyl chain with an average value of two double bonds per molecule (Figure 6), together with minor amount of cardol (3-\( n \)-pentadecylresorcinol) and methyl cardol (2-methyl-5-\( n \)-pentadecylresorcinol).

![One of the unsaturated component of cardanol](image)

**Figure 6**

Hydrogenation of the double bonds in the side-chain of distilled cardanol leads to 3-\( n \)-pentadecylphenol. This was used to prepare allyl derivatives \(^{104-106}\) and cyclocarbonylated in the presence of palladium acetate and dppb in toluene to give selectively 7-membered ring lactones \(^{107-109}\) in relative good yields (Scheme 61).\(^{74}\)

![Scheme 61](image)

\(^{104}\) (\( R = H \))
\(^{105}\) (\( R = t - \text{Bu} \))
\(^{106}\) (\( R = t - \text{Amyl} \))
The bis-allyl 3-n-pentadecyl resorcinol derivative 110, under the same reaction conditions gave 7-membered ring bis-lactones 111 (Scheme 62).

3.2. More hetero atoms in the cyclic system

Palladium(0) catalysts are able to catalyse carbonylation of both isolable 1,2-diaza-1,3-butadienes and those generated in situ by extrusion of SO2 and CO2. The reaction have been demonstrated proceed easily at room temperature and under CO atmosphere affording 2,3-pyrazol-1(5H)-ones in good yields.75

Costa and co-workers reported the synthesis of β- and γ-lactams obtained by oxidative carbonylation of acetylenic amines catalysed by PdI2-KI and evidenced in same case the formation different oxazolidin-2-one derivatives.76

3.3. 8,9-Membered and larger rings compounds

One more exciting field is the synthesis of more larger rings and only recently it has been reported a chemoselective and regioselective catalytic way to novel nine-membered lactones. In particular, cyclocarbonylation of dihydromyrcenol into the corresponding lactone has been selectively performed in the presence of PdCl2(PPh3)2/SnCl2·2H2O and molecular sieves.77

In this context Yoneda and co-workers reported the synthesis of eight-membered lactones by carbonylation of 7-hydroxyhepta-1,2-dienes as an extension of analogous reactions performed on 6-hydroxyhexa-1,2-dienes transformed into the corresponding seven-membered lactones using Ru3(CO)12 as the catalyst and triethylamine as the solvent.78

3.4. Heterogeneous catalyzed cyclocarbonylations

Very few examples of carbonylation reactions in heterogeneous phase have been reported in the literature. Recently, in view of possible future development of environmental sustainable processes, it has been reported an heterogeneous catalytic systems for cyclocarbonylation reactions.79 In particular, it was observed that palladium on commercial activated carbon or on carbon obtained from vegetable wastes, in the presence of dppb as ligand promoted cyclocarbonylation reactions of various allylphenol derivatives into the corresponding lactones. The authors showed that the regioselectivity in this case resulted different compared to the homogeneous one and dependent on the reaction conditions (CO/H2 ratio, solvent, temperature). Palladium-montmorillonite clay, as reported by Alper and co-workers, was also effective catalyst for cyclocarbonylation reactions of 2-allylphenols affording seven membered ring lactones as the principal products.80

3.5. Enantioselective cyclocarbonylation reactions

The synthesis of optically active lactones and lactams has polarized a great interest in the last years. In fact, heterocyclic structures are presents in large variety of natural or synthetic products having biologic or pharmacologic activity.

Despite the great potential for asymmetric carbonylation reactions and the extensive effort devoted to this reaction, only moderate success (<90% ee) has been achieved, and the development of efficient asymmetric carbonylations is still viewed as one of the most challenging problems in asymmetric catalysis.
Alper and co-workers have extensively studied palladium-catalyzed cyclocarbonylation of allylic alcohols and developed the first enantioselective variant of this reaction using commercially available chiral bisphosphine ligands obtaining reasonable ee’s.

Treatment of but-2-en-1-ol 112 with carbon monoxide, oxygen copper(II) salts and hydrochloridric acid in tetrahydrofuran containing palladium chloride and polyleucine affords (R)-α-methy-γ-butyrolactone 113 in 61% enantiomeric excess; (L)-diethyl tartrate and (R)-and (S)-‘bis(diphenylphosphino)-1, 1’ binaphthyl (BINAP) can also produce the optically active lactone, but in lower optical purity (Scheme 63).

Various chiral agents (L*) were used (D-menthol, (R),1,1-bi-2naphthol, L-DET, D-DET, (-)-DMBT (D.S)CHIRAPHOS, (S)-BINAP, (R)-BINAP,Poly-L-leucine. Poly-D-alanine.

In the paper it was evidenced that the use of diethyl tartrate or poly-L-leucine as chiral ligand resulted in the synthesis of optically active lactones in good enantiomeric excess. Furthermore this is the first example of the use of poly-a-aminoacids as added chiral ligands in homogeneous catalysis.

However, the asymmetric reaction is restricted to β-substituted allylic alcohols with dialkyl substitution at the α position (geminal dialkyl effect) (Scheme 64). Cyclocarbonylation reaction of allylic alcohols catalyzed by palladium complexes with BICP (see Figure 7) and related ligands produced good enantiomeric excess.

Another major advance in this study was the development of the first highly enantioselective cyclocarbonylation of β, γ-substituted allylic alcohols bearing geminal dialkyl substituents in α–position
(Scheme 65), which significantly increases the scope and synthetic utility of the asymmetric carbonylation reaction.\(^{82}\)

\[
\begin{align*}
\text{L1: BICP Ar=Ph} \\
\text{L2: Xyl-BICP Ar3,5-dimethyl phenyl}
\end{align*}
\]

Figure 7

\(\beta,\gamma\)-Substituted allylic alcohols react with CO in the presence of catalytic quantities of palladium acetate and 1,4-bis(diphenylphosphino)butane affording \(\alpha,\beta\)-substituted-\(\gamma\)-butyrolactones in 42-85% isolated yields. The complete stereoselectivity observed in some cases is a significant feature of the lactonization reaction.

\[
\begin{align*}
\text{Scheme 66}
\end{align*}
\]

Depending on the structure of the allylic alcohol the formation of the corresponding alkene or the \(\beta,\gamma\)-unsaturated carboxylic acid was also observed as a side or the principal reaction.\(^{83}\) This represented the first stereoselective palladium-catalyzed cyclocarbonylation of \(\beta,\gamma\)-substituted allylic alcohols \(\text{Pd(OOCF}_3\text{)}_2/(S)\text{-BINAP (Pd/L = 2)}\) to produce high yields of enantiomerically enriched cyclopentenones up to 96% ee (Scheme 66).\(^{84}\)

The asymmetric cyclocarbonylation of 2-vinylaniline derivatives catalyzed by palladium acetate 2(\(-\))DIOP produced 3,4-dihydro-4-methyl-2(1H)-quinolin-2-ones in up to 54 enantiomeric excess (Scheme 67).\(^{85}\)

\[
\begin{align*}
\text{Scheme 67}
\end{align*}
\]

Iridium salts in the presence of chiral diphosphine were able also to catalyze highly enantioselective intra and intermolecular Pauson-Khand type reactions producing various chiral cyclic enones in high enantiomeric excesses.\(^{86}\)
3.6. Cyclocarbonylated products as building blocks for new materials

Cyclocarbonylation reactions have been recently applied to transform particular substrates containing different functionalities (cyano, formyl, fullerene groups etc.), for the preparation of new compounds which can be used as building blocks for new compounds.

Macrocyclic molecules such as phthalocyanines (Pcs) or metal phthalocyanines (MPcs) or their analogous structural derivatives have been receiving an increasing interest due to their various applications in the area of new materials such as active layers for gas sensors, homogeneous and/or heterogeneous catalysts, modified electrodes and so on. \(^{87}\)

It is well known also that the presence of alkyl or aryl groups in such molecules is important not only because can increase the solubility in the most common organic solvents, but can also change the aggregation state in solution as well as the physical and photo-physical properties. \(^{88}\)

Pcs containing lactone moiety in their structure represent a very stimulating area for the preparation of novel classes of “functional” Pcs.

![Scheme 68](image)

It is noteworthy that some of the most used methodologies for the synthesis of a variety of phthalocyanines consist into the tetramerization reaction of phthalonitrile derivatives.

For this reason a particular significance was associated to the synthesis of the dicyano lactone derivative 117 which was easily prepared by cyclocarbonylation reaction of 116 (Scheme 68) in terms of precursor of novel phthalocyanines.

In particular, lactone 117 was prepared in high yield by cyclocarbonylation reaction of 116 in toluene and syn-gas condition in a process catalyzed by Pd (OAc)\(_2\) and dppb.

Another stimulating area in new material science involve the fullerene [C\(_{60}\)] chemistry. Many fundamental properties of fullerene derivatives have been discovered and reported\(^{89}\) and their metal complexes evidence attractive characteristics, such as superconductivity\(^{90,91,92}\) or charge-transfer behaviour.\(^{93,94,95}\) It is well known also that the ball-like structure of C\(_{60}\) molecules is very rigid, hydrophobic, and exhibit peculiar properties totally different from those of rod-like self-assembling amphiphilic molecules.

Further, the use of highly organized fullerene derivatives in the form of supramolecular array (thin films, nanotubes etc.) could represent new technological potentialities and one of the most common approaches to control the architecture of organized thin films containing the fullerene moiety\(^{96,97}\) is the functionalisation of C\(_{60}\).

Cyclocarbonylation reaction catalyzed by palladium acetate dppb were used to synthesize novel functionalized fulleropyrrolidines C\(_{60}\)-based molecules having polar groups suitable to study their behaviour at the air water interface and their transfer onto solid surfaces.
Compounds 120 and 121 were used as aldehydic precursors in the reaction in the presence of sarcosine and C$_{60}$ giving the corresponding fulleropyrrolidine 122 and 123 respectively in 45 and 50% yields (Scheme 69). Two different synthetic strategies have been pursued for the preparation of new molecules that contain both the fullerene moiety and the lactone group.

Fulleropyrrolidines 123 was successively hydrolysed treating a their chloroform solution with a 10 % solution of NaOH for 2-7 h at 70 °C. The compound 124 was recovered after neutralisation and chloroform extraction of the mixture of reaction.

In particular, compound 121 was synthesised by cyclocarbonylation reaction of 3-allyl-4-hydroxybenzaldehyde 120 in presence of CO and H$_2$ using Pd(OAc)$_2$ and 1,4-bis(diphenylphosphino)butane (dppb) as catalytic system (Scheme 70).
4. Conclusion

A variety of heterocyclic compounds such as lactones, lactams, pyrrolidinones, and others can be achieved by cyclocarbonylation reactions catalysed by various transition metals and their complexes. The cyclocarbonylation reaction methodology is useful for the preparation of cyclic compounds containing five-, six-, seven- and other membered ring lactones and lactams. Another important area of application is the catalytic asymmetric cyclocarbonylation and the preparation of cyclocarbonylated products as building block for new materials.

References
72. Cashew Nut tree is a plant species (its botanical name is Anacardium Occidentale Linn) founds in many parts of the world Asia (eastern coast of India), Africa (Bay of Bengal), South America (Brazil).
PREPARATION AND SYNTHETIC APPLICATIONS OF (S)- AND (R)-N-BOC-N,O-ISOPROPYLDENE-α-METHYLSERINALS

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Abstract. This report describes the behaviour of (S)- and (R)-N-Boc-N,O-isopropylidene-α-methylserinals, two new versatile chiral building blocks in organic synthesis. The preparation of both compounds on a multigram scale is reported. Likewise, we explored the applications of these compounds in asymmetric synthesis. Several products of considerable importance have been synthesised including α-methyl-α-amino acids and carbohydrates of glycopeptide antibiotics.

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1. Introduction

The synthesis of optically active organic compounds is one of the most important challenges in contemporary chemistry.¹ Stereochemical control is an essential feature of the synthesis of these organic molecules. There are several methods for achieving enantiopure compounds and the field of asymmetric (enantioselective and diastereoselective) synthesis has certainly contributed greatly to progress in the highly controlled formation of new stereogenic centres.² In diastereoselective synthesis with chiral reagents, it is important that starting materials are readily available. Natural products (monosaccharides, amino acids, and their derivatives) constitute an attractive source of chirality for asymmetric synthesis. This is due in part to the commercial availability of these substances or to the small number of steps required for their synthesis from available starting materials.
In the last decade there has been sustained interest in the development of chiral N-protected \( \alpha \)-amino aldehydes\(^3 \)–compounds that are derived from natural products. These compounds are of great interest due either to their intrinsic properties or for use as powerful synthetic intermediates. In particular, (\( S \))-N-Boc-\( N, O \)-isopropylideneserinal 1, known as Garner’s aldehyde, and its \( R \)-enantiomer 2 (Figure 1) are widely used as chiral building blocks in organic synthesis.\(^4 \) The presence of the formyl group and the suitably protected amino and hydroxyl groups in the oxazolidine ring has been used in several synthetic strategies that involve stereochemical control, transformation and/or deprotection reactions to form part of an essential backbone in biologically active compounds.

Since Garner published the synthesis of 1 in 1987,\(^5 \) the versatility of 1 and its enantiomer 2 in stereocontrolled organic chemistry has been reported in more than 300 articles.\(^4 \) Furthermore, the syntheses of these compounds from readily available chiral sources, (\( S \))- and (\( R \))-serine, have been optimised\(^6 \) to provide a simple and practical gram-scale procedure – a situation that is crucial in their extensive applications in synthesis. Nevertheless, \( \alpha \)-amino aldehydes are often susceptible to racemization and, as such, special attention must be paid to the reaction conditions employed. Several authors have observed partial racemization during reactions with Garner’s aldehyde (e.g. Wittig olefination,\(^6a,7 \) Swern oxidation\(^8 \)).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Figure 1}
\end{figure}

In this context, and as a part of our research project on asymmetric synthesis, we focused our attention on a number of biologically active natural products that contain quaternary carbon atom(s) (amino acids, amino alcohols, antibiotics, carbohydrates, terpenes, alkaloids). Interest in the synthesis of molecules with quaternary stereocentres is reflected in the increase in the number of articles that have been published in this area in the last decade.\(^9 \)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Figure 2}
\end{figure}

Bearing in mind that the stereocontrolled chemistry of the 4-formyl-1,3-oxazolidine group in Garner's aldehyde has been widely studied, we fixed our interest on the synthesis of the \( \alpha \)-methyl homologues of
serinals 1 and 2, the (S)- and (R)-N-Boc-N,O-isopropylidene-\(\alpha\)-methylserinals 3 and 4 (Figure 2). These new chiral building blocks are convenient precursors of methyl quaternary compounds:
- the formyl group can be transformed to obtain several compounds with a quaternary carbon atom;
- the oxazolidine ring can be used as a chiral inductor in diastereoselective reactions with the generation of new stereogenic centres;
- the problem of racemization is not an issue.

The development of a convenient large-scale procedure for the preparation of compounds 3 and 4 is important for the use of these chirons in asymmetric synthesis.

The present review covers the synthesis of (S)- and (R)-N-Boc-N,O-isopropylidene-\(\alpha\)-methylserinals 3 and 4, as well as their versatility in stereocontrolled organic synthesis as methyl quaternary chiral building blocks.

2. Synthesis of (S)- and (R)-N-Boc-N,O-isopropylidene-\(\alpha\)-methylserinals

In the same way as (S)- and (R)-serine were used as starting materials in the preparation of chiral aldehydes 1 and 2, Cativiela et al. described\(^9\) the first synthesis of serinal derivative 3, on a milligram scale, starting from (S)-\(\alpha\)-methylserine.

This amino acid was synthesized using the methodology developed by them for the asymmetric synthesis of \(\alpha\)-\(\alpha\)-dialkyl-\(\alpha\)-amino acids. Indeed, \(\alpha\)-methylserine was obtained by a diastereoselective alkylation reaction between chiral 2-cyanopropanoate 5 and methoxymethyl iodide (LDA as base and HMPA or LiCl as external lithium complexing agent) and appropriate transformations: carboxylic ester group to amino group (Curtius-type rearrangement) and cyano group to carboxylic acid group (acid hydrolysis).

![Scheme 1](image-url)
Serinal derivative 3 was later obtained by a similar procedure to that described for Garner’s aldehyde. Treatment of the free amino acid with di-tert-butyldicarbonate (Boc₂O) using conditions reported by Johnson¹¹ (NMe₂OH, CH₃CN) and subsequent esterification of the carboxylic acid group (diazomethane) afforded compound 6.

Formation of the oxazolidine ring was achieved with 2,2-dimethoxypropane (DMP) and a catalytic amount of p-toluenesulfonic acid (TsOH) to give compound 7. Finally, N-Boc-N,O-isopropylidene-α-methylserinal 3 was obtained by a convenient route, which involved a reduction-oxidation sequence (LiAlH₄ and Swern oxidation), in 34% overall yield starting from (S)-α-methylserine (19% starting from 2-cyano ester 5) (Scheme 1).

The ready access to both chiral building blocks through a simple and economically viable gram-scale procedure is crucial to the extensive applications of these materials in synthesis. However, this procedure cannot translate to larger scale due to the expense involved in the synthesis of enantiomerically pure α-methylserine (either by this method or by any other asymmetric synthesis reported to date).

In 1999, we reported a new and more convenient synthetic procedure for (S)- and (R)-α-methylserinals (3 and 4) on a multigram scale.¹² Starting from the commercially available (R)-2-methylglycidol 8, and employing a stereodivergent synthetic route, we carried out a short and easy procedure for the preparation of both enantiomers (Figure 3).

As shown in Scheme 2, (R)-2-methylglycidol 8 (94% ee) was transformed according to the procedure described by Hatekeyama,¹³ which involves as a key step the regioselective Et₂AlCl-catalysed intramolecular cyclization of the trichloroacetimidate derivative of glycidol 8. Subsequent acylation with PivCl followed by hydrolysis of the oxazoline ring and N-Boc protection gave alcohol 9 with an overall yield of 75% from 8. A stereodivergent route with selective protection and deprotection reactions of compound 9 afforded the two serinal acetones 3 and 4.

In the first strategy (Scheme 2),¹² alcohol 9 was converted into oxazolidine 10 using DMP with boron trifluoride etherate as catalyst. Cleavage of the pivaloate ester was achieved by reduction with DIBAL-H. Alcohol 11 was therefore oxidised under Swern conditions to obtain the required (S)-N-Boc-N,O-isopropylidene-α-methylserinal 3 (82% overall yield from alcohol 9 and 61% overall yield from commercially available glycidol 8).

In the second route (Scheme 2),¹² the hydroxyl group of compound 9 was protected with tert-butylidiphenylsilyl chloride (TBDPSCI) to give orthogonally protected compound 12. In this case, cleavage of the pivaloate ester (DIBAL-H) and acetonide formation using DMP with TsOH as catalyst afforded compound 13. This compound was desilylated by treatment with tetrabutylammonium fluoride (TBAF 3H₂O) to give alcohol 14. Finally, oxidation of alcohol 14 under Swern conditions was completed to give the required (R)-N-Boc-N,O-isopropylidene-α-methylserinal 4 in high yield (48% overall yield from alcohol 9 and 36% overall yield from commercially available glycidol 8).
Unfortunately, glycidol 8 is no longer commercially available and, because of this, we had to develop an alternative synthetic route\textsuperscript{14} to obtain serinal derivatives 3 and 4 on a multigram scale. In order to achieve this goal, we envisaged Sharpless asymmetric aminohydroxylation (AA) of 2-methyl-2-propenoic acid derivatives to be the quickest method to obtain the convenient precursors for serinal acetonides 3 and 4, but all attempts gave the opposite regioisomer.\textsuperscript{15} Nevertheless, the correct regioisomer was synthesised by a sequence reaction that involves two key steps: Sharpless asymmetric dihydroxylation (AD)\textsuperscript{16} and regioselective nucleophilic substitution of a cyclic sulfite derivative.\textsuperscript{17}

\begin{equation}
\begin{aligned}
8 & \xrightarrow{75\% \text{ ref. 13}} \text{HO} \quad \text{S} \quad \text{NHBOc} \\
9 & \xrightarrow{90\% \text{ DMP, BF}_3\text{-Et}_2\text{O}} \text{O} \quad \text{S} \quad \text{OPi} \quad \text{BocN} \\
10 & \xrightarrow{67\%} \text{O} \quad \text{S} \quad \text{OPi} \quad \text{BocN} \\
11 & \xrightarrow{95\% \text{ DIBAL-H, -78°C}} \text{O} \quad \text{S} \quad \text{CHO} \quad \text{NHBOc} \\
12 & \xrightarrow{61\% \text{ overall yield from glycidol 8}} \text{O} \quad \text{S} \quad \text{CHO} \quad \text{NHBOc} \\
13 & \xrightarrow{61\% \text{ overall yield from glycidol 8}} \text{O} \quad \text{S} \quad \text{CHO} \quad \text{NHBOc} \\
14 & \xrightarrow{36\% \text{ overall yield from glycidol 8}} \text{O} \quad \text{S} \quad \text{CHO} \quad \text{NHBOc}
\end{aligned}
\end{equation}

Scheme 2

Thus, commercially available 2-methyl-2-propenoic acid was transformed into the corresponding Weinreb amide 15. The AD reaction of 15 in the presence of AD-mix α [(DHQ)\textsubscript{2}PHAL] proceeded efficiently to yield the diol 16 with excellent enantiomeric excess.\textsuperscript{14} The amide group of the diol was converted into the corresponding methyl ester to give diol 17 in two steps: basic hydrolysis and esterification with AcCl in MeOH. This diol was transformed into its 2,3-cyclic sulfite 18 by treatment with thionyl chloride (Scheme 3).
The second key step is the reaction of sulfite 18 with NaN₃ in the presence of DMF as a solvent. Nucleophilic substitution occurred with high yield and a regioselectivity of 4:1 in favour of the α-azido ester 19. Once separated, α-azido ester 19 was readily hydrogenated in MeOH in the presence of palladium to give the corresponding α-amino ester, which was subsequently treated with Boc₂O in a basic medium to give compound 6. This compound was converted into the required building block by the same reaction sequence described above: formation of the oxazolidine ring and reduction-oxidation sequence. (S)-α-Methylserinal 3 was obtained on a multigram scale from commercially available 2-methyl-2-propenoic acid with an overall yield of 24%.¹⁴

Scheme 3

The other enantiomer, (R)-α-methylserinal 4, was also obtained from the Weinreb amide of 2-methyl-2-propenoic acid using the same strategy, but changing the chiral catalytic ligand to AD-mix β in the AD reaction to give compound 20 (Scheme 4).¹⁴

Scheme 4

3. Synthetic applications

3.1. α-Methyl-α-amino acids

The conformational flexibility of peptides is one of the limitations of their use as drug leads. In recent years, several conformationally restricted analogues of bioactive peptides (pseudopeptides and/or peptidomimetics) have therefore been developed in order to establish a three-dimensional structure-
bioactivity relationship and to design new pharmacological agents with more selective properties than the original peptides. \(18\) \(\alpha\)-Alkyl-\(\alpha\)-amino acids have been shown to impart well-defined conformational constraints to a peptide backbone and thereby change their biological activity and stability. \(19\) For this reason, \(\alpha\)-alkyl-\(\alpha\)-amino acids have attracted a great deal of research interest and a number of interesting approaches have been developed. \(9c,\ 20\)

In this sense, \(\left(\text{S}\right)\) and \(\left(\text{R}\right)\)-\(N\text{-Boc-}\alpha\text{-methylserinal acetonides } 3\) and \(4\) have recently been reported \(12,\ 21\) as excellent chiral building blocks in the preparation of enantiomerically pure \(\alpha\)-substituted alanines by transformation of the aldehyde group. In this methodology, the serinal derivatives \(3\) and \(4\) contribute the stereogenic centres and the amino acid moiety is protected as an oxazolidine ring. Transformation reactions on the aldehyde group afforded the different alanine derivatives.

Moreover, the oxazolidine ring can be used as a chiral inductor in diastereoselective reactions with the generation of new stereogenic centres (Figure 2). The diastereomeric excess obtained in the asymmetric Grignard addition reaction to aldehydes \(3\) and \(4\) proved that these compounds are better chiral inductors than Garner's aldehyde and its enantiomer. As an example, the four enantiomerically pure \(\alpha\)-methyl-\(\beta\)-phenylserines have been synthesised using this methodology.

3.1.1. Enantiomerically pure \(\alpha\)-substituted alanines

3.1.1.1. \((\text{R})\)- and \((\text{S})\)-Isovaline

\((\text{R})\)- and \((\text{S})\)-2-Amino-2-methylbutanoic acids \((24\) and \(25\)) (Iva) are important chiral \(\alpha\)-alkyl-\(\alpha\)-amino acids that play a special role in the design of peptides with antimicrobial activity (peptaibols) by stabilisation of specific conformations. \(22\) Both enantiomers of isovaline (Iva) \(24\) and \(25\) have been obtained starting from \((\text{S})\)- and \((\text{R})\)-\(\alpha\)-methylserinals \(3\) and \(4\) with an overall yield of 61\%. \(12\)

The initial step involved Wittig methylenation of \((\text{S})\)-methylserinal \(3\), a reaction that was carried out under salt-free Wittig conditions using methyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide (KHMDs) as base. Olefin \(21\) was then hydrogenated using Pd-C to give

![Scheme 5](image-url)
oxazolidine 22. Cleavage of the acetonide moiety of 22 was achieved using Sc(OTf)_3 (10 mol%) to yield alcohol 23, which was oxidised by treatment with Jones’ reagent to give the corresponding protected amino acid. Acid hydrolysis and liberation of the amino acid from its hydrochloride salt with propylene oxide gave (R)-isovaline 24 in high yield (Scheme 5).

(S)-Iva 25 was obtained using the same strategy but starting from (R)-α-methylserinal 4 (Scheme 5).^{12}

3.1.1.2. Unsaturated α-substituted alanines: vinylalanines and ethynylalanines

β,γ-Unsaturated amino acid derivatives have received special attention since they are important enzyme inhibitors.^{23,24} Serinal derivatives 3 and 4 have been used as chiral starting materials in a straightforward route for the synthesis of β,γ-unsaturated α-methyl-α-amino acids: enantiomerically pure vinylalanines and ethynylalanines.\(^{21}\)

Starting from olefin 21, the N,O-deprotection was carried out by acid hydrolysis (HCl). The corresponding amino alcohol hydrochloride was then protected with Boc\(_2\)O to give 26. The transformation of this compound into the quaternary amino acid (R)-α-vinylalanine 27 was achieved according to the protocol described above (Jones’ oxidation, acid hydrolysis and liberation of the hydrochloride salt) (Scheme 6).\(^{21}\)

The (S)-vinylalanine 28 was obtained using the same strategy but starting from (R)-α-methylserinal 4. Both enantiomers of α-vinylalanine were obtained with an excellent overall yield (49%)\(^{21}\) starting from N,O-protected α-methylserinals 3 and 4 (Scheme 6).

![Scheme 6](image6.png)

![Scheme 7](image7.png)
Finally, \((R)\)– and \((S)\)-ethynylalanines 31 and 32 were also obtained from \(N,O\)-protected \(\alpha\)-methylserinals 3 and 4 with an overall yield of 32\% (Scheme 7).21

The aldehyde-to-acetylene conversion was undertaken in two steps using a dibromovinyl intermediate (the Corey–Fuchs strategy). The chiral building block 3 was converted into the corresponding alkyne 30 using the vinyl intermediate 29. The conversion of alkyne derivative 30 into \((R)\)-ethynylalanine 31 was achieved in the same way as described above for the preparation of amino acid 24 from alcohol 23 (Scheme 7). The enantiomer of 31, \((S)\)-ethynylalanine 32, was obtained by the same strategy but employing \(\alpha\)-methylserinal 4 as the chiral starting material (Scheme 7).

### 3.1.2. \(\alpha\)-Methyl \(\alpha\)-amino acids with two stereogenic centres

In this methodology the oxazolidine ring can be exploited as the precursor of the amino acid moiety and, at the same time, as an inductor auxiliary to create a new stereogenic centre. The first diastereoselective reaction to be explored was the addition of phenyl nucleophiles to aldehydes 3 and 4, which behaved as excellent chiral building blocks in asymmetric synthesis. The addition of phenylmagnesium bromide and phenyllithium to aldehyde 3 was carried out under several sets of conditions.25 In general, the results obtained indicate that the model proposed to explain the diastereoselectivity observed in the nucleophilic additions is similar to that described for Garner aldehyde 1,3a,4,6b The sole difference observed is a significant increase in the diastereoselectivity in favour of the \(anti\) diastereoisomer product when serinals 3 and 4 were used. Nucleophilic addition of phenylmagnesium bromide to aldehyde 3 occurs as a non-chelation-controlled Felkin–Ahn attack on the least hindered face to give the \(anti\)-33 isomer as the major adduct. The diastereoselectivity is affected by temperature, solvent and additives.6b,26 The best conditions involve THF as solvent, \(-78\,^\circ\text{C}\) and without chelation control to obtain \(anti\)-33 (d.r. 98/2) (Scheme 8).

![Scheme 8](image)

Starting from enantiomerically pure \(anti\)-33, \((2R,3R)\)- and \((2R,3S)\)-\(\alpha\)-methyl-\(\beta\)-phenylserines 35 and 37 have been synthesised using two different characteristics of compound 33 in the intramolecular cyclization (Scheme 9).25
The first intramolecular cyclization was promoted by attack of the alkoxide ion on the carbonylic carbon of the Boc group to give the bicyclic compound 34. Selective deprotection of the acetonide moiety of 34 by the action of BF$_3$:2AcOH gave the corresponding oxazolidinone, which was oxidised with Jones' reagent. Acid hydrolysis and liberation of the amino acid from its hydrochloride salt afforded the (2R,3R)-α-methyl-β-phenylserine 35 with an overall yield of 54% from anti-33 (53% from α-methylserinal 3).^{25}

\[ \text{Scheme 9} \]

The second intramolecular cyclization used triflic anhydride. The oxygen of carbonyl of Boc group, that is described as a good nucleophile in basic conditions,^{6b,27} attack to activated benzylic carbon with inversion of configuration, to give the bicyclic compound 36 (Scheme 9). The strategy described above was then used and amino acid 37 was obtained from compound 36 with an overall yield of 43% from anti-33 (42% from α-methylserinal 3).^{25}

The enantiomers (2S,3S)- and (2S,3R)-α-methyl-β-phenylserines 40 and 42 were also obtained using the strategy represented in Scheme 9, but starting from (R)-α-methylserinal 4 (Scheme 10).^{25}

\[ \text{Scheme 10} \]

### 3.2. Carbohydrates of glycopeptide antibiotics

During the last decade, the glycopeptide antibiotics have been intensively investigated^{28} and two new antibiotics are in clinical use; vancomycin (Figure 4) and teicoplanin, which are considered to be the last line of defence for many bacterial infections.^{29}

However, resistance to vancomycin is unfortunately now on the increase.^{30} Although the structure-activity relationship (SAR) of the glycopeptide antibiotics has been extensively studied, the modifications
necessary to improve the resistance situation remain unclear. Because of this, many investigations aimed at enhancing the activity of the vancomycin group of glycopeptide antibiotics are in progress.\textsuperscript{31}

In this sense, different vancomycin derivatives are currently under investigation; for example A82846B (vancomycin plus one additional carbohydrate substituent: 4-\textit{epi}-vancosamine) and LY333328 (a vancomycin derivative that features both the chlorobiphenyl side chain and the additional sugar substituent of A82846B) are highly efficient against vancomycin-resistant enterococci (VRE) and methicillin-resistant \textit{Staphylococcus aureus} (MRSA) and are now undergoing clinical trials.\textsuperscript{32} The structures of vancomycin and the aforementioned derivatives are shown in Figure 4.

![Figure 4](image-url)

**Figure 4**

Taking into account the importance of glycopeptide antibiotics, and in order to construct combinatorial libraries of vancomycin analogs for biological screening, the synthesis of vancosamine donors has been the focus of many researchers. To this end, several stereoselective syntheses of protected vancosamines have been described.\textsuperscript{33} Nevertheless, the synthesis of 4-\textit{epi}-vancosamine derivatives has received little attention.\textsuperscript{34}
In this context, the asymmetric synthesis of a suitably protected 4-epi-vanosamine has been receiving our attention. The synthesis involves, as the key step, the asymmetric cis-dihydroxylation of the Z-olefin 43, which is derived from the chiral building block (S)-N,O-protected-α-methylserinal 3 (Scheme 11).

The synthesis started with the Wittig olefination of N-protected α-amino aldehyde 3, using ethyltriphénylphosphonium bromide and KHMDs as base, to give the expected Z-olefin 43 in high yield. The diol derivative was obtained by double asymmetric induction by Sharpless asymmetric dihydroxylation (AD) using AD-mix α as the catalyst. Good stereoselection was obtained in favour of the syn diol 44 (anti/syn = 20/80), which has the three stereocentres required for the final product – the protected 4-epi-vanosamine. The anti- and syn-diol mixture was transformed by acid hydrolysis and subsequent treatment with Boc₂O. Both compounds were easily separated by column chromatography to give enantiomerically pure 45. The absolute configuration of their stereogenic centres was determined by X-ray analysis, showing that the stereochemistry of the major compound 44 is 1S,2R,3S (Scheme 12).

![Scheme 12](image)

The three hydroxyl groups of the major compound 45 were orthogonally protected. First, the primary alcohol was protected with a pivaloyl group and then one secondary alcohol with a MOM group; the structure was again established by X-ray analysis. Finally, the NH and OH groups of compound 46 were protected at the same time by addition of DMP and TsOH, generating the corresponding oxazolidine ring. The primary alcohol was then deprotected (DIBAL-H) to afford compound 47. In order to synthesize the arabino-hexosa skeleton of 4-epi-vanosamine, it was necessary to increase the chain length by one additional carbon. This transformation was achieved by the following reaction sequence: oxidation of the alcohol to the aldehyde, Wittig methylation of this aldehyde, regioselective hydrobororation-oxidation of the
terminal olefin to give the primary alcohol 48 and oxidation of the primary alcohol to the aldehyde using Dess–Martin periodinone. Finally, the compound was suitably protected to obtain the enantiomerically pure N,O-dibenzoyl-4-epi-vancosamine as a mixture of two anomers 49a(α) and 49b(β) in a 75/25 ratio with an overall yield of 11% from α-methylserinal 3 (Scheme 12).\(^3\)

4. Conclusions

In this report, we have described the synthesis of the enantiomers (S)- and (R)-N-Boc-N,O-isopropylidene-α-methylserinals 3 and 4, respectively. In a very short time these compounds have proved to be extremely useful as chiral building blocks in organic chemistry. The simplicity and, at the same time, the key groups present in the structure of methylserinals (amino and hydroxyl groups – protected as the oxazolidine ring – and the aldehyde group) make these compounds valuable chiral starting materials in the synthesis of different quaternary methyl products. A simple transformation of the aldehyde group afforded α-methyl-α-amino acids in which one stereogenic carbon was provided by the oxazolidine ring. Moreover, this ring gives rise to excellent diastereoselectivity as a chiral inductor in asymmetric reactions. The use of this strategy has allowed the synthesis of several stereogenic multicentre compounds of biological interest (quaternary amino acids and carbohydrates of antibiotics).

Acknowledgements

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Asymmetry


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SYNTHESIS AND REACTIVITY OF 1-(2,4,6-TRIALKYLPHENYL)PHOSPHOLES WITH A FLATTENED P-PYRAMID

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Abstract. Due to their flattened P-pyramid, the title phospholes are of aromatic character and hence they undergo aromatic electrophilic substitution, such as Friedel-Crafts acylations. The arylphospholes were functionalized via the site-selective reaction with phosphorus tribromide to provide substituted phospholes that are appropriate ligands in rhodium complexes used in hydroformylations. Despite their aromaticity, the arylphospholes take part in Diels-Alder reaction with dienophiles to result in the formation of phosphanorbornene derivatives useful in fragmentation related phosphorylations. At 150 °C, the 1H-phospholes were converted to the 2H-derivatives by a sigmatropic rearrangement to give, after trapping, 1-phosphanorbornadienes. The complexation and the oxidation reactions of the arylphospholes also revealed special features due to the presence of the trialkylphenyl substituent.

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1. Introduction
1.1. General considerations
The phosphacyclopentadienes with phosphine function called 1H-phospholes form perhaps the most important part of contemporary P-heterocyclic chemistry. The field under discussion has undergone an
enormous development. This is well demonstrated by the fact that while in the first edition of Comprehensive Heterocyclic Chemistry (1984) only four pages were devoted to phospholes,\textsuperscript{1} the second edition (1996) discusses the field in a lengthy chapter.\textsuperscript{2} Moreover, exhaustive monographs have been published in P-heterocyclic chemistry incorporating also the new developments of phosphole chemistry.\textsuperscript{3,4} The first review in the subject was written by Mathey.\textsuperscript{5}

Besides the problem of aromaticity and syntheses there are a number of fascinating reactions, such as substitutions, (cyclo)additions, modification of the phosphorus atom, rearrangements, conversion to metallic derivatives and to coordination complexes etc. showing how rich the chemistry of phospholes is.

At the Department of Organic Chemical Technology, Budapest University of Technology and Economics, we have been dealing with the synthesis and utilization of P-heterocycles for more than 1.5 decades. In this paper the synthesis and properties of phospholes with sterically demanding substituent on the phosphorus atom are described.

1.2. Synthesis of phospholes

The most practical synthesis of phospholes (2) was suggested by Mathey. The method involves the double dehydrohalogenation of phospholium salts (1) by e.g. \(\alpha\)-picoline (Scheme 1).\textsuperscript{6,7}

\[
\begin{align*}
\text{Scheme 1} & \\
R^1, R^2 & = \text{H, Me, CO}_2\text{Me, } R^3 = \text{Me, Ph, CH}_2\text{Ph, } n-\text{Bu}
\end{align*}
\]
The phospholium salts (1) are available by the McCormack cycloaddition of butadiene derivatives with phosphonous dihalogenides (route A/Scheme 2), by the quaternisation of chlorophospholenes (3) with alkylhalogenides (route B/Scheme 2) or by the reaction of alkylphospholenes (4) with bromine or chlorine (route C/Scheme 2).

A “historical” method for the preparation of phospholes involves the bromination of phospholene oxides (5), the deoxygenation of the dibromophospholane oxides (6) so obtained and finally the dehydrobromination of dibromophospholanes 7 (Scheme 3).

![Scheme 3](image)

### 1.3. Aromaticity of phospholes

One may consider the phospholes to be close relatives of the family of pyrrole, furan and thiophene. A significant difference is, however, that the phospholes described in the literature are not aromatic at all, or they display only a slight extent of aromaticity.

![Figure 1](image)

**Figure 1.** The aromaticity of five-membered heterocycles characterised by the Bird-Index

![Figure 2](image)

**Figure 2.** Stereostructure of the phospholes
This is well demonstrated by the comparison of the Bird-indexes\textsuperscript{14} of benzylphosphole,\textsuperscript{15} furan, pyrrole and thiophene (Figure 1). The Bird-index is an indicator of aromaticity based on the bond-equalization. It is the maximum (100) for benzene.

![Planar Structure](image1.png)

**Figure 3.** Stereostructure and electron-delocalisation in hypothetical phospholes

**Table 1.** The effect of *ortho* alkyl substituents on the flattening of the phosphorus atom in substituted arylphospholes (10)

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<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>R\textsuperscript{4}</th>
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</table>

Beside the bigger atomic size of phosphorus atom, as compared to that of the nitrogen, the lack of aromaticity is due to the pyramidal geometry around the phosphorus atom: the criterion of coplanarity is not fulfilled and hence the lone electron pair of the phosphorus cannot overlap with the p\textsubscript{z} orbitals of the sp\textsuperscript{2} carbon atoms (Figure 2, the stereostructure of benzylphosphole 9 is also shown\textsuperscript{15}). While in the case of
pyrrole, the aromatic stabilization covers the energy requirement of the planarization, with phospholes there is a bigger barrier for the inversion.

The electron-delocalisation in the hypothetical planar phospoles is shown in Figure 3.

An excellent review has been published recently on the aromaticity of phospholes and on the possibilities to create aromatic phospholes.\textsuperscript{16}

We thought that the phosphole molecule (10) might perhaps be planarized by the introduction of a bulky P-substituent and hence the aromaticity may be increased. Semiempirical and, in some cases, \textit{ab initio} calculations were carried out to evaluate the effect of the ortho alkyl substituent of the aryl ring on the geometry of the phosphole molecule. The calculations suggested that with the increase in the size of the alkyl groups, the extent of the planarization was also increased. The planarization was measured by the "Out of Plane" angle that means the angle connecting the P–C$_1$ bond to the C$_2$–P–C$_5$ plane. Already two methyl groups have some planarizing effect, but the presence of two \textit{tert}-butyl groups is much more efficient. The most promising molecules contained bigger substituents also in positions 2 and 5 of the hetero ring (Table 1).\textsuperscript{17}

2. Synthesis of 1-(2,4,6-trialkylphenyl)phospholes

We have elaborated the synthesis of phospholes (17) with 2,4,6-trialkylphenyl substituent on the phosphorus atom. The chlorine atom of the chlorophospholene oxide (11a-c) could not be substituted due to the considerable steric hindrance.

![Scheme 4](image-url)
After deoxygenation of the phosphinic chloride $11a$-$c$, the aryl group could, however, be easily introduced by the reaction of phosphinous chloride $12a$-$c$ with arylmagnesium bromide. Following the oxidation of arylphospholene $13a$-$c$, bromine was added onto the double-bond of phospholene oxide $14a$-$c$ and the oxygen atom was again removed. The elimination of two molecules of hydrogen bromide from intermediate $16a$-$c$ took place spontaneously to afford the expected phospholes ($17a$-$c$), *method A*, Scheme 4. In the case of supermesityl substituent, the steric hindrance was so considerable that it prevented the deoxygenation of the dibromophospholane oxide ($15d$). We were lucky to experience that the phosphorus atom of the arylphospholene ($13d$) reacted with one equivalent of bromine in a selective manner leaving the double-bond completely intact. The phosphonium salt ($18d$) so obtained could be easily dehydrohalogenated to give the corresponding phosphole ($17d$), *method B*, Scheme 4. Method B was also efficient in the preparation of arylphospholes $17b,c$.

3. Aromaticity of 1-(2,4,6-trialkylphenyl)phospholes

The new arylphospholes were examined by means of photoelectron spectroscopy and, in two cases, by X-ray crystallography. The ionization energy of 7.5 eV obtained for the supermesityl phosphole ($17d$) is the smallest value that have ever been recorded for phospholes.22

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<td>t-Bu</td>
<td>Me</td>
<td>7.9</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-Bu</td>
<td>t-Bu</td>
<td>7.5</td>
<td>45</td>
<td>1.750</td>
<td>1.390</td>
</tr>
</tbody>
</table>

*for phosphole $9^{14,15}$
The OOP angles calculated from the ionization energies were in good agreement with the angles predicted by the semiempirical calculations.\(^{17}\) With increasing planarization, the P–C and the C\(_3\)–C\(_4\) bonds were significantly shortened, at the same time the double-bonds somewhat elongated. This equalization in the bond lengths refers to a considerable aromatic stabilization (Table 2).\(^ {18,21}\) The Bird-index of 55 obtained for the supermesitylphosphole (17d) sets a new record and suggests an aromaticity that is comparable with that of pyrrole and thiophene. Hence, the supermesitylphosphole (17d) indeed belongs to the family of heteroaromatic compounds with five-membered ring.

The X-ray structure of the triisopropylphenyl- and the tri-tert-butylphenylphospholes (17b and 17d, respectively) are shown in Figure 4. In the latter case, the OOP angle is 11 degrees smaller, than in the other instance.

\[\text{Figure 4. X-ray structure of selected trialkylphenylphospholes}\]

4. Reactivity of 1-(2,4,6-trialkylphenyl)phospholes

4.1. Aromatic electrophilic substitutions

The 3,4-dimethyl-1-phenylphosphole entered into Friedel-Crafts reaction with acetyl chloride only through the molybdenum complex (20). Elimination of the metallic group from complex 21 furnished 2-
acylphosphole 22 (Scheme 5). Aromatic electrophilic acylations were described only in the coordination sphere of the phospholide anion involving phosphacymantrenes or phosphaferrocenes.

Scheme 5

Aromaticity of the supermesitylphosphole (17d) was also manifested in chemical reactions: the phosphole under discussion underwent aromatic electrophilic substitution. In Friedel-Crafts reaction with acetyl chloride, the mixture of 2-, 4- and 5-acetyl phospholes (23a, 24a and 25a, respectively), as well as a diacetyl derivative (26a) was formed. Interestingly, the most crowded 2-acetyl derivative (23a) was the main component. A similar situation was observed for 3-methylpyrrol (Scheme 6).

<table>
<thead>
<tr>
<th>R</th>
<th>Product composition [%]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Me</td>
<td>(a)</td>
<td>31</td>
</tr>
<tr>
<td>Et</td>
<td>(b)</td>
<td>~60</td>
</tr>
<tr>
<td>n-Pr</td>
<td>(c)</td>
<td>~60</td>
</tr>
</tbody>
</table>

*not relevant

Scheme 6
The use of other carboxylic acid chlorides, such as propionyl chloride and butyryl chloride led to similar results: the corresponding monoacyl- and diacyl-phospholes (23b,c and 26b,c, respectively) were found to form. In these cases, the 2-acylphosphole (23b,c) was practically the only monoacylderivative formed (Scheme 6).

We wished to check the reactivity of triisopropylphenylphosphole (17b), exhibiting a somewhat smaller Bird-index, than the tri tert -butyl derivative (17d). We learned that the acylation of the hetero ring took place only to a small extent. Acylation of the trialkylphenyl ring was a concurrent reaction path, but the major product was 2-acyl-5-aryl-bromophosphole (29) shown in Scheme 7.

According to our explanation, a 2H-phosphole (31) formed by a sigmatropic rearrangement from the starting acylphosphole (30), might be the key-intermediate for the unexpected by-product. It is not clear, however, how the 2H-phosphole (31) is converted to the 1H-derivative (29). One possibility is that a prototropic rearrangement of the 2H-phosphole (31) to another 1H-derivative (32) is involved, driven by the energy gain of aromatization (Scheme 8).
4.2. Reactions with phosphorus tribromide

We observed that the supermesitylphosphole (17d) entered into reaction with phosphorus tribromide to afford the 3-dibromophosphoniophosphole (33), after reaction with secondary amines the phosphonous diamides (34), and finally after oxidation the phosphonic diamides (35) (Scheme 9).\textsuperscript{28,29} It is noteworthy that the phosphorus atom of the phosphole ring resisted oxidation. Spectral parameters including stereospecific J\textsubscript{PP} and J\textsubscript{PC} couplings confirmed position 3 of the P-function introduced.

By reaction of intermediate 33 with diisopropylamine, only one of the bromine atoms could be replaced, to give a H-phosphinic amide (37) after hydrolysis (Scheme 9).\textsuperscript{29}

Also monosubstitution was the result of the reaction of the dibromophosphine (33) with alcohol to furnish a H-phosphinate (39) after hydrolysis (Scheme 9).\textsuperscript{29}

A similar series of reactions of the triisopropylphenylphosphole or with the mesitylphosphole (17b and 17a, respectively) with phosphorus tribromide led to the corresponding 2-substituted products. The reaction of dibromophosphine 40 with nucleophiles followed by oxidation or by hydrolysis gave phosphonic or H-phosphinic derivatives (42 or 44, respectively) (Scheme 10).\textsuperscript{28,29} The regioselectivity is obviously the consequence of the presence or the lack of the steric hindrance; with ortho tert-butyl groups, only position 3 is available, while with the smaller triisopropyl substituent, position 2 is the appropriate reaction site.
The mechanism may involve a nucleophilic attack of the double-bond of the phosphole (17) on the phosphorus atom of phosphorus tribromide to yield two kinds of intermediates (45 or 46) that are stabilized by the loss of proton, pseudorotation and finally by the departure of a bromide anion (Scheme 11).
According to our recent studies, phospholes without any aromaticity could also be involved in reaction with phosphorus tribromide, although these reactions were not so efficient. This means that the above substitution protocol does not have too much to do with the heteroaromaticity.

4.3. Diels-Alder cycloadditions

The Diels-Alder reaction of phospholes was not studied in details previously. It is known, however, that the cycloaddition of the Mathey phosphole (50) with N-phenylmaleimide afforded phosphanorbornene 51 (Scheme 12). Similar reactions with fumaronitrile or with another unit of phosphole led to products with the same configuration of the bridging P-moiety.31,32

![Scheme 12](image)

Despite their heteroaromaticity, the aryl phospholes (17) could also be involved in Diels-Alder reaction. In cycloaddition with N-phenylmaleimide, mostly the endo ring-fused phosphanorbornene containing the aryl group anti to the double-bond (52) was formed. In certain cases, the other isomer with similar P-configuration, but with exo ring fusion (54) was also formed. Stereostucture of the phosphanorborenes (52 and 54) was confirmed by stereospecific $^2J_{PC}$ couplings obtained from the $^{13}$C NMR spectra. We think that initially, under kinetic control, the syn isomer (53) is formed that is inverted at phosphorus to give the thermodynamically more stable anti product (54) (Scheme 13).33-35 It was experienced that the Diels-Alder cycloaddition became reluctant with the increase of the aromaticity and the steric hindrance. To obtain stable products, the phosphines (52 and 54) were oxidized to phosphine oxides (55 and 56, respectively). In this case, another inversion at the phosphorus atom of species 56 was observed to take place (Scheme 13).33-35

The analogue (60) of isomer (57) was prepared by a structure proving synthesis (Scheme 14). It was proved that the syn isomer (61) obtained after deoxygenation is transformed spontaneously to the anti form (62). The phosphine (62) was stabilized as the phoshene oxide (63) (Scheme 15).35

4.4. Sigmatropic rearrangements

It was found that the P-phenyl substituent of phospholes underwent migration to carbon forming the corresponding 2H-phosphole intermediate.36,37 The reaction is illustrated on the double rearrangement of biphosphole 64 to give intermediate 65 that was trapped by two equivalents of diphenylacetylene. The optically active form of product 66 is known as BIPNOR that is a useful bidental ligand (Scheme 16).38
Scheme 13

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Q</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>N–Ph</td>
<td>52</td>
</tr>
<tr>
<td>i-Pr</td>
<td>i-Pr</td>
<td>N–Ph</td>
<td>68</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Me</td>
<td>N–Ph</td>
<td>61</td>
</tr>
<tr>
<td>t-Bu</td>
<td>t-Bu</td>
<td>N–Ph</td>
<td>43</td>
</tr>
<tr>
<td>i-Pr</td>
<td>i-Pr</td>
<td>N–Me</td>
<td>53</td>
</tr>
<tr>
<td>i-Pr</td>
<td>O</td>
<td></td>
<td>33</td>
</tr>
</tbody>
</table>

*based on phosphine oxide(s)
The trialkylphenylphospholes (17b and 17c) were found to have been isomerised at 150 °C to the corresponding 2H-phospholes (67b and 67c, respectively) by a sigmatropic rearrangement. The intermediates (67b and 67c) were trapped by tolane to give the corresponding cycloadducts (68b and 68c, respectively). The phosphines (68b,c) were oxidized to phosphine oxides (69b,c) (Scheme 17).\(^{39}\)
4.5. Complexation reactions

The phospholes are important ligands in transient metal complex catalysts. The complexing ability of trialkylphenylphospholes (17) differs significantly from that of “common or garden variety” phospholes. In reaction with dichlorodibenzonitril platinum, the complexes containing one or two phosphole ligands 70 and 71 were found to form as shown in Scheme 18.\textsuperscript{40,41} Stereostructure of the complexes (70 and 71) was evaluated utilizing the stereospecific Pt–P NMR couplings.

\begin{center}
\begin{tabular}{c|cc}
 & R\textsuperscript{1} & R\textsuperscript{2} \\
\hline
a & i-Pr & i-Pr \\
b & t-Bu & Me \\
c & t-Bu & t-Bu \\
\end{tabular}
\end{center}

Scheme 18

It can be seen that the outcome of the complex forming reaction of the Mathey phosphole (50) is quite different (Scheme 19).\textsuperscript{42}

\begin{center}
\begin{tabular}{c|ccc}
 & & & \\
\hline
 & Me & Me \\
\end{tabular}
\end{center}

Scheme 19

With increasing steric hindrance, the rate of the reaction of the trialkylphenylphospholes (17a-c) with dichlorodibenzonitril platinum decreased, but due to the electron-releasing ability of the trialkylphenyl ring, the complexation took place in all cases on the P-center.

4.6. Oxidation reactions

It is known that the phosphole oxides (76), obtained either by the oxidation of phospholes (2) or by the dehydrobromination of dibromophospholane oxides (75) undergo dimerization to furnish cycloadducts 77 (Scheme 20).\textsuperscript{4,43}
Generating the phosphole oxides (78) in the presence of trapping agents, such as maleic acid derivatives, phosphanorbarenones of type 79 were obtained (Scheme 21). \(^{4,43}\)

\[
\text{Scheme 20}
\]

\[
\text{Scheme 21}
\]

\[
\text{Scheme 22}
\]
Oxidation of the arylphospholes (17) by peroxides led to phosphole oxides (80) that dimerized instantly to the corresponding phosphanorbornene derivatives (81) (Scheme 22).\textsuperscript{18,20,44} As in earlier cases, the cyclodimerization took place in a regio- and stereospecific manner. The interesting observation was that, due to the bulky P-substituent, the oxidation got slower and the phosphole oxides (80) became relatively stable; hence, they could be characterized by NMR. The diagram included in Figure 5 shows the concentration of the P-species (17, 80 and 81) involved in the oxidation–cyclodimerization consecutive series of reactions.\textsuperscript{44} X-Ray structure of the dimer with supermesityl substituent on the phosphorus atoms (81d) indicated a considerable steric compression around the heteroatoms (Figure 6).\textsuperscript{44}

![Figure 5](image-url)  
**Figure 5.** Regio- and stereospecific dimerization of phosphole oxide 80d

![Figure 6](image-url)  
**Figure 6.** X-ray structure of phosphole oxide dimer 81d

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Considering the cyclodimerization of the phosphole oxides, it is recalled that although a number of isomers could be envisaged, only a single isomer is formed in all cases. If there is a methyl group in position 3, all together 64 isomers can be imagined; if there is no methyl group, the number of the possible isomers is 8 (see Scheme 23). The favoured isomer is where the phosphole rings are connected in the endo fusion and where the oxygen atoms of the phosphoryl groups are directed towards the center of the molecule (e.g. as in isomer 83).

Semiempirical and \textit{ab initio} calculations were performed on the cyclodimerization of 1-methylphosphole oxide (82). The relative order of the values of the heat of formation for the transient states leading to the possible isomers (83-90) confirmed that the formation of the single isomer having in hand (83) is indeed favored to a high extent (Scheme 23).\textsuperscript{45} The selectivity can be explained by steric reasons and by kinetic factors.

\begin{center}
\textbf{Scheme 23}
\end{center}
Scheme 24
Mixed phosphole oxide dimers (94 and 85) were prepared by the possible combinations of two different phosphole oxides (92 and 80d) generated simultaneously in the same flask. In the reaction shown homo dimers 93 and 81d were also formed (Scheme 24).46

5. Phosphole ligands in rhodium complexes

The phospholes are widely used ligands in transient metal complexes used as catalysts.

It was evaluated how the phosphorylation of the arylphosphole ligands (17b,d) affects the activity of the in situ rhodium complex in the hydroformylation of styrene (Scheme 25).

Scheme 25

Table 3. Hydroformylation of styrene in the presence of [Rh(nbd)Cl]2 + 4L phosphole ligands at 100 °C, 40 bar

<table>
<thead>
<tr>
<th>Y</th>
<th>Reaction time</th>
<th>Conversion</th>
<th>R_b</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>6</td>
<td>99</td>
<td>66</td>
</tr>
<tr>
<td>O(\text{N}O)</td>
<td>6</td>
<td>98</td>
<td>57</td>
</tr>
<tr>
<td>OEt</td>
<td>6</td>
<td>99</td>
<td>62</td>
</tr>
<tr>
<td>NH\text{Pr}_2</td>
<td>6</td>
<td>90</td>
<td>72</td>
</tr>
<tr>
<td>OMe</td>
<td>2</td>
<td>98</td>
<td>75</td>
</tr>
<tr>
<td>OEt</td>
<td>2</td>
<td>99</td>
<td>80</td>
</tr>
</tbody>
</table>
The chemoselectivity ($R_c = \frac{\text{mol} \, 96 + \text{mol} \, 97}{\text{mol} \, 96 + \text{mol} \, 97 + \text{mol} \, 98} \times 100$) was found to be excellent ($\geq 98\%$) in all cases, while the regioselectivity ($R = \frac{\text{mol} \, 96}{\text{mol} \, 96 + \text{mol} \, 97} \times 100$) was improved in the case of certain substituents (Table 3).$^{29,47}$

6. Fragmentation of phosphole-based phosphanorbornenes

The photolysis of phosphanorbornenes (e.g. 99) was suggested to provide phosphinidenes (e.g. 100) that reacted with the alcohol to give H-phosphinates (e.g. 101) (Scheme 26).$^{48,50}$

![Scheme 26](image)

Later on, an intermediate with a pentavalent pentacoordinated phosphorus atom (102) was suggested on the basis of kinetic examinations.$^{51}$

![Scheme 27](image)

The P-aryl phosphanorbornenes (81 and 103) prepared by us served as excellent model compounds in photoinduced fragmentation-related phosphorylations. On one hand, new H-phosphinates (104) were prepared (Scheme 27), while on the other hand, our experiments showing a high sensitivity towards the steric effects confirmed the AE mechanism involving a pentacoordinated intermediate (105) (Scheme 28).$^{52,53}$

Concurrent reactions applying either equimolar mixtures of methanol and isopropylalcohol or equimolar mixtures of two different precursors (109 and 60) (Schemes 29 and 30, respectively) again underlined the importance of the steric factors.

7. Conclusions

The new class of phospholes with 2,4,6-trialkylphenyl substituent on the phosphorus atom display, in many respects, a special reactivity. Due to the flattening of the P-pyramid, the arylphospholes are of
aromaticity and hence they entered into aromatic electrophilic Friedel-Crafts acylations. The site-selective functionalization through reaction with phosphorus tribromide furnished a variety of phospholes with an exocyclic P-moiety that were useful ligands in rhodium complexes used as catalysts in hydroformylations. The phosphole platinum complexes prepared are also of novelty.

![Scheme 27](image)

Despite the planarization of the P-pyramid, the arylphospholes could also be involved in Diels-Alder reactions to give new type of phosphanorbornenes. These products together with the phosphanorbornenes obtained by the region- and stereospecific dimerization of arylphosphate oxides were useful model compounds in the UV light mediated fragmentation-related phosphorylation of alcohols. A novel mechanism

![Scheme 28](image)
was substantiated. The sigmatropic rearrangement of 1H-phospholes to the 2H derivatives gives a new entry to novel 1-phosphanorbornadienes after trapping with diphenylacetylene.

![Scheme 29](image)

**Scheme 29**

![Scheme 30](image)

**Scheme 30**

**Acknowledgment**

Gy. K. thanks the Hungarian National Science Foundation (OTKA, Grant No. T 029039 and T 042479) for the financial support and is indebted to the co-authors whose names appear in the references.

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CHIRAL β-AMINOALCOHOLS AND DERIVATIVES IN THE ASYMMETRIC SYNTHESIS OF TETRAHYDROIQUINOLINES

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Abstract. We describe herein different synthetic procedures for the stereocontrolled synthesis of 1,2,3,4-tetrahydroisoquinolines and derived alkaloids, which are of crucial interest because of the interesting biological activities displayed by this group of products. Our strategy relies on the use of chiral β-aminoalcohols as chirality source. In this context, (S)-phenylglycinol has been used as chiral building block, which is afterwards completely or partially incorporated into the structure of the final heterocycles. Alternatively, we have used (S,S)-pseudoephedrine as chiral auxiliary which is recovered after the creation of the desired stereogenic centre. The described methodologies have allowed us to prepare a wide range of differently substituted tetrahydroisoquinolines and, in some cases, other more elaborated alkaloids like isopavines, protoberberines or benzo[c]phenanthridines have also been prepared.

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   1.3. β-Aminoalcohols and derivatives as chiral ligands
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   2.1. Asymmetric synthesis of 3-aryltetrahydroisoquinolines
   2.2. Diastereodivergent synthesis of 1,3-disubstituted tetrahydroisoquinolines
   2.3. Asymmetric synthesis of protoberberines
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3. (S)-Arylglycinols as chiral templates
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5. Concluding remarks
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1. Introduction
   The isoquinoline core is a structural feature common to a large and diverse family of natural products with a widespread occurrence in nature and which play a very important role in the secondary metabolism of
numerous vegetal families. Among the members of this family, those in which the nitrogen-containing ring is partially hydrogenated, that is, the 1,2,3,4-tetrahydroisoquinolines, constitute the major group into this class of interesting alkaloids (Figure 1).

![The 1,2,3,4-tetrahydroisoquinoline nucleus with the adopted numbering scheme.](image)

There are a wide number of different groups of alkaloids containing the tetrahydroisoquinoline core in their structure (Figure 2). When analysing the constitution of these alkaloids, it can be found that several stereogenic centres are present in their carbon skeleton. As it is very often found in these cases, one enantiomer is normally the responsible of the biological activity of the product while the other results to be inactive or toxic. Consequently, the design of synthetic routes for their obtention in an enantiopure form becomes a field of increasing interest for the organic chemists.

![Different groups of alkaloids](image)

In this review, the quest for new procedures for the stereocontrolled synthesis of differently substituted tetrahydroisoquinolines in which our research group has been engaged during the last years will be presented. In some cases, the obtained heterocycles have also been used as key synthetic intermediates for the preparation of other naturally occurring isoquinoline alkaloids. The common feature to the methodologies developed by us relies upon the use of the β-aminoalcohols (S)-phenylglycinol or (S,S)-pseudoephedrine as chirality sources, which can act either as building blocks or auxiliaries in the course of the designed synthetic scheme. Prior to the presentation of the most outstanding results obtained by us, a revision of related works by other research groups worldwide will be performed.
1.1. β-Aminoalcohols and derivatives as chiral building blocks

The first reported attempts in this area belong to the use of chiral 2-arylethylamines as starting materials in which any of the typical heterocyclization procedures, i.e. Pictet-Spengler, Bischler-Napieralsky or Pommeranz-Fritsch and related procedures, allowed the access to the final heterocycles.

In this context, Bates has employed epinephrine and norepinefrine as starting materials, which, after a Pictet-Spengler reaction with formaldehyde in slightly acidic medium afforded the corresponding heterocycles in good yields (Scheme 1). The use of acetaldehyde was examined as well, but no 1,4-asymmetric induction was found to occur in this case and a 1:1 mixture of epimers was obtained.

\[
\begin{align*}
\text{Norepinephrine} & \quad \xrightarrow{(i)} \quad \text{Heterocycle} \\
\text{Reagents and conditions: (i) HCHO, HCl, pH=6.5, rt.} \\
\end{align*}
\]

Scheme 1

Analogously, Davies has used N-benzylephedrine as chiral precursor for the synthesis of 4-phenyl-3-methyl-6,7-dimethoxytetrahydroisoquinoline, using in this case an asymmetric variant of the classical Pommeranz-Fritsch heterocyclization. Acid promoted cyclization of these derivatives occurred with complete diastereoselection to give exclusively the 3,4-trans derivatives, although previous aryl complexation with \(\text{Cr(CO)}_3\) was necessary in order to stabilize the intermediate carbocation (Scheme 2). The same procedure was applied using (-)-pseudoephedrine and (+)-2-amino-1-phenylethanol with excellent results.

\[
\begin{align*}
\text{Reagents and conditions: (i) 1. TFA/H}_2\text{SO}_4 \text{ refl. or HBF}_4, \text{CH}_2\text{Cl}_2, -20^\circ\text{C. 2. Air oxidation} \\
\end{align*}
\]

Scheme 2

Rozwadwoska has followed a similar approach and has succeeded in the synthesis of 3,4-disubstituted tetrahydroisoquinolines starting from the chiral aminoalcohol \((1S,2S)-\text{thiomicamine}\). In this case, the acid-catalyzed cyclization was achieved in refluxing 40% HBr. More recently, similar derivatives have been prepared by Friedel-Crafts cyclization of chiral \(N,N\)-dibenzylaminoethanols, which were prepared via diastereoselective addition of \(\text{ArMgCl}\) to the corresponding \(N,N\)-dibenzyl-\(\alpha\)-aminoaldehydes derived from the corresponding aminoacids (Scheme 3).

Another chiral modification of the Pommeranz-Fritsch cyclization has been applied by Wipf for the stereocontrolled synthesis of the AB-ring system of \textit{tetrazomine}, an alkaloid belonging to the naphthyridinomycin/bioxalomycin class of antitumour antibiotics. In this way, the first stereocentre was introduced by means of an asymmetric dihydroxylation/Mitsunobu reaction sequence. Further transformations led to a 2-aryl-2-aminoethanol with the convenient substitution pattern at the aromatic...
moiety, which was converted into the corresponding $N$-(2-hydroxyacetyl) derivative. Subsequent Swern oxidation and acid-catalyzed cyclization afforded the target chiral nonracemic 1-substituted 4-hydroxytetrahydroisoquinolin-3-one. Further elaboration led to the synthesis of the final heterocyclic system (Scheme 4).

Reagents and conditions: (i) 1. PhCHO, MeOH, CuSO$_4$; 2. NaBH$_4$, MeOH (ii) 40% HBr, refl. (iii) AlCl$_3$, CH$_2$Cl$_2$, rt.

Scheme 3

Reagents and conditions: (i) AD-Mix-α, t-BuOH/H$_2$O, 0 °C (ii) 1. Phtalimide, Ph$_3$P, DEAD, THF; 2. H$_2$NNH$_2$, H$_2$O, refl. (iii) 1. (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$; 2. p-TsOH, dioxane, refl.

Scheme 4

In the same context, a report by Hirsenkorn can be found in which an asymmetric Pomeranz-Fritsch cyclization is employed for the building up of the isoquinoline skeleton.$^{16}$ The required starting chiral material is a 2-amino-1,2-diarylethanol, which was obtained in an enantioenriched form by asymmetric Sharpless dihydroxylation of an styrene derivative, followed by formation of a cyclic sulfate and subsequent nucleophilic ring-opening reaction with methylaminoacetaldehyde dimethylacetal (MADMA). Once the chiral aminoalcohol was obtained, the cyclization was achieved under carefully controlled conditions in order to avoid formation of pavine and isopavine side products.$^{17}$ Final removal of the protecting groups together with dehydroxylation of the benzylic alcohol moieties afforded the 1-benzyltetrahydroisoquinoline
(-)-reticuline. Alternatively, 1,2-dihydroisoquinolines are obtained if modified conditions are employed at the cyclization step (Scheme 5).\textsuperscript{18}

![Scheme 5](image)

Reagents and conditions: (i) 1. OsCl\textsubscript{3}, dihydroquinidine 4-chlorobenzoate, NMO, acetone/H\textsubscript{2}O, rt. 2. SOCl\textsubscript{2}, Et\textsubscript{3}N, Et\textsubscript{2}O, 0 °C to rt; 3. RuCl\textsubscript{3}, NaOCl, CH\textsubscript{3}CN. (ii) 1. MADMA, 130 °C. 2. Ac\textsubscript{2}O, NaOAc, xylene, refl. (iii) HCl/acetone, 0 °C.

Very recently, Hanessian has succeeded in preparing functionalized isopavines starting from chiral nonracemic 13-substituted dihydromethanodiazocines via [1,2]-Stevens rearrangements.\textsuperscript{19} These tetracyclic key synthetic intermediates were easily prepared from \(N, N\)-dibenzyl substituted enantioenriched \(\beta\)-aminoalcohols by Swern oxidation followed by a Lewis acid-catalyzed double cyclization process. The subsequently performed Stevens rearrangements\textsuperscript{20} proceeded with high selectivity and the final isopavines were obtained as single diastereoisomers (Scheme 6).

![Scheme 6](image)

Reagents and conditions: (i) 1. Swern oxidation; 2. AlCl\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C. (ii) MeI, acetone, refl. (iii) \(t\)-BuOK, 1,4-dioxane, 80 °C.

The aminoalcohol (1R,2S)-ephedrine has also been used by Schultz as chiral building block for the stereocontrolled synthesis of 3-methyl-1,2,3,4-tetrahydroisoquinolin-1-ones.\textsuperscript{21} In this case, the cyclization procedure for the construction of the heterocyclic ring involved the formation of an intermediate uretane which was subsequently cyclized with methanesulfonic acid/P\textsubscript{2}O\textsubscript{5} under a previously reported procedure.\textsuperscript{22} Prior to the cyclization, the OH group from ephedrine was removed via Raney Nickel hydrogenolysis. The obtained heterocycle was used afterwards for the preparation of different analogues of the potent analgesic
agent levorphanol. The key step in this transformation consisted on a Birch reduction procedure followed by diastereoselective trapping of the intermediate enolate with a benzylic bromide (Scheme 7).

\[
\begin{align*}
&\text{Reagents and conditions: (i) 1. CICO}_2\text{Et, NaHCO}_3, \text{CH}_2\text{Cl}_2/\text{H}_2\text{O}, 0 \, ^\circ\text{C}; 2. \text{Raney Ni, H}_2, \text{EtOH, refl.} \\
&\text{(ii) MeSO}_3\text{H, P}_2\text{O}_5, 120 ^\circ\text{C} (\text{iii) Li, NH}_3/\text{THF, } t-\text{BuOH, ArCH}_2\text{Br, } -78 ^\circ\text{C.}}
\end{align*}
\]

Scheme 7

In a different approach, chiral nonracemic tetrahydroisoquinoline 3-carboxylate derivatives are also readily available via Pictet-Spengler cyclization using phenylalanine as precursor.\textsuperscript{23} Schultz himself used this approach for the synthesis of 3-substituted tetrahydroisoquinolin-1-ones,\textsuperscript{21} Burger has prepared tetrahydroisoquinoline-1,3-dicarboxylates in a similar way\textsuperscript{24} and very recently, tricyclic tetrahydroisoquinolines incorporating the BCD subunit of the protoberberine skeleton have been prepared by cyclization of a phenylalaninol-derived bicyclic lactam via a N-acyliminium intermediate.\textsuperscript{25} In addition, Katritzky has applied his benzotriazole chemistry for the synthesis of different analogues of the natural product podophyllotoxin.\textsuperscript{26} In the latter case, the oxazolidin-2-one derived from phenylalaninol was treated with benzotriazole/RCHO and the obtained adducts were subjected to cyclization under Friedel-Crafts conditions, affording 5-substituted oxazolo[3,4-b]tetrahydroisoquinolin-3-ones as pure diastereoisomers.\textsuperscript{27} In a recent paper, the asymmetric synthesis of tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones applying the same concept has been reported (Scheme 8).\textsuperscript{28}

\[
\begin{align*}
&\text{Reagents and conditions: (i) HCHO, HCl, 85 ^\circ\text{C} (ii) BtH, RCHO, toluene, or CH}_2\text{Cl}_2, p-\text{TsOH (cat), Dean-Stark. (iii) TiCl}_4, \text{CH}_3\text{CN or CH}_2\text{Cl}_2, 60 ^\circ\text{C.}}
\end{align*}
\]

Scheme 8

Another useful and versatile approach to 1,3-disubstituted tetrahydroisoquinolines starting from phenylalanine relies on the diastereoselective heteroatom-directed metallation/alkylation sequence which has
been set up by Seebach\textsuperscript{29} and subsequently applied for the asymmetric synthesis of the phtalide alkaloid (+)-corlumine.\textsuperscript{30} N-Pivaloyltetrahydroisoquinoline-3-carboxylic acid was prepared by Pictet-Spengler cyclization of phenylalanine followed by esterification/N-pivaloylation/hydrolysis. This compound was metallated with 2 eq. of t-BuLi and the obtained carbanion reacted with several carbon electrophiles, affording the corresponding 1,3-disubstituted heterocycles in good yields and diastereoselectivities. It has to be pointed out that, in some cases, transmetallation with MgBr\textsubscript{2} was necessary prior to the reaction with the electrophile in order to reach to high diastereoselection. For the synthesis of (+)-curlumine a 3,4-dimethoxylated derivative of (S)-phenylalanine\textsuperscript{31} had to be used as starting material and a highly functionalized aromatic aldehyde as the required electrophile. A similar approach for the alkylation of 3-substituted tetrahydroisoquinolines has been employed by Laschat, but in this case the O-TBS protected derivative of phenylalaninol was used as chiral starting material (Scheme 9).\textsuperscript{32}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_9}
\caption{Scheme 9}
\end{figure}
\end{center}

Reagents and conditions: (i) 1. t-BuLi, THF, -78 °C; 2. RX or RCHO. (ii) t-BuLi, THF, -78 °C; 2. MgBr\textsubscript{2}.OEt\textsubscript{2}; 3. ArCHO

Analogously, Yamaguchi has proven that efficient 1,3-asymmetric induction can be achieved in the diastereoselective 1,2-addition of organometallic reagents to chiral 3,4-dihydroisoquinolines derived from phenylalaninol.\textsuperscript{33} In this context, the asymmetric synthesis of 7,8-dimethoxyberbane systems was achieved through a tin mediated three component coupling.\textsuperscript{34} The already mentioned chiral starting material, a 3,4-dimethoxyphenylalaninol derived dihydroisoquinoline, was prepared starting from (S)-DOPA via first Pictet-Spengler heterocyclization followed by reduction/O-silylation\textsuperscript{35} and final oxidation of the obtained tetrahydroisoquinoline, thus building up the C=N moiety into the heterocyclic ring. When 1,2-dihydroisoquinoline was made to react with 2,4-pentadienyltributyltin, in the presence of acryloyl chloride, a diastereoselective addition of the organometallic reagent across the C=N double bond occurred together with N-acylation, and the obtained adduct underwent a subsequent intramolecular Diels-Alder cyclization to afford, in a single step, the berbane system with very high diastereoselectivity. Inverting the nature of reagents, that is, using allyltributyl tin and 2,4-pentadienoyl chloride, the addition/acylation/Diels-Alder reaction also took place smoothly to afford the corresponding isomer with comparable degree of diastereoselection (Scheme 10).
Reagents and conditions: (i) CH₂=CHCH₂SnBu₃, CH₂=CHCOCl, CH₂Cl₂, rt.  
(ii) CH₂=CHCH₂SnBu₃, CH₂=CHCH=CHCOCl, CH₂Cl₂, refl.

Scheme 10

When other different tetrahydroisoquinoline-3-carboxylates are needed, particularly in the case of special substitution patterns at the aromatic ring, the natural aminoacid phenylalanine is not a suitable starting material. In this context, Ohba has prepared an O-trimethyl analogue of the natural product *imbricatine*, a 1-benzyltetrahydroisoquinoline-3-carboxylate, starting from an aryllalanine analogue.³⁶ This modified aminoacid was prepared in an enantioenriched form by electrophilic addition of an appropriately substituted benzyl chloride with the organolithium reagent that results from the lithiation of (2S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine,³⁷ a valine-based heterocycle. Base hydrolysis of the addition product afforded the desired arylalanine methyl ester which was converted into the corresponding N-(p-methoxyphenyl)acetyl derivative under standard reaction conditions. Next, Bischler-Napieralsky cyclization procedure followed by diastereoselective reduction was performed, leaving to the 1,3-disubstituted heterocycle in the right 1,3-cis relationship. Further elaboration on this synthetic intermediate led to the target O-trimethylated derivative of the already mentioned natural product (Scheme 11).

The nucleophilic addition to 3,4-dihydroisoquinolines has also been applied to the synthesis of simple chiral nonracemic 1-alkyltetrahydroisoquinolines, incorporating the chiral information at the nitrogen. In this sense, Yamato has prepared several 1-alkyl substituted derivatives in high optical purity using (R)-phenylglycinol as chirality source.³⁸ Bromination of isochromanones in the presence of sunlight afforded differently substituted 2-(2-bromoethyl)benzaldehydes and afterwards they reacted with the chiral aminoalcohol to yield the corresponding 1,2-dihydroisoquinolinium salt, that, upon base-induced
cyclization, afforded the oxazolo[2,3-α]isoquinolines, in which a masked C=N bond is present at the oxazolidine ring junction in the form of a N,O-acetal.³⁹

Reagents and conditions: (i) THF, -50 °C. (ii) HCl, MeOH, rt. (iii) (p-MeOC₆H₄)CH₂COCl, Na₂CO₃, H₂O/C₆H₆. (iv) 1. trimethylsilylpolypophosphate, CHCl₃, refl. 2. NaBH₄, MeOH, -78 °C.

Scheme 11

Reagents and conditions: (i) 1. Br₂, light; 2. (R)-Phenylglycinol, EtOH, rt.; 3. Et₃N, -78 °C. (ii) R²MgX or ArCH₂Ti(O'Pr)₃, Et₂O, -78 °C. (iii) H₂, Pd/C.

Scheme 12

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These tricyclic derivatives were subjected to nucleophilic addition with different Grignard reagents to afford, after removal of the chiral appendage by a simple hydrogenolysis procedure, the target 1-alkyltetrahydroisoquinolines in good to excellent enantiomeric excesses. This methodology allowed the authors to synthesize the biologically active products (-)-salsolidine, (+)-cryptostyline II, and (-)-homolaudanosine. In the same way, the use of benzyltitanium reagents as nucleophiles allowed the preparation of (-)-laudanosine, (-)-norarmepavine and (-)-trimetoquinol. Alternatively, Roussi has applied the same strategy for the asymmetric synthesis of (+)-cryptostyline I, although the employed synthetic pathway to the key oxazolo[2,3-b]isoquinolines was slightly different (Scheme 12).

Similarly, Kibayashi has applied this methodology to the addition of Grignard reagents to chiral hydrazonium ions derived from O-protected prolinol, which were prepared starting from the corresponding N-formyl hydrazine via Bischler-Napieralsky cyclization. The nucleophilic addition of the corresponding organometallic reagent led to the obtention of enantioenriched 1-alkyltetrahydroisoquinolines after removal of the chiral appendage by means of reductive N-N bond cleavage. Alternatively, the same compounds were obtained by Lewis acid promoted nucleophilic addition of Grignard reagents to 6,3a,4]oxadiazaindano[5,4-a]isoquinolines, which were prepared starting from the corresponding 2-(2-bromoethyl)benzaldehydes and (S)-N-aminoprolinol. The synthetic potential of this method was demonstrated with the total synthesis of (-)-salsolidine (Scheme 13).

Reagents and conditions: (i) POCl₃, benzene, refl. (ii) R₂MgX, THF, -50 °C. (iii) BH₃, THF, refl. (iv) (S)-N-amino-O-benzylprolinol, toluene, refl. (v) 1. (S)-N-aminoprolinol, AcOH, EtOH; 2. Et₃N. (vi) R₂MgX, Et₂AlCl, THF, -80 °C.

Scheme 13

In the same way, isoquinolinium salts derived from (R)-phenylglycinol have been employed as suitable chiral starting materials which are prone to undergo nucleophilic addition with carbon nucleophiles, thus allowing the preparation of 1,2-dihydroisoquinolines, which yield the final 1-substituted heterocycles in high enantiomeric excess after C=C bond reduction. Besides, these 1,2-dihydro derivatives are also appropriate compounds to undergo a second base cyclization procedure, in order to afford an oxazolo[2,3-b]isoquinoline that can undergo alkylation with a second Grignard reagent, yielding 1,3-disubstituted tetrahydroisoquinolines. This procedure has also been applied to the asymmetric synthesis of (-)-salsolidine. More recently, other authors have reached to chiral nonracemic 1-benzyltetrahydroisoquinolines, which have been prepared by diastereoselective reduction of 1-benzyl substituted 1,2-dihydroisoquinolinium salts derived from phenylglycinol (Scheme 14).
In a similar context, Meyers has also successfully employed his bicyclic lactam methodology\(^{47}\) to the asymmetric synthesis of 1-substituted tetrahydroisoquinolines.\(^{48}\) According to this procedure, a properly substituted \(\delta\)-ketoacid reacted with \((S)\)-phenylglycinol affording the key chiral nonracemic bicyclic lactam which, upon diastereoselective reduction with a hydride reagent, yielded the corresponding 1-substituted tetrahydroisoquinolin-3-one as a single diastereoisomer. Further reduction of the amide moiety and removal of the \(N\)-substituent furnished the final compounds. This methodology has been applied to the asymmetric synthesis of the natural tetrahydroisoquinolines \((-)\)-salsolidine,\(^{48}\) \((+)-cryptostyline II,\(^{48}\) the protoberberine \((-)\)-xylopinine\(^{49}\) and the pavine \((-)\)-argemonine (Scheme 15).\(^{49}\)

\[
\begin{align*}
\text{Reagents and conditions: (i) } & \text{R}_1^1\text{MgX, THF, 0}^\circ\text{C (ii) 1. NaBH}_4, \text{AcOH, THF; 2. H}_2, \text{Pd/C.} \\
\text{(iii) 1. R}_2^2\text{MgX, toluene, 0}^\circ\text{C; 2. H}_2, \text{Pd/C.}
\end{align*}
\]

\textbf{Scheme 14}

Chiral nonracemic 1,3-disubstituted tetrahydroisoquinolines have also been prepared in an similar way by Husson using his CN(\(R,S\)) method.\(^{50}\) The condensation of the properly substituted \(\delta\)-ketoacid with \((S)\)-phenylglycinol led to the corresponding amide, which was cyclized to the corresponding isoquinolinium salt by treatment with \(\text{TFA}\). Diastereoselective reduction of this synthetic intermediate afforded, depending upon the conditions employed, fully reduced 1-substituted tetrahydroisoquinoline \((-)\)-\(\text{norcryptostyline III}\) or an oxazolo[2,3-\(b\)]isoquinoline as a result of a single reduction step.\(^{51}\) In the same way as previously indicated, the latter is a suitable substrate to undergo nucleophilic addition with carbon nucleophiles, thus leaving to 1,3-trans disubstituted tetrahydroisoquinolines. Now, application of the CN(\(R,S\)) method allowed the synthesis of the 1,3-trans diastereoisomers starting from the same chiral synthetic intermediate.\(^{52}\) The
authors applied the same methodology for the asymmetric synthesis of hydroxylated analogues of podophyllotoxin, an antitumour benzoquinolizidine alkaloid (Scheme 16).

Reagents and conditions: (i) 1. (R)-phenylglycinol, DCC, C₆H₅OH rt; 2. TFA, toluene, refl. (ii) NaBH₄ (8 eq.), MeOH, rt. (iii) NaBH₄ (4 eq.), MeOH, -10 °C. (iv) H₂, Pd/C. (v) TMSCN, toluene, AlCl₃, rt. (vi) 1. RMgX, toluene, AlCl₃, rt; 2. H₂, Pd/C. (vii) LDA, RX, THF, -78 °C. (viii) HF, CH₃CN, rt. (ix) 1. NaBH₄, TFA, THF, 0 °C; 2. H₂, Pd/C.

Scheme 16

The nucleophilic ring-opening reaction of aminoalcohol-derived cyclic N,O-acetals has also been brightly employed by Pedrosa for the synthesis of 1-alkyltetrahydroisoquinolines using a conceptually different approach. In this report, aryllithium reagents undergo intramolecular addition to a conveniently located N,O-acetal derived from (-)-8-aminomenthol. The final compounds were obtained after removal of the chiral appendage by oxidation/hydrolysis. Analogously, 4-substituted derivatives have been prepared by intramolecular carbolithiation with a double bond moiety linked to the nitrogen substituent (Scheme 17).

(R)- and (S)-Phenylglycinol have also been extensively used as chirality sources in the synthesis of piperidines and piperazines in an optically active form by diastereoselective alkylation of lactams based on the already mentioned aminoalcohols. This methodology has found further application in the asymmetric synthesis of 4-substituted tetrahydroisoquinolines. In this case, the commonly used methodology involves
the use of the corresponding 1,2,3,4-tetrahydroisoquinolin-3-ones derived from (S)- or (R)-phenylglycinol which can be deprotonated and alkylated with a variety of carbon electrophiles to afford the corresponding alkylation products.

Reagents and conditions: (i) 1. t-BuLi, Et₂O, -90 °C; 2. Et₂AlCl, -90 °C to rt. (ii) 1. PCC, NaOAc buffer, mol. sieves, CH₂Cl₂; 2. KOH, MeOH/THF. (iii) 1. LiAlH₄, AlCl₃, THF, -20 °C; 2. PCC, NaOAc buffer, mol. sieves, CH₂Cl₂; 3. KOH, MeOH/THF.

Scheme 17

Subsequent reduction of the amide function and removal of the chiral appendage by hydrogenolysis leaves to the target heterocycles. In this way simple 4-alkyl or 4,4-dialkyl substituted tetrahydroisoquinolines have been prepared in moderate to good optical purities. Conceptually similar is a later work, in which 4-aryl substituted tetrahydroisoquinolines, which are not susceptible to be prepared by alkylation of the aforementioned lactams, were prepared by deprotonation/diastereoselective protonation of the corresponding 4-aryl substituted analogues (Scheme 18).

Reagents and conditions: (i) 1. LDA or LHMDS, THF, -78 °C; 2. R¹X. (ii) n-BuLi, HMPA, THF, -78 °C; 2. R²X. (iii) 1. LAH, THF, refl.; 2. H₂, Pd/C.

Scheme 18

Applying this methodology to open-chain amides, the same authors succeeded in preparing enantioenriched 2-alkylphenethylamines, which acted as versatile building blocks for the asymmetric synthesis of 1,4-disubstituted tetrahydroisoquinolines. A Bischler-Napieralsky cyclization procedure was used for the building up of the heterocyclic core followed by diastereoselective reduction. This procedure was also applied to the asymmetric synthesis of a benzyl-substituted pyrroloisoquinoline (Scheme 19).

The O-methylated analogue of (R)-phenylglycinol has also been used as chirality source in the stereocontrolled synthesis of quaternary tetrahydroisoquinoline-3-carboxylic acid derivatives. In this
example, starting from the 3-tert-butoxycarbonyloxazolidine prepared from this aminoether, a diastereoselective alkylation with differently substituted benzyl iodides was performed as key step of the proposed synthesis. Next, a Lewis acid catalysed cyclization followed by removal of the chiral appendage by hydrogenolysis furnished the final heterocycles (Scheme 20).  

\[
\begin{align*}
R^1 & \overset{(i)}{\longrightarrow} R^1 \\
\text{Me} & \overset{(ii)}{\longrightarrow} \text{Me} \\
\text{N} & \overset{(iii)}{\longrightarrow} \text{N}
\end{align*}
\]

Reagents and conditions: (i) 1. s-BuLi, DMPU, THF, -78 °C 2. R\(^2\)X. (ii) 1. LiALH\(_4\), THF, refl.; 2. H\(_2\), Pd/C. (iii) 1. N-acylation; 2. POCl\(_3\), toluene, refl.; 3. NaBH\(_4\), MeOH, 0 °C. (iv) 1. s-BuLi, DMPU, THF, -78 °C; 2. BnCl.; 3. LiALH\(_4\), THF, refl.; 4. H\(_2\), Pd/C. (v) Br(CH\(_2\))\(_3\)CO\(_2\)Et, DBU, EtOH, refl. (vi) 1. POCl\(_3\), toluene, refl.; 2. NaBH\(_4\), MeOH, 0 °C.

**Scheme 19**

\[
\begin{align*}
\text{R} & \overset{(i)}{\longrightarrow} \text{R} \\
\text{Me} & \overset{(ii)}{\longrightarrow} \text{Me} \\
\text{N} & \overset{(iii)}{\longrightarrow} \text{N}
\end{align*}
\]

Reagents and conditions: (i) 1. KHMDS, THF, -78 °C; 2. ArCH\(_2\)I. (ii) 1. TiCl\(_4\), Et\(_3\)N, CH\(_2\)Cl\(_2\), rt.; 2. H\(_2\), Pd/C, EtOH/H\(_2\)O.

**Scheme 20**

The aminoacid L-serine has also been employed as chirality source for the asymmetric synthesis of isoquinoline alkaloids. Zaragoza has obtained enantiopure tetrahydroisoquinoline 3,3-dicarboxylates by [1,2]-Stevens rearrangement of spiroammonium ylides derived from dihydroisoindoles, which were accessible by N-alkylation of N-alkyldihydroisoindoles with electrophilic rhodium carbenoids (Scheme 21).  

\[
\begin{align*}
\text{HO} & \overset{(i)}{\longrightarrow} \text{EtO}_2\text{C} \\
\text{NH}_2 & \overset{(ii)}{\longrightarrow} \text{EtO}_2\text{C}
\end{align*}
\]

Reagents and conditions: (i) Rh\(_2\)(OAc)$_4$, CH\(_2\)Cl\(_2\), refl.

**Scheme 21**

Hanessian has obtained highly functionalized chiral nonracemic 3,4-disubstituted tetrahydroisoquinolines started from the same aminoacid. Key steps in this approach rely on a
stereocontrolled conjugate addition of diarylmagnesiocuprates to a chiral \(\alpha,\beta\)-unsaturated ester derived from the starting material, subsequent transformation of the amino group into the corresponding isocyanate and final Friedel-Crafts intramolecular cyclization to provide the key chiral nonracemic tetrahydroisoquinolin-1-ones. Further elaboration on these synthetic intermediates furnished the target heterocycles (Scheme 22).

\[
\begin{align*}
\text{HO-C_2H_5} & \rightarrow \text{O-NBoc-C_2H_5} \quad \text{(i)} \\
\text{HO} & \rightarrow \text{X} \quad \text{(ii) (iii) (X=OH)}
\end{align*}
\]

\text{Reagents and conditions: (i) Ar}_2\text{CuMgCl, TMSCl, THF, -78 °C. (ii) AlCl}_3, \text{CH}_2\text{Cl}_2, \text{rt. (iii) LiAlH}_4.}

\textbf{Scheme 22}

\(\alpha\)-Aminoacids and their alcohol counterparts have also been incorporated as a part of the tetrahydroisoquinoline skeleton in the particular case of 3-substituted derivatives, in the sense that the substituent at the stereogenic centre at the 3 position results to be the aminoacid alkyl chain. This approach has been used by Liebscher, via intramolecular acylation of aryllithium reagents derived from \(N\)-(o-bromobenzyl)aminoesters. Tietze has applied an intramolecular Heck reaction of \(N\)-(o-iodobenzyl)-\(N\)-allylamines, also prepared from chiral \(\beta\)-aminoalcohols, in order to reach to 3-alkyl-4-vinyl-1,2,3,4-tetrahydroisoquinolines in highly enantioenriched form and in a different approach, Hruby has prepared 3,4-disubstituted tetrahydroisoquinolines starting from the corresponding chiral nonracemic 1,2-diarylethylamines via Pictet-Spengler reaction. These key amines were prepared by alkylation of an alanine-based imidazolin-4-one enolate with racemic (1-bromo)ethylbenzene, which occurred together with a kinetic resolution process. In a more recent work, \(\alpha\)-aminoacids have been incorporated into diketopiperazine-fused tetrahydroisoquinoline derivatives in which the heterocyclic core was built up by means of \(N\)-acyliminium chemistry (Scheme 23).

Radical cyclizations have also been applied to the synthesis of isoquinoline heterocycles. Gennari and Scolastico have reported the asymmetric synthesis of 4-substituted derivatives via diastereoselective 6-exo-trig radical cyclization of a norephedrine-derived \(o\)-bromobenzamide. This key reaction leaves to the corresponding tricyclic \(\delta\)-lactam which, upon reduction/removal of the chiral appendage, afforded the enantiomerically enriched target compounds. In a different work, Kita and Zenk have described an easy and straightforward procedure for the stereocontrolled synthesis of (+)-\textit{maritidine}, an amarillidaceae isoquinoline alkaloid, by oxidative phenolic coupling of a \(N\)-benzyl substituted \(L\)-tyrosine methyl ester derivative, using the hypervalent iodine(III) reagent PIFA as key step (Scheme 24).
Reagents and conditions: (i) (S)-RCH(NHTs)CO₂Me, K₂CO₃, MeCN. (ii) t-BuLi, THF, -78 °C.

(iii) 1. (COCl)₂, DMSO, NMM, CH₂Cl₂, -65 °C; 2. NaNH₂, BrP₃H₃Et, THF, -78 °C.

(iv) 2-iodobenzyl iodide, KH, THF, 0 °C. (v) Pd(OAc)₂, PPh₃, KOAc, TPAB, DMF, 80 °C. (vi) 1. LDA, THF, -78 °C; 2. PhCH(Br)Me. (vii) 1. 6M HCl, refl.; 2. HCHO, concd. HCl, refl.

Scheme 23

Reagents and conditions: (i) Bu₃SnH, AIBN, benzene, refl. (ii) 1. LiAlH₄, AlCl₃, THF, -78 °C;

2. MeI, MeOH; 3. NaH, dioxane, refl. (iii) PIFA, CF₃CH₂OH, -40 °C.

Scheme 24

1.2. β-Aminoalcohols and derivatives as chiral auxiliaries

Aminoalcohols can as well be employed as chiral auxiliaries, that is, as compounds that act as the source of chiral information during the creation of one or more stereogenic centres and which are subsequently removed and recovered, ready to be used again for further reactions. In this way, chiral β-aminoalcohols derived from natural α-aminoacids are promising candidates for these purposes because they are normally cheap reagents and are usually available in both enantiomeric forms.⁷³

The most important contribution made in this field is the Meyers work related to the use of formamidines as chiral auxiliaries.⁷⁴ This methodology has proved to be extremely useful and versatile for the preparation of enantioenriched 1-substituted tetrahydroisoquinolines, which have also been employed as extremely useful synthetic intermediates for the preparation of a large variety of other isoquinoline alkaloids.
The designed strategy involves C-metallation/alkylation of a tetrahydroisoquinoline derivative which bears the chiral information linked to the nitrogen heterocycle in the form of a formamidine moiety, which derives from a chiral β-aminoalcohol, typically valinol tert-butyl or methyl ether. The presence of the formamidine moiety not only contributes to stabilize the formed carbanion but also provides a chiral environment via coordination of the ether moiety of the aminoalcohol chain to the metal center, therefore allowing stereochemical control on the incoming of the carbon electrophile (Scheme 25)."75

![Scheme 25](image)

This methodology has successfully been applied by the authors to the synthesis of natural and unnatural products in high enantiomeric excess. Among them, the asymmetric synthesis of several isoquinoline alkaloids has been reported: 1-alkyltetrahydroisoquinolines like (-)-salsolidine, (+)-homolaudanosine"76 or (+)-reticuline,"77 protoberberines like (-)-xylopine"74b or (-)-tetrahydropalmatine,"78 aporphines like (+)-ocoteine,"79 (+)-glaucine"80 or (+)-homoglaucine,"80 isopavines like (-)-O-methylthalisopavine or (-)-reframoline"76 and the bis-isoquinoline alkaloid (-)-emetine (Figure 3)."81

![Figure 3](image)

The other example of chiral auxiliary mediated asymmetric synthesis of tetrahydroisoquinolines found in the literature consists on the stereocontrolled addition of silyl enol ethers to isoquinolines in the presence of α-aminoacid-derived chiral acyl chlorides.82 The procedure consisted on the activation of the
isoquinoline ring by N-acylation and the formed N-acyliminium ion subsequently underwent nucleophilic addition with several silyl enol ethers, thus furnishing 1-alkyl-1,2-dihydroisoquinolines with an excellent degree of diastereoselection. Next, hydrogenation of the intramolecular C=C bond was performed, followed by removal of the chiral auxiliary, leaving to simple 1-alkylated tetrahydroisoquinolines. This methodology was successfully applied to the total synthesis of (-)-homolaudanosine (Scheme 26).  

![Scheme 26](image)

**Reagents and conditions:** (i) Silyl enol ether, (S)-N-(p-nitrophenylsulphonyl)alanyl chloride, CH$_2$Cl$_2$, -78 °C.

### 1.3. β-Aminoalcohols and derivatives as chiral ligands

β-Aminoalcohols have also been employed as chiral ligands in the asymmetric synthesis of tetrahydroisoquinoline alkaloids. The efforts in this field belong mainly to the preparation of 1-substituted derivatives using chiral benzylamines as precursors. The preparation of these key chiral amines in an enantioenriched form involves an enantioselective 1,2-addition reaction of an organometallic species across the C=N bond of an aromatic imine or related species in the presence of the already mentioned chiral β-aminoaalcohol or derivatives as ligands.

In this context, Tomioka has exploited the use of a phenylalaninol-based chiral ligand in the asymmetric addition of organolithium reagents to an adequately substituted N-aryl-N-benzylidenamine. The addition proceeded with moderate to good enantioselectivity and the final 1-alkyl substituted tetrahydrosisoquinolines were obtained after hydroboration, followed by an oxidation/cyclization step and final removal of the N-aryl group. This approach has been successfully applied to the asymmetric synthesis of (+)-salsolidine (Scheme 27).

![Scheme 27](image)

**Reagents and conditions:** (i) RLi, chiral ligand, toluene, -95 °C.

In a similar approach, Rozwadowska has exploited the enantioselective addition of methyllithium to an imine derived from veratraldehyde and aminoacetaldehyde dimethylacetal (AADA). In this way, the obtained amine was susceptible to undergo Pommeranz-Fritsch cyclization to afford directly the desired 1-
methyl-1,2,3,4-tetrahydroisoquinoline. The asymmetric addition reaction was carried out in the presence of different enantiopure oxazolidine derived from the aminoalcohol (+)-thiomicamine as chiral ligand (Scheme 28). However, the enantioselectivity of the reaction was moderate and the obtained amines did not exceed 50% ee.

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (i) \text{MeLi, chiral ligand, toluene, -65 °C.} \\
& \quad (ii) 1. 6M HCl, rt; 2. H_2, Pd/C. \\
\end{align*}
\]

Scheme 28

Finally, Kaufman has optimized a conceptually different design for the asymmetric synthesis of (-)-salsolidine. In this case, the key chiral starting material is a benzyl alcohol, which was prepared in an enantioselective way by oxazaborolidine-catalyzed asymmetric reduction of the corresponding aryl methyl ketone. The synthesis of the target heterocycle was completed by introduction of an aminoacetaldehyde moiety by Mitsunobu reaction, followed by Pomeranz-Fritsch cyclization (Scheme 29).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (i) \text{BH}_3\text{SMe}_2, \text{chiral ligand, THF, -20 °C.} \\
& \quad (ii) \text{TsNHCH}_2\text{CH(O)}\text{Me}_2, \text{PPh}_3, \text{DEAD, THF, rt.} \\
& \quad (iii) 1. \text{CH}_2\text{N}_2, \text{EtOH} / \text{Et}_2\text{O, pyridine, rt.;} \\
& \quad 2. 6M \text{HCl, dioxane, refl.;} \\
& \quad 3. \text{H}_2, \text{Pd/C;} \\
& \quad 4. \text{Na/NH}_3; \\
& \quad 5. \text{NH}_4\text{Cl.} \\
\end{align*}
\]

Scheme 29

With all this efforts in mind, in the last years our research group has been engaged in a major effort directed towards the design of new general routes to the asymmetric synthesis of isoquinoline alkaloids using two \( \beta \)-aminoalcohols as chirality source: (S)-phenylglycinol and (S,S)-pseudoephedrine, both readily available from cheap commercial sources. The most important results obtained in the last years will be presented in the following pages.
2. (S)-Phenyglycinol as chirality source

2.1. Asymmetric synthesis of 3-aryltetrahydroisoquinolines

As it can be seen from the introduction, although chiral non racemic 3-aryltetrahydroisoquinolines are of considerable interest, both as a pharmacologically active compounds as well as versatile building blocks for the preparation of other alkaloids like protoberberines, or benzo[c]phenanthridines, the research towards their stereoselective synthesis is not as extended as in the case of the parent 1-substituted analogues. It is clear that some papers have appeared for the asymmetric synthesis of these derivatives when the substituent at C-3 bears an alkyl chain, but only few reports can be found when at this specific position aryl moiety is located.

As shown before, one of the most widely employed methods for the construction of the isoquinoline core involves a heterocyclization procedure using either Pictet-Spengler or Bischler-Napieralsky cyclizations and therefore, starting from chiral nonracemic 1,2-diarylethylamines, the already mentioned 3-aryl-1,2,3,4-tetrahydroisoquinolines should be accessible in an enantiopure form (Scheme 30). For that reason, the asymmetric 1,2-addition of a benzyl-type Grignard reagent across a C=N bond of an aromatic imine using (S)-phenylglycinol as chirality source should be a good approach for the obtention of these key 1,2-diarylethylamines in an enantioenriched form.

\[
\begin{align*}
R^1(NR^3) & \quad \text{MgX} \\
\text{R}^1 & \quad \text{NHR}^3 \\
\text{R}^2 & \quad \text{Ph}
\end{align*}
\]

Scheme 30

The synthesis of the 1,2-diarylethylamines 2a-d (Scheme 31) started with the reaction between freshly prepared Grignard benzylic reagents and imines 1a-b. These imines were synthesized, in turn, in good yields by condensation of the corresponding \( \beta \)-amino-alcohol (readily prepared by reduction of (S)-phenylglycine) with aryl aldehydes in refluxing benzene. The so-obtained condensation derivatives were stable and proved to consist of the typical imine-oxazolidine tautomeric mixture. The aldimines 1a-b were assumed to be in the \( E \) configuration based upon the report by Hine and \( 1^{3} \text{C-NMR} \) studies which showed only a single resonance for the amino carbon (163 ppm). At this point, imines 1a-b were submitted to addition reactions with various Grignard reagents, prepared \( \textit{in situ} \), exhibiting good to excellent levels of diasteroselection. The transformations were carried out with 5 equivalents of the organometallic reagent at -10 °C; then, the crude was later heated at 45-50 °C for 5 hours, quenched with ammonium chloride and worked up in the usual manner. Next, the chiral appendage was cleanly removed from (1S,1'S)-2a-d by hydrogenolysis, thus providing the corresponding primary (S)-amines 3a-d in high yields without racemization. The optical purity in all the cases studied was shown to be greater than 94% by HPLC. Finally, the enantioselective preparation of the target (3S)-3-aryl-tetrahydroisoquinolines 4a-d was accomplished by reaction of amines 3a-d, with formaldehyde in acidic medium, thus, affording the target heterocycles in high yield (80%) and without racemization.

We presume that the remarkable stereocontrol observed in the alkylation reactions of imines 1a-b can be attributed to the formation of an internal chelate between the magnesium atom of the Grignard reagent...
with the hydroxy group and the lone pair electrons of the nitrogen atom. Thus, the re and si faces are differentiated towards the attack of the nucleophile because of the bulkiness of the group at the α position of the imines. Consequently, the attack of the nucleophile occurs from the less hindered si-si face of the C=N bond (Figure 4) leading to the (1S, 1'S) isomer formation.\(^6\)

![Scheme 31](image-url)

**Reagents and conditions:** (i) ArCH\(_2\)MgCl, THF, 40 °C. (ii) H\(_2\), Pd/C, EtOH. (iii) HCHO, 1M HCl, 60 °C.

![Figure 4](image-url)

**Figure 4**

### 2.2. Diastereodivergent synthesis of 1,3-disubstituted tetrahydroisoquinolines

As already shown in the introduction,\(^7\) some examples on the enantioselective syntheses of 1,3-disubstituted tetrahydroisoquinolines are known but, in all cases reported, alkyl but not aryl substituents were placed at C-3.

![Scheme 32](image-url)
In this context, the chiral nonracemic 1,2-diarylethylamines 3 can be suitable starting materials for the stereocontrolled synthesis of C-1 substituted 3-aryl-1,2,3,4-tetrahydroisoquinolines and, by choosing the adequate reaction conditions for the formation of the isoquinoline ring, both epimers at the 1 position 5 or 6 can be obtained (Scheme 32).

When 1,2-diarylethylamines 3a-c were subjected to Pictet-Spengler cyclization under similar conditions as employed before (vide supra), but using acetaldehyde instead of formaldehyde, a series of (1S,3S)-1-methyl-3-aryl-tetrahydroisoquinolines 5a-c were respectively obtained, in good yields (70-82%) and as a single enantiomer in each case. NMR studies (nOe experiments) proved the 1,3-cis relationship between the substituents at both stereogenic centres. This result can be explained by assuming that in the transition state the intermediate iminium salt is stabilized in a chair-like conformation with the aryl substituent in an equatorial position, and where the C=N bond adopts (E) configuration, as it has been previously rationalized for the cyclization of related compounds. In this preferred conformation, the attack of the aryl ring leads to the observed stereochemistry in isoquinolines 5a-c. Moreover, since the unique stereoisomer obtained is the less sterically hindered one, the corresponding heterocyclization reaction seems to be a thermodynamically controlled process.

Reagents and conditions: (i) MeCHO, H₂SO₄. (ii) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt.. (iii) PCl₅, MeCN. (iv) H₂, Pd/C or NaBH(OAc)₃, CH₂Cl₂, refl.

Scheme 33

Once the stereocontrolled synthesis of 1,3-cis disubstituted tetrahydroisoquinolines 5a-c has been optimized, a second synthetic alternative was evaluated and optimized for the obtention of the corresponding 1,3-trans derivatives (Scheme 33). For that purpose, we first evaluated the Bischler-Napieralsky/reduction protocol and dihydroisoquinoline 8a was prepared using amine 3a as precursor via heterocyclization of the acetamide intermediate 7a. The subsequent reduction of the azomethine function in dihydroisoquinoline 8a was studied under different conditions. Disappointingly, the major diastereoisomer obtained in all cases was the 1,3-cis isomer 5a, regardless the nature of the reducing agent (nucleophilic hydride source or catalytic hydrogenation).
In order to circumvent the difficulties found during the preparation of the target 1,3-trans disubstituted heterocycles 6, a modified synthetic route was evaluated (Scheme 34). Oxazolidine 9a, quantitatively prepared from the aminoalcohol precursor 2a by reaction with aqueous formaldehyde, was heated in 1N HCl to attempt heterocyclization, yielding the expected tetrahydroisoquinoline 10a. Thus, after oxidation and subsequent treatment with a base, the 5,10b-trans-oxazolotetrahydroisoquinoline 11a (no nOe was observed between the protons at C-10b and C-5 or C-3) was obtained as a single diastereoisomer. To conclude the projected synthesis, the diastereoselective methylation of 11a was performed by nucleophilic ring-opening reaction of the N,O-acetal moiety with MeMgBr, affording the target 1,3-disubstituted derivative 12a which, after removal of the chiral appendage with H2 (Pd-C), yielded the 1,3-trans tetrahydroisoquinoline 6a (de >95% by 1H-NMR). The observed stereocontrol at C-1 during the formation of tetrahydroisoquinoline 12a can be attributed to the nucleophilic attack to the less hindered face of the developing iminium intermediate formed with simultaneous opening of the oxazolidine ring. This stereochemical proposal was confirmed a posteriori by nOe experiments carried out on the final heterocycle 6a.

Reagents and conditions: (i) HCHO, CH2Cl2, rt. (ii) 1M HCl, 60 °C. (iii) 1. I2, NaOAc, EtOH; 2. Et3N, CH2Cl2. (iv) MeMgI, THF, 0 °C. (v) H2, Pd/C.

Scheme 34

2.3. Asymmetric synthesis of protoberberines

Once the feasibility of the proposed strategies for the preparation of different non-racemic 1,3-disubstituted tetrahydroisoquinoline derivatives had been demonstrated, we moved to our next synthetic goal, which was the stereoselective synthesis of protoberberine derivatives of type 13 (Scheme 35). This protocol illustrates the possible diastereoselection that the presence of the adjacent asymmetric carbon would induce in the generation of the new stereogenic centre.

Thereby, the already available isoquinoline 10a was oxidized under Swern conditions to give the corresponding labile α-aminoaldehyde. When treating this compound with an acetone solution of aqueous HCl it was transformed into (5S,6S,14S)-5-hydroxy-6-phenyl-2,3,10,11-tetramethoxy protoberberine 13a with complete diastereoselection, as a result of a very effective 1,2-induction exerted by the presence of an adjacent stereogenic centre (de >95% by 1H-NMR). The relative configuration at the newly created stereogenic centre accounts for the observation of an intense nOe between H-5 and H-6.
Reagents and conditions: (i) DMSO, (COCl)$_2$, DIPEA, CH$_2$Cl$_2$, -40 °C (ii) 1M HCl/acetone, 0 °C.

Scheme 35

In order to confirm that the presence of a substituent (i.e. phenyl) adjacent to the new stereogenic centre was required to obtain diastereoselection in the above-mentioned synthesis of protoberberine 13a, the following experiment was designed (Scheme 36). Acetal 14a, prepared from tetrahydroisoquinoline 4a by N-alkylation with bromoacetaldehyde diethyl acetal (BADA), was submitted to the same cyclization conditions as mentioned above. In this case, the acidic treatment$^{102}$ of acetal 14a yielded protoberberine 15a as a separable 1:1 diastereomeric mixture of protoberberines (S,R)-15a and (S,S)-15a respectively, which resulted to be hydroxylated analogs of the naturally occurring protoberberine (-)-xylopine. For both diastereoisomers, the ee (95%) was determined by chiral HPLC analysis under conditions optimized for racemic standard of each of them.

Reagents and conditions: (i) BADA, KOH, DMSO, rt. (ii) 1M HCl/acetone, 0 °C.

Scheme 36

2.4. Asymmetric synthesis of isopavines

Isopavines are a small group of natural products which have shown to display important pharmacological properties for the treatment of the nerve system disorders: Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis and Parkinson's and Down's syndromes.$^{103,2}$ Few examples of syntheses of these compounds have been reported up to date.$^{104}$ Moreover, the enantioselective synthesis of isopavines has not been deeply developed yet, although their interest for future pharmacological studies should be emphasized. As far as we know, there is only one example in the literature where the synthesis of an enantiomerically enriched naturally occurring isopavine does not involve a resolution step of any of the intermediates$^{76}$ and furthermore, in all the cases reported, the final cyclization step takes place in moderate yields requiring rather long reaction times.

The projected synthesis is shown in Scheme 37 and starts from the chiral nonracemic 1,2-diarylethylamines 3a-d.$^{105}$ These substrates were alkylated with bromoacetaldehyde diethyl acetal (BADA) to afford the corresponding acetals 16a-d and, at this stage, isopavines 17a-d were successfully obtained in one step by acid-catalyzed double cyclization. The observed behavior can be explained by assuming that the synthetic route involves two sequential electrophilic cyclizations probably through a 1-
It is noteworthy to point out that, when compared with other previously reported synthesis of isopavines, the method employed by our group, which uses H$_2$SO$_4$/HOAc as cyclizing agent at room temperature, allows the preparation, in a short reaction time, of the isopavine framework in almost quantitative yield. Besides, racemization processes are not observed under the reaction conditions chosen. These conditions gave better results than other methods previously reported for this kind of double cyclization. Finally, in order to accomplish the final products, a N-methylation reaction was carried out, thus affording a series of N-methylated isopavines 18a-d with optical purities greater than 94%. Noteworthy, two of these final compounds resulted to be the natural alkaloids (-)-O-methylthalisopavine (18a: R$^1$=R$^2$=R$^4$=R$^5$=OMe, R$^3$=H) and (-)-amurensinine (18d: R$^1$=R$^2$=OMe, R$^3$=H, R$^4$=R$^5$=OCH$_2$O).

Reagents and conditions: (i) BADA, Na$_2$CO$_3$, MeCN, refl. (ii) H$_2$SO$_4$/AcOH, rt. (iii) HCHO$_{aq}$, NaBH$_3$CN, CH$_3$CN, rt.

Scheme 37

It should also be pointed out that an alternative sequence of steps in the route towards the synthesis of N-methylisopavines 18a-d was also studied. In this case (Scheme 38), when the methylation step was carried out prior to the final cyclization process, a partial racemization was detected in the final product. This low optical purity was also observed in dialkylated amine 19a and was calculated to be 88% ca. by HPLC.

Reagents and conditions: (i) 1. HCONMe$_2$, 140 °C; 2. LiAlH$_4$, THF, refl. (ii) 1. BADA, Na$_2$CO$_3$, MeCN, refl. 2. H$_2$SO$_4$/AcOH, rt.

Scheme 38

2.5. Asymmetric synthesis of 4-alkyl tetrahydroisoquinolines

Although 4-substituted tetrahydroisoquinoline derivatives are of considerable interest due to their biological activity and as naturally occurring alkaloids, the research towards their stereoselective synthesis is not as extended as in the case of the 1-substituted tetrahydroisoquinolines. As seen in the introduction, some papers have appeared for the asymmetric synthesis of tetrahydroisoquinoline derivatives when the substituent at C-4 bears a hydroxy function but only few reports can be found when the substitution at this
position is not an heteroarom,

which occurs in nature quite often e.g. in *nomifensine*, *cherylline* and the spermidine alkaloids *cyclocelabencine* and *isocyclocelabencine* (Figure 5).

![Nomifensine, Cherylline, Cyclocelabencine](image)

**Figure 4**

In this context, we have developed a suitable and general enantioselective synthetic method to obtain simple 4-alkyl-1,2,3,4-tetrahydroisoquinolines starting from chiral arylethylamine precursors,

which were prepared employing an asymmetric metalloenamine alkylation protocol starting from an imine derived from homoveratraldehyde and (R)-(+) phenylglycinol methyl ether.

The developed protocol is interesting from a synthetic point of view taking into account the possibility of introducing any kind of alkyl chain at the 4-position of the isoquinoline core. This can lead to the synthesis of a wide range of naturally and unnaturally occurring isoquinoline derivatives.

The starting imine 20 was subjected to deprotonation with LDA at –78 °C followed by alkylation with several alkyl halides at the same temperature and the crude reaction mixture was reduced *in situ* with NaBH₄ yielding the aminoethers 21a-d in good yields and moderate to good diastereoselectivities (Scheme 39). Concerning to this topic, it was observed that when increasing the steric bulk of the incoming electrophile, the 21/21' ratio became notably improved varying from 67/33 when R=Me to 93/7 when R=Bn. In all cases, it was possible to isolate and fully characterize each of the obtained diastereomers by flash column chromatography purification of the reaction crude. The stereochemistry of the newly created chiral centre in the major isomers 21a-d was provisionally assigned as (S) attending to the mechanism proposed by Meyers for a similar case.

![Scheme 39](image)

**Scheme 39**

Proceeding with the planned synthesis, the aminoethers 21a-d were N-methylated under standard conditions and the obtained products 22a-d were subjected to a hydrogenolysis procedure to remove the benzylic part of the chiral appendix, yielding the corresponding 2-substituted 2-arylethylamines 23a-d in good yields (Scheme 40). Their analysis by chiral HPLC showed that they were obtained as only one detectable enantiomer, indicating that both processes, N-methylation and hydrogenolysis, proceeded without racemization in the previously formed chiral centre. The fact that amine 23a is a known product allowed us
to unambiguously establish the absolute configuration of its chiral centre by comparison of the obtained \([\alpha]_D^{20}\) value \((|\alpha|_D^{20}=-16.3, c=1.75, \text{CHCl}_3\) for the \(R\) enantiomer), thus confirming the previously assigned \(S\) configuration for 23a and, by extension, to the rest of amines 23b-d and all the obtained aminoethers 21a-d, and 22a-d. Finally, in order to complete the synthesis, the amines 23a-d were converted into the target heterocycles by Pictet-Spengler heterocyclization reaction and the isoquinolines 24a-d were obtained in excellent yields and again as only one detectable enantiomer as chiral HPLC analysis indicated.

Scheme 40

3. (S)-Arylglycinols as chiral templates

3.1. Synthesis of 3-aryl-4-hydroxytetrahydroisoquinolines

Tetrahydroisoquinoline-4-ol derivatives are of considerable interest due to their biological activity and as naturally occurring alkaloids and, as shown before, some papers have appeared for the asymmetric synthesis of these kind of derivatives. However, only few reports can be found when additionally the substitution at the 3-position is an aryl moiety, which is found in nature quite often e.g. in the protoberberine alkaloids ophiocarpine or papaverberine among others (Figure 6).

As previously demonstrated in the asymmetric synthesis of 3-aryl tetrahydroisoquinolines, a suitable method, and one of the most widely employed one for the construction of the isoquinoline core involves an heterocyclization procedure using either Pictet-Spengler or Bischler-Napieralsky cyclizations. Therefore, starting from chiral nonracemic 1,2-diarylaminoethanols, the already mentioned 3-aryl-1,2,3,4-tetrahydroisoquinoline-4-ols should be obtained in an enantiopure form. However, the use of these cyclization procedures as key steps in the construction of the heterocyclic system has a very strong limitation, which is that the substitution pattern at the aromatic ring of the isoquinoline skeleton becomes imposed by the electronic requirements of the cyclization step. This, for example, makes these already mentioned procedures unviable for the synthesis of derivatives with any desired substitution pattern, and
becomes a very important problem when 7,8-disubstituted heterocycles have to be prepared, which is the most common substitution pattern found in many of the isolated natural products belonging to this family. (see Figure 6).

A straightforward solution to this problem could be the use of an alternative heterocyclization procedure for the construction of the heterocyclic system and, in this context, the Pomeranz-Fritsch cyclization can be considered as a very promising tactic. In fact, the presence of the aminooxalcohol moiety in aminoalcohols 2a-d should allow us to use these compounds as suitable starting materials because hypothetical oxidation of the hydroxylic function should provide the \( \alpha \)-aminooxaldehyde moiety required for the Pomeranz-Fritsch cyclization.

This hypothesis was positively confirmed (Scheme 41) when aminoalcohol 2a was N-methylated and oxidized under Swern reaction conditions to \( \alpha \)-aminooxaldehyde 26a. Due to its lability, it was immediately made to react with an acetone solution of conc. HCl, yielding the corresponding tetrahydroisoquinolin-4-ol 27a as the major 3,4-\( cis \) diastereoisomer (d.e.=80%), assigning the relative configuration of the major stereoisomer on the basis of nOe experiments. Thus, a 3,4-\( cis \) relationship between the substituents at C-3 and C-4 accounts for the observation of that effect between H-3 and H-4, as well as H-3 and the NMe group, which is in good agreement with the absence of nOe in the corresponding minor C-4 epimer.

![Scheme 41](image)

**Reagents and conditions:** (i) HCHO\(_{aq}\), NaBH\(_3\)CN, CH\(_3\)CN, rt. (ii) DMSO, (COCl)\(_2\), DIPEA, CH\(_2\)Cl\(_2\), -40 °C. (iii) HCl/acetone, 0 °C.

**Scheme 41**

This approach was also applied to the asymmetric synthesis of 3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol\(_1\), the parent compound without substitution at the 1-position. For this purpose, (S)-phenylglycinol-based imine 1a was used as starting material, which, upon reduction of the C=\( N \) bond furnished the corresponding amine 28a. Next, N-methylation, Swern oxidation and acid-catalyzed cyclization afforded the isoquinolin-4-ol in good yield and as a single 3,4-\( cis \) diastereoisomer (Scheme 42).

This strategy, in principle, would provide us an easy and straightforward access to tetrahydroisoquinolin-4-ols with any desired substitution pattern at the isoquinoline aromatic ring. However, the wanted 3-aryl substituent would be limited just to the phenyl ring due to the fact that phenylglycine (from which phenylglycinol is prepared) is the only commercially available arylglycine. Therefore, the development of a general procedure for the stereocontrolled synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols with any substitution pattern implies to have an easy and straightforward method for synthesizing arylglycines in an enantiopure form.\(^{116}\)
Reagents and conditions: (i) NaBH₄, MeOH, rt. (ii) HCHOaq, NaBH₃CN, CH₃CN, rt.
(iii) 1. DMSO, (COCl)₂, DIPEA, CH₂Cl₂, -40 °C; 2. HCl/acetone, 0 °C.

Scheme 42

In this context, and taking into account that many of the methods reported for the stereocontrolled synthesis of arylglycines, although quite effective, they often require multistep syntheses, the use of highly toxic reagents, laborious separation of diastereoisomers, harsh reaction conditions or they lack of the required high chemo- and diastereoselectivity for subsequent synthetic purposes, we have recently developed a suitable, easy to perform and high-yielding procedure for the stereocontrolled synthesis of this particular kind of racemization-prone amino acids (Scheme 43). The access to these derivatives was achieved by means of a stereocontrolled amination reaction of arylacetamide enolates using (S,S)-(+)-pseudoephedrine as chiral auxiliary as key reaction. Then, the N-N bond cleavage followed by hydrolysis of the obtained adducts would afford the wanted α-aminoacids which upon reduction under the usual conditions furnished the target arylglycinols 35a-c in a highly enantioenriched form.

Reagents and conditions: (i) 1.LDA, THF, -78 °C; 2. BocN=NBoc, -105 °C. (ii) H₂, Ni/Raney.
(iii) 9M H₂SO₄, dioxane, refl. (i) LiBH₄, TMSCl, THF, 0 °C.

Scheme 43

Focussing now in the stereocontrolled synthesis of the target 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols, arylglycinols 35a-c and the simple phenylglycinol were easily transformed into the corresponding N-benzyl derivatives 29a-d by previous formation of an imine intermediate 1a-c with a conveniently substituted aromatic aldehyde, followed by reduction with NaBH₄ and N-methylation (Scheme 44). Then, proceeding in the same way as previously indicated, Swern oxidation and final acid-catalyzed cyclization furnished the target 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols in good yields and high optical purity.
Remarkably, we were able to introduce an extended variety of different kind of substitutions at both the isoquinoline and the 3-aryl aromatic rings, including the valuable 7,8-disubstitution pattern (30b).

\[
\begin{array}{cccccc}
R^1 & R^2 & R^3 & R^4 & R^5 \\
30a & \text{OMe} & \text{OMe} & H & H & H \\
30b & H & \text{OMe} & \text{OBn} & H & H \\
30c & \text{OMe} & \text{OMe} & H & \text{OMe} & \text{OMe} \\
30d & \text{OMe} & \text{OMe} & H & \text{OCH}_2\text{O} \\
\end{array}
\]

Reagents and conditions: (i) ArCHO, C6H6, refl. (ii) 1. NaBH4, MeOH, rt. 2. HCHOaq, NaBH3CN, CH3CN, rt. (iii) 1. DMSO, (COCl)2, DIPEA, CH2Cl2, -40 °C; 2. HCl/acetone, 0 °C.

Scheme 44

3.2. General procedure for the asymmetric synthesis of 3-aryl tetrahydroisoquinolines

The 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols 30a-d could constitute extremely useful starting materials for the synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolines, provided that a procedure is found for removing the OH moiety present at C-4. This transformation was successfully achieved with the help of an ionic hydrogenation procedure, which has shown to be a very effective method to convert alcohols into alkanes, especially in the particular case of benzylic alcohols as it is our case.120

Therefore, isoquinolin-4-ols 30a-d were treated with NaBH4 in trifluoroacetic acid as solvent,121 thus affording the desired reduced heterocycles 36a-d in excellent yields and, which is more important, with no loss of optical purity which concerns to the stereogenic centre still present at C-3 in the final compounds 36a-d (Scheme 45).

Reagents and conditions: (i) NaBH4, TFA, CH2Cl2, 0 °C.

Scheme 45

This procedure results to be a complementary method for the stereocontrolled synthesis of 3-aryl tetrahydroisoquinolines to the already employed (Section 2.1.), which proceeds via Pictet-Spengler
cyclization of 1,2-diarylalkylamines 3a-d. However, in former case, although more synthetic steps are required compared to the later, any desired substitution pattern can be introduced at the 3-aryl substituent and at the aromatic ring of the tetrahydroisoquinoline core.

4. (S,S)-(+) -Pseudoephedrine as chiral auxiliary

Pseudoephedrine, which is a cheap and commercially available reagent in both enantiomeric forms, has been recently used as chiral auxiliary in asymmetric enolate-addition reactions with excellent results. In this context, we decided to engage in the task of applying the chemistry developed around this aminoalcohol as chiral auxiliary in enolate alkylation reactions to the asymmetric synthesis of tetrahydroisoquinoline alkaloids.

4.1. Asymmetric synthesis of 4-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines

As we have already showed, some papers have appeared for the asymmetric synthesis of tetrahydroisoquinoline derivatives when the substituent at C-4 bears an hydroxy function but only few reports can be found when the substitution at this position is an alkyl chain and none can be found in which additionally the substitution at the 3 position is an aryl moiety, which is also found in nature quite often e.g. in the protoberberine alkaloids thalictrifoline and corydaline methyl ester (Figure 7).

![Thalictrifoline and Corydaline methyl ester](image_url)

Figure 7

In this context, we have developed a suitable and general stereoselective synthetic method to obtain 4-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinolines in which the key step concerning to the stereochemical control of the stereocentres present in the final compounds relies on the asymmetric alkylation of arylacetamide enolates using (S,S)-(+) -pseudoephedrine as chiral auxiliary. The developed protocol is interesting from a synthetic point of view taking into account the possibility of introducing any kind of alkyl chain at the 4 position of the isoquinoline core and the high degree of stereoselectivity in which all the chiral centres in the molecule are generated.

The projected synthesis started with the already mentioned asymmetric alkylation of (S,S)-(+) -pseudoephedrine derived arylacetamide 31a by kinetic deprotonation with LDA/LiCl in THF at -78 °C and followed by electrophilic attack of the corresponding alkyl halide to the formed dianion (Scheme 46). The diastereoselectivity of this reaction was determined by 1H-NMR spectroscopy and was found to be >95% in all cases. The relative stereochemistry of the final product resulted to be 1,4-syn, which was a posteriori confirmed on the arylacetic acids 38a-d by chemical correlation. The chiral inductor was cleanly removed by hydrolysis thus providing, after typical acid-base work-up, the α-alkylated arylacetic acids 38a-d in
excellent yields. Additionally, from the extracts obtained from the aqueous basic layer it was possible to recover the chiral auxiliary (S,S)-(+)pseudoephedrine in 88% yield after crystallization (hexanes/ethyl acetate 1:1) and without any racemization as the measurements of the [α]D 20 value indicated. Finally, the so obtained α-alkylated arylacetic acids were converted into the corresponding acid chloride derivatives and subjected to Friedel-Crafts acylation with 1,2-dimethoxybenzene (veratrole) using AlCl3 as Lewis acid, yielding the corresponding ketones 39a-d in good yields and with no loss of enantiomeric purity compared with the starting amides 37a-d, as chiral HPLC analysis showed.

\[ \text{Reagents and conditions: (i) 1. LDA, THF, -78 °C; 2. RI. (ii) 9M H}_2\text{SO}_4, \text{ dioxane refl. (iii) 1. SOCl}_2, \text{CH}_2\text{Cl}_2, \text{refl.; 2. veratrole, AlCl}_3, \text{CH}_2\text{Cl}_2, -20 °C; (iv) 1. BnNH}_2, \text{TiCl}_4, \text{Et}_3\text{N, CH}_2\text{Cl}_2, -20 °C; 2. NaBH}_4, \text{MeOH, -20 °C. (v) HCHO, 1M HCl, 60 °C.} \]

\[ \text{Scheme 46} \]

Proceeding with the synthesis, the ketones 39a-d were converted into N-benzylketimine intermediates125 which were reduced in situ with several reducing agents yielding the wanted 1,2-diarylethylamines 40a-d as N-benzyl derivatives in good yields and with a variable diastereomeric ratio (anti/syn ratio ranging from 78:22 to 94:6). Among all the hydride reagents employed, the most efficient one was proved to be NaBH4. Bulkier metal hydride reagents like sodium triacetoxyborohydride or lithium triethylborohydride were not able to react with the intermediate ketimines. The two obtained diastereoisomers were separated by flash column chromatography and it could be determined that the major product showed the relative stereochemistry of the two stereogenic centres to be anti from the value of the coupling constant J(H-H) between the two benzylic protons of the 1,2-diarylethylamine moiety. This could also be proved a posteriori in the stereochemistry of the final tetrahydroisoquinoline derivatives employing nOe difference experiments. As the absolute configuration of the remaining stereogenic centre at C-2 was already known and it remains unchanged, it can also be proposed a (1S,2S) absolute configuration for the anti 1,2-diarylethylamines 40a-d. The choice of temperature when forming the intermediate imine was found to have a critical effect in the ee of the final product. At high temperatures the imine-enamine tautomerism takes place at a fast enough rate to allow notable racemization in the molecule but when lowering the temperature to -20 °C no racemization occurred and the wanted 1,2-diarylethylamines were obtained with no loss of enantiomeric purity compared to the starting ketones.

Finally, in order to complete the synthesis, the amines 40a-d were subjected to the standard Pictet-Spengler cyclization procedure (Scheme 46), yielding the wanted 4-alkyl-3-aryl-1,2,3,4-
tetrahydroisoquinolines 41a-d in excellent yield and with no racemization as the optical purity in all cases was shown to be higher than 99% by HPLC.

4.2. Asymmetric synthesis of B/C-hexahydrobenzo[c]phenanthridines

The B/C-hexahydrobenzo[c]phenanthridines are a group of isoquinoline alkaloids that naturally occur in papaveraceous and rutaceous plants and are characterized by the basic skeleton shown in the examples of in Figure 8. Most of the members of this family have shown interesting antitumor and antileukemic properties as well as inhibiting HIV 1 and 2 reverse transcriptases. However, toxicity problems have precluded their medical application. As a result of that there is a growing interest in determining structure-activity relationships and in developing structural analogues of these compounds with improved pharmacological properties. Most of the synthetic studies on benzo[c]phenanthridines have been mainly focussed towards fully aromatised derivatives and only limited efforts towards the synthesis of B/C hexahydrobenzo[c]phenanthridines have been previously reported. Additionally, just a few of them have been directed towards stereocontrolled procedures.

![Figure 8](image)

The basic benzo[c]phenanthidine skeleton should be accessible from a 3-aryl-1,2,3,4-tetrahydroisoquinoline, with an appropriately functionalized substituent at the 4-position, which should be easily obtained in a stereocontrolled way by the methodology shown in section 4.1. Therefore, the designed synthetic pathway (Scheme 47) involves the introduction of an allyl group as the functionalized substituent in the 2-position of the starting (S,S)-(+)pseudoephedrine arylacetamide. Subsequent hydrolysis and acylation followed by reductive amination of the resulting ketone would lead to the key 2-allyl-1,2-diairethylethylamine precursor in which the configuration of the newly created stereogenic centre should be controlled by the other stereogenic centre present in the starting amide. Next, the B ring closure should leave a 4-allyl functionalized 3-aryl-1,2,3,4-tetrahydroisoquinoline which on the last C ring formation step should give raise to the target heterocycles in which again a new stereogenic centre has been created during the cyclization having a well defined stereochemistry which has been controlled by the other stereogenic centres present in the molecule. Therefore, the starting arylacetic acid based pseudoephedrine amides 31a-c were diastereoselectively alkylated with allyl bromide affording the corresponding alkylated amides 42a-c in excellent yields and diastereoselectivities as could be seen by $^1$H-NMR spectroscopy (Scheme 48). The stereochemistry of the newly created stereogenic centre was assigned as S as previously found for the alkylation of the same kind of substrates with similar carbon electrophiles.
The resulting amides 42a-c were hydrolized to yield the corresponding enantiomerically enriched 2-aryl-4-pentenoic acids 43a-c after standard acid-base work-up procedure from which the basic aqueous layers it could be recovered pure (S,S)-(+)pseudoephedrine in ca 83% yield and with no racemization which allows its recycylation for further uses. The acids 43a-c were subjected to Friedel-Crafts acylation either with 1,2-dimethoxybenzene (veratrole) or 1,2-methylenedioxybenzene yielding the corresponding aryl benzyl ketones 44a-d in excellent optical purities (ee >99%) as chiral HPLC analysis demonstrated. When methylenedioxy bridges were present either at the starting arylacetic acid (44c) or at the alkoxybenzene moiety (44d) the Friedel-Crafts acylation reaction had to be performed using SnCl₄ as the activating Lewis acid, because the use of AlCl₃ yielded mixtures of products in which the mentioned methylenedioxy bridge was broken.\(^\text{134}\)

Continuing with the synthesis, the ketones 44a-d were subjected to the next stereocontrolled reductive amination reaction (Scheme 48) yielding the wanted 1,2-diarylethylamines 45a-d with an excellent degree of diastereoselectivity (anti/sin ratio 98:2) and again in excellent optical purities. The tetrahydroisoquinolines 46a-d were then obtained by the subsequent standard Pictet-Spengler cyclization procedure (84-91% yield). The final cyclization step in order to obtain the desired benzo[c]phenanthridines was performed using acidic reaction conditions that lead to the formation of a carbocation at the alkene moiety followed by electrophilic aromatic substitution leading to the ring closure. In this way, treatment of

\[ \text{Reagents and conditions: (i) 1. LDA, THF, -78 °C; 2 allyl bromide. (ii) 9M H₂SO₄, dioxane refl.} \]
\[ \text{(iii) 1. SOCl₂, CH₂Cl₂, refl.; 2. Arene, AlCl₃ or SnCl₄, CH₂Cl₂, -20 °C. (iv) 1. BnNH₂, TiCl₄, Et₃N, CH₂Cl₂, -20 °C; 2. NaBH₄, MeOH, -20 °C. (v) HCHO, 1M HCl, 60 °C.} \]
the isoquinolines **46a-d** with poliphosphoric acid (PPA) at 60 °C for 24h led to the obtention of the desired final heterocycles **47a-d** in excellent yields and optical purities, indicating that both Pictet-Spengler and PPA-catalyzed cyclizations proceed without racemization in any of the stereogenic centres present in the molecule. The last cyclization step showed to be highly diastereoselective as only one of the two possible epimers could be observed by $^1$H-NMR. The stereochemistry of this newly created stereogenic centre was assigned to be \((S)\) as nOe difference experiments indicated.

Another approach to the benzo[c]phenanthridine skeleton could be the one envisaged in Scheme 50. As it can be seen in this scheme, the heterocyclic skeleton would be built up from a 2-aryl-1-naphtylamine which could be prepared by reductive amination of a chiral 2-tetralone. This ketone should be available in an enantiopure form by using our methodology of diastereoselective alkylation of \((S,S)-(+)\)-pseudoephedrine based arylacetamides.

The synthesis starts with the alkylation of the arylacetic based \((S,S)-(+)\)-pseudoephedrine amides **31a-c** with 2-aryl-1-iodoethane derivatives yielding the final products in good yields and excellent stereoselectivities (Scheme 51). The amides **48a-d** were hydrolized to the corresponding acids **49a-d** and subjected to intramolecular Friedel-Crafts acylation reaction, yielding the wanted 2-aryl tetralones **50a-d** in more than 99% enantiomeric excesses, as chiral HPLC analysis showed. Again, the selected Lewis acid employed to activate the acyl chloride in the acylation reaction was critical and in the cases where methylenedioxy bridges were present in the substrates, the commonly used AlCl$_3$ had to be changed for the milder SnCl$_4$ Lewis acid.

Proceeding with the synthesis, the tetralones **50a-d** were subjected to the subsequent stereocontrolled reductive amination procedure and the wanted amines **51a-d** were obtained as the only detectable syn diastereoisomer from the two possible ones, concerning to the newly created stereogenic centre. Again, careful temperature control was necessary during all this procedure as when reaching temperatures over -20 °C epimerization was observed on the stereogenic centre of the starting tetralone.

The so obtained 2-aryl-1,2,3,4-tetrahydro-1-naphtylamines **51a-d** were subjected to a standard Pictet-Spengler cyclization procedure yielding the target heterocycles **52a-d** in high yields. The relative stereochemistry of the newly created stereogenic centre during the reductive amination step was determined.
as cis by NOe difference spectroscopy experiments which also makes the stereochemistry of the B/C ring junction in the final benzo[c]phenanthridines to be cis and therefore the absolute stereochemistry of the stereogenic centres in the final heterocycles 52a-d could be assigned as (4bR, 10bS).

Reagents and conditions: (i) 1. LDA, THF, -78 °C; 2. ArCH₂CH₂I. (ii) 9M H₂SO₄, dioxane refl. (iii) 1. SOCl₂, CH₂Cl₂, refl.; 2. AlCl₃ or SnCl₄, CH₂Cl₂, -20 °C. (iv) 1. BnNH₂, TiCl₄, Et₃N, CH₂Cl₂, -20 °C; 2. NaBH₄, MeOH, -20 °C. (v) HCHO, 1M HCl, 60 °C.

Scheme 51

The determination of enantiomeric purities by chiral HPLC analysis showed that all the products were >99% ee, which also indicates that all the synthetic steps proceed without any racemization especially, concerning to the very racemization prone benzylic carbon atom in the tetralones 49a-d.

5. Concluding remarks

The β-aminoalcohols (S)-phenylglycinol and (S,S)-pseudoephedrine have shown to be excellent chiral starting materials for the asymmetric synthesis of differently substituted 1,2,3,4-tetrahydroisoquinolines. In most cases, the synthesis involves a common 2-arylethylamine precursor which, upon Pictet-Spengler cyclization furnishes the final isoquinolines. Therefore, depending upon the nature of this key synthetic intermediates 3-aryl, and 1,3-cis or 1,3-trans 1-methyl-3-aryl tetrahydroisoquinolines can be prepared from amines 3, 4-alkyltetrahydroisoquinolines from amines 23 and 4-alkyl-3-aryl substituted derivatives from amines 40. Besides, additional synthetic procedures have been found for the conversion of some of these precursors into naturally occurring alkaloids like isopavines, protoberberines and benzo[c]phenanthridines.

On the other hand, a general and straightforward procedure has been settled up for the synthesis of 3-aryltetrahydroisoquinolines with any desired substitution pattern at any of the aromatic rings present in their structure by means of a chiral version of the Pommeranz-Fritsch cyclization and using arylglycinols 35 (also prepared with the help of (S,S)-pseudoephedrine as chiral auxiliary) as very versatile chiral building blocks.

Acknowledgments

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When the $^1$H-NMR spectra were carried out in CDCl$_3$, equilibrium mixtures of the imines 2 and the corresponding tautomeric oxazolidines were observed, whereas the $^1$H-NMR in CD$_2$OD showed resonances for only the open chain structures. For studies in imine-oxazolidine tautomerism see: (a). Lambert, J. B.; Majchrzak, M. W. J. Am. Chem. Soc. 1980, 102, 3588. (b) Lázár, L.; Lakatos, A. G.; Fülöp, F.; Bernáth, G.; Riddell, F. G. Tetrahedron. 1997, 53, 1081 and references therein.


STEREOSELECTIVE SYNTHESIS OF NITROGEN HETEROCYCLES OF ENANTIOPURE 3-HYDROXY ESTERS THROUGH ELECTROPHILIC AMINATION

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Abstract. The electrophilic amination of enantiopure 3-hydroxy esters with azocarboxylates leads to anti 2-hydrazino 3-hydroxy esters which are versatile building-blocks for the stereoselective synthesis of nitrogen heterocycles.

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1. Introduction

The electrophilic amination of carbanions allows the preparation of a wide range of amines through unconventional C-N bond-forming reactions. Carbon-nitrogen bonds are usually formed by attack of a nucleophilic nitrogen atom at an electrophilic carbon bearing a leaving group via S\textsubscript{N}2 type reaction. A major limitation is the difficult access to electrophilic precursors, particularly for multifunctional derivatives.

The reverse process, electrophilic amination, constitutes an example of «Umpolung» methodology for the direct introduction of an amino group into organometallic compounds.\textsuperscript{1} It is now an important synthetic process to create C-N bonds, and stereoselective C-N bond forming reactions have been developed based on the addition of chiral carbon nucleophiles to «neutral» aminating agents.
Azodicarboxylates are efficient sources of positive nitrogen as synthetic equivalent of an \([\text{NH-NH}_2]^+\) synthon. They were used in the stereoselective synthesis of \(\alpha\)-hydrazino and \(\alpha\)-amino acids starting from chiral enolates.\(^2\) Di-\(t\)-butyl\(^1\) and dibenzyl\(^4\) azodicarboxylates are the most commonly used reagents for diastereoselective electrophilic amination. Both compounds are commercially available.

The following account discusses recent advances in the area of electrophilic amination of enantiopure 3-hydroxy esters and related compounds such as 1,3-dioxan-4-ones. \textit{Anti} 2-hydrazino-3-hydroxyesters are obtained with high diastereoselectivity by this method (Scheme 1).

![Scheme 1](image)

These compounds could be functionalized on the side chain (X: CH=CHR, CH(OMe)\(_2\), CH\(_2\)OR) and are synthetic precursors of nitrogen heterocycles.

2. Diastereoselective synthesis of \textit{anti} 2-hydrazino 3-hydroxy esters

2.1. Electrophilic amination of 1,3-dioxan-4-ones

1,3-Dioxan-4-ones are well known substrates for diastereoselective alkylation reactions developed by Frater\(^5\) and Seebach.\(^6\) These chiral compounds have been also aminated at the \(\alpha\)-carbon with high stereoselectivity.

Thus, 1,3-dioxan-4-ones 1 were deprotonated and the resulting enolates were exposed to di-\(t\)-butylazodicarboxylate (DTBAD) at \(-78^\circ\text{C}\). The ensuing electrophilic amination afforded the corresponding \textit{trans} adducts 2 in good yields and high diastereomeric excesses >95\% (Scheme 2).

![Scheme 2](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH(_3)</td>
<td>CH(_2)CH(_2)Ph</td>
<td>95</td>
</tr>
<tr>
<td>b</td>
<td>CF(_3)</td>
<td>(t)-Bu</td>
<td>57</td>
</tr>
<tr>
<td>c</td>
<td>CH(_3)</td>
<td>H</td>
<td>90</td>
</tr>
<tr>
<td>d</td>
<td>C(<em>9)H(</em>{11})</td>
<td>H</td>
<td>66</td>
</tr>
</tbody>
</table>

b: \(t\)-BuLi as base; de>98%

The \textit{trans} 2-hydrazino-1,3-dioxan-4-ones 2 are precursors to \textit{anti} 2-amino-3-hydroxy acids: optically pure \(D\)-allothreonine was obtained from 2a after acidic deprotection and hydrogenolysis\(^7\) and \(L\)-trifluoro allothreonine methyl ester has been synthetized from 2b using a related approach.\(^8\)
An additional bulky group on the dioxanone moiety was not required for stereoinduction and excellent diastereomeric excesses were also obtained starting from 1,3-dioxan-4-ones derived from paraformaldehyde (R = H) 1c and 1d.9

2.2. Electrophilic amination of 3-hydroxy esters

The electrophilic amination of enantiopure 3-hydroxy esters occurred with anti selectivity.

3-Hydroxy esters 3 were deprotonated with excess LDA and the resulting β-oxidoenolates reacted rapidly with DTBAD at low temperature to give an easily separable mixture of syn and anti adducts 4 in which the anti diastereomer was the major compound (Scheme 3).7,10 The adducts are very useful intermediates since compounds with anti stereochemistry are not easily accessible by other established methods for α-amino β-hydroxy acids synthesis.

![Scheme 3](image)

The moderate diastereoselectivities observed in the electrophilic amination of 3-hydroxy esters with DTBAD may be due to the weakly chelated nature of the intervening dianion. Improved diastereoselectivities may be obtained by stabilizing the chelated form of the dianion with suitable organometallic species.9 Thus, deprotonation of 3 with LDA in the presence of MeZnBr gave exclusively the anti aminated product 4 (d.e.>98%) in chemical yields up to 70%, using DTBAD or dibenzylazodicarboxylate (DBAD) as aminating agents (Scheme 4).

Functionalized 3-hydroxy esters 3e-h were obtained quantitatively with excellent enantiomeric excesses (>98%) by hydrogenation of β-ketoesters in the presence of chiral ruthenium catalysts. This convenient methodology gives either optical antipodes with equal ease, depending on whether the (R) or (S) atropoisomer of the ligand is used in the metal complex.11
By coupling the two sequential reactions, catalytic hydrogenation and electrophilic amination, a general and practical method for the preparation of both enantiomers of \textit{anti}-2-hydrazino-3-hydroxy esters \((R,R)-4\) and \((S,S)-4\) from the corresponding \(\beta\)-ketoesters \(6\) has been proposed (Scheme 5).

\begin{scheme}
\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & \(R^1\) & \(R^2\) & \(R\) & Yield (%) \\
\hline
a & CH\(_3\) & C\(_2\)H\(_5\) & \(t\)-Bu & 63 \\
b & C\(_2\)H\(_5\) & \(t\)-Bu & 58 \\
c & C\(_5\)H\(_{11}\) & \(t\)-Bu & 66 \\
d & Ph & \(t\)-Bu & 70 \\
e & EtCH=CH & \(t\)-Bu & 53 \\
f & Me\(_2\)C=CH-CH\(_3\) & \(t\)-Bu & 55 \\
g & (MeO)\(_2\)CH-CH\(_2\) & PhCH\(_3\) & 66 \\
h & (MeO)\(_2\)CH & PhCH\(_3\) & 66 \\
\hline
\end{tabular}
\end{center}
\end{scheme}

By coupling the two sequential reactions, catalytic hydrogenation and electrophilic amination, a general and practical method for the preparation of both enantiomers of \textit{anti}-2-hydrazino-3-hydroxy esters \((R,R)-4\) and \((S,S)-4\) from the corresponding \(\beta\)-ketoesters \(6\) has been proposed (Scheme 5).

\begin{scheme}
\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
& \(5\) & \(\text{cat : (R)-L}-2^*\text{RuBr}_2\) & \(\text{1) hydrogenation}\) \\
& & & \(\text{2) electrophilic amination}\) \\
\hline
& & & \(\text{cat : (S)-L}-2^*\text{RuBr}_2\) \\
\hline
\hline
& & & \(\text{cat : (R)-L}-2^*\text{RuBr}_2\) \\
& & & \(\text{1) hydrogenation}\) \\
& & & \(\text{2) electrophilic amination}\) \\
\hline
\end{tabular}
\end{center}
\end{scheme}

These 2-hydrazino-3-hydroxy esters \(4\) were used as chiral building blocks for the synthesis of functionalized nitrogen heterocycles.

3. Syntheses of nitrogen heterocycles

3.1. Six-membered rings

3.1.1. \((3S, 4S)-4\)-Hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid

\((3S, 4S)-4\)-Hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid \(6\) is an unusual amino acid constituent of Luzopeptin A. Luzopeptin A was isolated from \textit{Actinomadura luzonensis} and is a dimeric cyclic depsipeptide constituted by six amino acids.\(^{13}\) It is an antibiotic antitumor agent and a bis-intercalator of DNA. The first synthesis of \(6\) has been reported starting from malonaldehyde dimethylacetal \textit{via}
Sharpless epoxidation and subsequent C-2 ring opening of the epoxyacid with hydrazine.\textsuperscript{14} More recently, the synthesis, chemistry and conformational properties of piperazic acids have been reviewed.\textsuperscript{15}

An efficient synthesis of 6 has been developed starting from (E)-methyl-3-oxooct-5enoate 5e (Scheme 6) and using the sequential reactions: enantio and chemoselective hydrogenation catalyzed by (S)-Biphemp Ru Br\textsubscript{2} at low pressure and diastereoselective electrophilic amination with DTBAD.\textsuperscript{16}

The 2-hydradino-3-hydroxy ester 4e presented a double bond at C-5 as a masked aldehyde necessary for the hydrazone formation. The N,N,O-protected compound 7 was converted to 2,3,4,5-tetrahydropyridazine 8 without purification of the intermediates. The ozonolysis was conducted under reductive conditions to give the corresponding aldehyde and the acidic treatment produced in one pot the cyclic product 8. To achieved the synthesis of (3S, 4S)-6, the silyl ether was deprotected and the ester saponified.

More recently, a shorter formal synthesis of (3R, 4R)-6 was published starting from methyl 5,5-dimethoxy-3-oxopentanoate 5g (Scheme 7).\textsuperscript{17} This C-5 acetal functionalized β-ketoester presented two symmetrical oxygens in γ positions to the carbonyl group: this could modify the chelation of the ruthenium complex and influence the enantioselectivity of the hydrogenation.

The hydrogenation was performed at room temperature and atmospheric pressure using 2 mol % of (R)-Binap Ru Br\textsubscript{2} generated \textit{in situ}.\textsuperscript{18} Methanol was used as solvent to avoid secondary reactions such as transacetalisation and transesterification. Under these mild conditions, the corresponding 3-hydroxy ester 3g was obtained with excellent enantiomeric excess (>95%). The diastereoselective amination was carried out with DBAD as electrophilic agent because the conditions of deprotection of a benzyl carbamate are compatible with the presence of an acetal function.

The (3R, 4R)-4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic methyl ester 9, which is the direct precursor of (3R, 4R)-6, was obtained quantitavely after hydrogenolysis of the carbamates and treatment of the crude deprotected product with aqueous trifluoroacetic acid.
3.1.2. Trans 3-hydroxypipecolic acid and application to (-)-swainsonine

Syntheses of polyhydroxypipecolic acids have been previously reported and these compounds have been screened as potential inhibitors of HIV replication. Surprisingly, the synthesis of 3-hydroxypipecolic acid is less well documented, although enantioselective preparations of the cis diastereomer have been reported. The first enantioselective synthesis of the trans diastereomer 10 was described starting from methyl 7-methyl-3-oxooct-6-enoate 5f via the 2-hydrazino-3-hydroxy ester 4f as key intermediate (Scheme 8). Later, others synthetic routes were described for the trans 3-hydroxypipecolic acid.

The β-ketoester 5f was hydrogenated under mild conditions in presence of (R)-Binap Ru Br₂ catalyst. This reaction at atmospheric pressure was highly enantioselective and completely chemoselective: the reduction of the carbonyl group was only observed without any hydrogenation of the double bond at C-6. After electrophilic amination of the resulting 3-hydroxy ester with DTBAD, the 2-hydrazino-3-hydroxy ester 4f was obtained with excellent enatio and diastereomeric excesses. After protection of the hydroxy group as a silyl ether, the double bond was easily transformed into a primary alcohol, which was mesylated without further purification to give compound 11 in 65% overall yield. The introduction of a primary amino group at C-2 was achieved by acidic hydrolysis of the t-butyl carbamates and hydrogenolysis of the hydrazine in

\[ \text{MeO} \quad \text{CO}_2\text{Me} \quad \text{O} \quad \text{MeO} \quad \text{CO}_2\text{Me} \quad \text{MeO} \quad \text{OH} \quad \text{CO}_2\text{Me} \quad \text{MeO} \quad \text{OH} \quad \text{CO}_2\text{Me} \quad \text{MeO} \quad \text{OH} \quad \text{CO}_2\text{Me} \]

\[ \text{(a), (b)} \quad \text{(c), (d)} \quad \text{(3R, 4R)-9} \]

Scheme 7

\[ \text{5g} \quad \text{OMe} \quad \text{CO}_2\text{Me} \quad \text{OMe} \quad \text{OH} \quad \text{CO}_2\text{Me} \quad \text{CbzN-HCbz} \]

Scheme 8
presence of Raney-Ni under ultrasounds. Under these conditions, partial cyclisation was observed and completion of the ring closure occurred in presence of triethylamine. The \((2R, 3R)-3\)-hydroxy piperolic acid \(5f\) was obtained after deprotection of the silyl ether and saponification of the methyl ester.

The compound \(12\) has the same \textit{trans} relationship than the piperidine ring of \((-\)-swainsonine \(13\) and was used as precursor for its total synthesis. Since its initial isolation from the \textit{fungus Rhizoctonia leguminicola}, \(13\) has aroused considerable interest due to its potent and highly specific \(\alpha\)-D-mannosidase inhibitory activity, immunoregulative properties and antimitastatic activity. Most of the previously reported methodologies utilized the chiral pool as starting material. Other approaches employed the Sharpless asymmetric epoxidation and the Masamune/Sharpless iterative methodology or kinetic resolution and the Sharpless asymmetric dihydroxylation.

Starting from the compound \(12\), the synthetic goals were achieved through homologation of the ester function and dihydroxylation of the resulting double bond (Scheme 9).

\[
\begin{align*}
12 & \xrightarrow{(a), (b), (c)} 14 \xrightarrow{(d)} 15 \xrightarrow{(e)} 16 \xrightarrow{(f), (g), (h)} 17 \xrightarrow{(i)} 13
\end{align*}
\]

(a) CbzCl, DMAP, CH\(_3\)CN (74%); (b) Ca(BH\(_4\))\(_2\) (91%); (c) i. (COCl)\(_2\), DMSO, CH\(_2\)Cl\(_2\), ii. Et,N then H\(_2\)O (100%); (d) (CF\(_3\)CH\(_2\))\(_2\)P(O)CH\(_2\)CO\(_2\)Me, K\(^+\), 18-crown-6 (83%, \(Z/E = 19:1\)); (e) OsO\(_4\), Me\(_3\)NO, ultrasounds (71%); (f) H\(_2\), Pd/C, MeOH (90%); (g) CH\(_2\)CH(OMe)\(_2\), Dowex H\(^+\) (97%); (h) BH\(_3\)-Me\(_2\)S (81%); (i) HCl, 1M then Dowex OH\(^-\) (96%)

\(\text{Scheme 9}\)

The piperidine \(12\) was first protected as a benzyl carbamate, the ester was reduced with Ca(BH\(_4\))\(_2\) and the corresponding alcohol was then oxidized to the aldehyde \(14\) under classical Swern conditions. The formation of the double bond was run under kinetic control using Still’s reagent to afford the \(Z\)-alkene \(15\) as the major stereomer (\(Z/E = 19:1\)). The \(Z/E\) mixture was not separable and the dihydroxylation proceeded smoothly under ultrasounds with catalytic osmium tetroxide and trimethylamine \(N\)-oxide as cooxidant. The desired optically pure diastereomer \(16\) was separated from the mixture by flash chromatography and isolated in 71% yield. The stereochemistry of \(16\) was correlated with those of the known compounds \(17\): cleavage of the benzyl carbamates provided the bicyclic lactam, protection of the 1,2-diol into acetonide by treatment with 2,2-dimethoxypropane in presence of an acidic ion exchange resin, cleaved simultaneously the silyl ether and reduction of the lactam with BH\(^-\)-Me\(_2\)S, gave the known product \(17\). The \((1S, 2R)\) configuration was confirmed at this stage. Finally deprotection of the acetonide produced \((-\)-swainsonine \(13\).

318
3.2. Five-membered rings

3.2.1. Trans 3-hydroxy-D-proline

Trans 3-hydroxy-L-proline is a constituent of naturally occurring peptides and has been isolated from mediterranean sponge and collagen hydrolysates. Several synthesis of trans 3-hydroxyproline and of its reduced form: trans 3-hydroxyprolinol have been developed in the literature starting from chiral sources.

The stereocontrolled synthesis of the unnatural trans 3-hydroxy-D-proline 18 has been described in six steps with 33% overall yield from the prochiral β-ketoester 5g. The key intermediate is the richly functionalized (2R, 3R) methyl 2-amino-5,5-dimethoxy-3-hydroxypentanoate 19 which presented three oxygenated groups at different oxidation degrees: an alcohol, an acetal and an ester. Its enantiomer, the (2S, 3S)-19 has been also synthetized from 5g through catalytic hydrogenation and electrophilic amination (Scheme 10). These two anti diastereomers are chiral building blocks which should be useful for the synthesis of various 2-amino-3-hydroxy acids of either L or D configurations.

Recently, the synthesis of N,O-diprotected 19 has been reported via aza-Achmatowicz reaction.

\[\text{MeO} - \text{OMe} - \text{OH} - \text{CO}_2\text{Me} \quad \text{MeO} - \text{OH} - \text{CO}_2\text{Me} \]

(2S, 3S)-19 (2R, 3R)-19

Scheme 10

The synthesis of the trans 3-hydroxy-D-proline 18 was developed from the 2-hydrazino-3-hydroxyester 4g (Scheme 11) obtained from the β-ketoester 5g as shown in 3.1.1. The principal step was the cleavage of the hydrazine bond.

The hydroxyl function was first protected as t-butyldimethylsilyl ether. After hydrogenolysis of the benzyl carbamates, classical conditions as H₂, PtO₂ or H₂, Raney Ni under ultrasounds were used to generate the amine, but degradation of the substrate was observed and no product could be isolated. Deprotection and cleavage of the hydrazine were run simultaneously: 20 was exposed to H₂ in presence of PtO₂-H₂O in methanol and 45% of the 2-aminoester 21 was recovered. Using a 1/1 mixture of methanol-water as solvent for these reactions, the yield increased to 71% of purified compound 21. This one pot deprotection-cleavage of the N-N bond of a diprotected hydrazine derivative is very efficient. The cyclisation to the proline ring was performed using aqueous trifluoroacetic acid and the silyl ether was cleaved under these conditions. The resulting iminium was reduced in situ by H₂ in presence of PtO₂-H₂O. The trifluoroacetic salt of methyl trans-hydroxy-D-proline 22 was obtained as a crude product and the methyl ester was saponified without further purification. After elution through an ion exchange resin column, the (2R, 3R)-trans-3-hydroxyproline 18 was isolated as a white solid.

3.2.2. (4S, 5R)-5-Carbomethoxy-4-hydroxy-Δ²-pyrazoline

A large number of Δ²-pyrazolines has been described in the literature due to their synthetic accessibility and important applications. Δ²-pyrazolines are also known for their biological activity as antinflammatory compounds. Procedures to obtain these systems in enantiomerically pure form are of great interest. Thus, Δ²-pyrazolines could be used as chiral precursors in the preparation of several heterocyclic
derivatives and as building blocks for the asymmetric synthesis of functionalized chiral acyclic synthons.\(^{35}\) Recently, two routes to enantiomerically pure \(\Delta^2\)-pyrazolines were reported: a diastereoselective dipolar cycloaddition reaction of \(\text{Me}_3\text{SiCHN}_2\) to optically active enoates\(^ {36}\) and a reaction of diazo compounds with alkenyl Fischer carbenes derived from chiral alcohols.\(^ {37}\)

\[
\begin{align*}
4g & \xrightarrow{(a)} \quad \text{OMe} & \quad \text{OTBDMS} & \quad \text{MeO} & \quad \text{CbzN-NHCbz} \\
& \quad \text{MeO} & \quad \text{CO}_2\text{Me} & \quad (b) & \quad \text{OMe} & \quad \text{OTBDMS} & \quad \text{MeO} & \quad \text{NH}_2 \\
& \quad \text{CbzN-NHCbz} & \quad \text{CO}_2\text{Me} & & \quad & \quad \text{NH}_2 & \quad \Theta & \quad \Theta \\
& \quad \Theta & \quad \Theta & \quad \Theta & \quad \Theta & \quad \Theta & \quad \Theta & \quad \Theta \\
\end{align*}
\]

(a) TBDMSOTf, 2,6-lutidine, \(\text{CH}_2\text{Cl}_2\), (96%); (b) \(\text{H}_2\), \(\text{PtO}_2\cdot\text{H}_2\text{O}\), \(\text{MeOH}-\text{H}_2\text{O}\) (1/1), r.t. (71%); (c) TFA, \(\text{H}_2\text{O}\), \(\text{H}_2\); \(\text{PtO}_2\cdot\text{H}_2\text{O}\); (d) KOH, \(\text{MeOH}-\text{H}_2\text{O}\), Dowex 50x4 (84% from 27)

**Scheme 11**

A concise and stereoselective synthesis of the chiral functionalized (4\(S\), 5\(R\))-5-carbomethoxy-4-hydroxy-\(\Delta^2\)-pyrazoline 23 was reported recently\(^ {38}\) (Scheme 12). 23 was obtained in four steps from the \(\beta\)-ketoester 5h in 38% overall yield.

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} & \quad (a), (b) & \quad \text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{MeO} & \quad \text{CbzN-NHCbz} & \quad (c), (d) & \quad \text{MeO} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

(a) \(\text{H}_2\), 1 mol\% [(R)-Binap \(\text{Ru Cl}_2\)], Et\(_3\)N, 1 atm., \(\text{MeOH}\), 65 °C, 18h. (83%, ee=90%); (b) i. \(\text{MeZnBr}\), ii. LDA, iii. DBAD (66%, de>95%); (c) \(\text{H}_2\), Pd/C, \(\text{MeOH}\) (quant.); (d) TFA (70%).

**Scheme 12**

The \(\beta\)-ketoester 5h was prepared by a two carbon homologation of methyl 2,2-dimethoxyethanoate using the Masamune procedure.\(^ {39}\) The highly functionalized chiral C-4 synthon 4h was produced by hydrogenation at atmospheric pressure of 5h in presence of 1 molecular % of [(R)-Binap \(\text{Ru Cl}_2\)\(_2\)-Et\(_3\)N]\(^ {40}\) and electrophilic amination of the resulting 3-hydroxy ester with DBAD. The use of (R)-Binap \(\text{Ru Br}_2\) for the asymmetric hydrogenation step was not successful and secondary reactions were observed giving methyl-3,4-dihydroxybutanoate and hydroxy-\(\delta\) lactone as side products. The cyclisation was performed after hydrogenolysis of the benzyl carbamates, by treatment of the crude product with trifluoroacetic acid at room temperature.
3.3. Four-membered rings

An efficient entry into cis monobactams has been reported.\textsuperscript{41} This synthetic approach is based on the diastereoselective electrophilic amination of 3-hydroxy esters and on Miller’s biomimetic synthesis of the β-lactam nucleus.\textsuperscript{42} Since 4-substituted monobactams are not accessible through microbiological methods, their preparation requires the development of total syntheses of the corresponding 3-amino monobactamic acids (3-AMA). The monobactams units: cis 4-methyl-3-AMA 24 and cis 4-carbamoyloxymethyl-3-AMA 25 of pharmacologically important cis aztreonam and carumonal, were prepared by this route.

3.3.1. Cis 4-methyl-3-AMA

The synthesis of cis 4-methyl-3-AMA 24 requires the quite expensive anti α-amino β-hydroxy acid: L-allothreonine as starting material (Scheme 13). The electrophilic amination of (S) ethyl 3-hydroxybutanoate 3a with DTBAD furnished the anti compound 4a which is a very useful building block for the synthesis of 24.

\[
\begin{align*}
\text{OH} & \quad \text{CO}_2\text{Et} \quad (a) \quad \text{OH} & \quad \text{CO}_2\text{Et} \quad (b) \quad \text{OH} & \quad \text{NHOBn} \\
3a & \quad \text{BocN-NHBoc} & 4a & \quad \text{BocN-NHBoc} & 26
\end{align*}
\]

(a) i. LDA, ii. DTBAD (75%, de=68%); (b) i. LiOH, ii. BnONH\textsubscript{2}.HCl (80%); (c) DEAD, PPh\textsubscript{3} (90%); (d) i. H\textsubscript{2}, Pd/C, EtOH, ii. TiCl\textsubscript{3}, H\textsubscript{2}O-MeOH (69%); (e) i. SO\textsubscript{3}.py, py. ii. n-Bu\textsubscript{4}NHSO\textsubscript{4}; iii. silica gel chromatography (96%); (f) TFA, CH\textsubscript{2}Cl\textsubscript{2}; (g) H\textsubscript{2}, PtO\textsubscript{2}, EtOH; (h) PhOCH\textsubscript{2}COCl, Et\textsubscript{3}N, DMF (52% from 28)

Scheme 13

The ester 4a was converted into the O-benzylhydroxamate 26 by saponification and coupling with O-benzylhydroxylamine. Cyclisation to the β-lactam 27 proceeded under Mitsunobu conditions. After removal of the benzyl protecting group, reductive cleavage of the N-OH bond was performed using TiCl\textsubscript{3}. The resulting azetidinone was sulfonated with pyridine-SO\textsubscript{3} complex to give the azetidine sulfonic acid 28. Finally the hydrazine was deprotected with trifluoroacetic acid and hydrogenated over PtO\textsubscript{2}. Cis 4-methyl-3-AMA 24 was obtained in 17% overall yield which is comparable with that obtained in the previous synthesis starting from L-allothreonine.\textsuperscript{42}

3.3.2. Cis 4-carbamoyloxymethyl-3-AMA

In order to obtain intermediates useful for the synthesis of carumonam, it is necessary to start from (R) methyl 3,4-dihydroxybutanoate selectively protected at the primary alcohol which can be prepared from commercially available (R) dimethyl malate 29, via regioselective reduction of the C-1 carboxylic methylester (Scheme 14).\textsuperscript{44}
If the primary alcohol was protected as a silyl ether 30a, the electrophilic amination step occurred with only moderate diastereoselectivity. An alternative route was developed using a trityl ether as protecting group. Furthermore, the stability of compound 30b under basic conditions allowed the use of higher reaction temperatures in the dianion formation, as well as in the condensation with DTBAD. In this case the diastereoselectivity was excellent. The β-lactam 32 was obtained by intramolecular Mitsunobu reaction after conversion of the ester into O-benzylhydroxamate. The primary alcohol was then selectively deprotected, the benzyl group hydrogenolysed and the N-OH bond reduced to afford 33. The removal of the t-butoxycarbonyl groups was carried out with trifluoroacetic acid and the resulting hydrazine salt directly hydrogenolysed. After in situ protection of the free amine, the hydroxyl group was converted into the corresponding carbamate 25.

This synthetic route constitutes a formal synthesis of carumonam which has been obtained from 25 by a three steps sequence.45

4. Conclusion

2-Hydrazone 3-hydroxy esters are useful intermediates for the elaboration of nitrogen heterocycles. Electrophilic aminations were run on functionalized 3-hydroxy esters with side chains bearing a double bond, an acetal function or a silyl ether and the anti adducts were obtained with high diastereomeric excesses. They were used as building-blocks for the synthesis of six, five and four membered rings as 2,3,4,5-tetrahydropyridazines, piperidines, Δ2-pyrazoline, pyrrolidine and β-lactams.

References


**RECENT TRENDS IN SYNTHESIS OF HETEROCYCLES USING KETENE DITHIOACETALS WITH ELECTRON ATTRACTING GROUPS**

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**Abstract.** New approaches for synthesis of different mono and polyheterocyclic derivatives utilising ketene dithioacetals are surveyed. The scope and limitation of the most important of these approaches are demonstrated.

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1. **Introduction**
   
   Interests in the field of ketene dithioacetals in heterocyclic synthesis are very high. It has been found that ketene dithioacetals are versatile reagents, which have been extensively utilized in the synthesis of many analogues of purine base, nucleosides and pyrimidines.\textsuperscript{1-81} Moreover the biological aspects of such class of compounds have been also the subject of a large number of publications as antimalarial activity and for the destruction of harmful organisms.\textsuperscript{5,48}

2. **Synthesis**
   
   Ketene dithioacetals 3a-u were obtained by the reaction of the corresponding active methylene compounds 1a-u with carbon disulfide in the presence of a base to give sodium salt of ketene dithioacetals 2a-u followed by alkylation (Scheme 1).\textsuperscript{82-126}
3. Utility in heterocyclic synthesis

3.1. Five-membered rings

3.1.1. Five-membered rings with one hetero-atom

The reaction of ketene dithioacetals 3a,c with \( \alpha \)-aminoesters 4 in ethanol triethylamine mixture afforded compounds 5, which were cyclized to yield the 5-(methylthio)-3-aminopyrrole-2-carboxylates 6 (Scheme 2).\(^{127,128}\)

![Scheme 2](image)

It has been reported that the reaction of 3a with nitromethane gave the 2,5-dihydro-5-hydroxyimino-2-oxo-4-(methylthio)pyrrole-3-carbonitrile 7, which was readily converted to the corresponding 2,5-dihydro-
2,5-dioxo-4-(methylthio)pyrrole-3-carbonitrile 8, by methylation with dimethylsulfate followed by hydrolysis with hydrochloric acid (Scheme 3).\textsuperscript{129-131}

Recently, Elgemeie et al. have reported that the ketene dithioacetals 3q-u were treated with formamide in refluxing ethanol containing catalytic amount of piperidine to afford the 3-amino-5-(methylthio)pyrrole-2-ones 9 (Scheme 4).\textsuperscript{123}

![Scheme 4](image)

Cycloketene S,S- and N,S-acetals 10 reacted with dimethylfumarate 11 in the presence of cesium floride to yield the thiophene and pyrrole derivative 12, respectively (Scheme 5).\textsuperscript{132}

![Scheme 5](image)

The reaction of compound 3a with methylthioglycolate 13 gave the thiophene derivative 14 (Scheme 6).\textsuperscript{92,133}

![Scheme 6](image)

The 2-methylthio-4-aryliothiophenes 17, were prepared from \(\alpha\)-oxoketene dithioacetals 3m,n,p under Simmons-Smith reaction conditions through the intermediates 15, 16 (Scheme 7).\textsuperscript{134}

Bhat et al. have shown the synthesis of 3,4-anellated thiophenes 19, through Simmons-Smith reaction from cycloalkanone dithioacetals 18 (Scheme 8).\textsuperscript{134}

Also, the tricyclic thiophene derivatives 21 have been developed through Simmons-Smith reaction on benzocycloalkanone dithioacetals 20 (Scheme 9).\textsuperscript{134}
3.1.2. Five-membered rings with two hetero-atoms

Peseke has reported that the cycloaddition of ketene dithioacetals 3b,c with semicarbazide or thiosemicarbazide hydrochloride 22a,b in refluxing ethanol yielded the corresponding 5-aminopyrazole derivatives 23 (Scheme 10).135,136

He has also found that the reaction of dithietane derivative 24 with 4-nitrophenylhydrazine gave the substituted pyrazole 25, which was alkylated in the presence of methyl halide to yield the 5-amino-3-
methylthiopyrazoles 26. The latter compound 26 has been synthesized by the reaction of 3c with 4-nitrophenylhydrazine (Scheme 11).\textsuperscript{137}

![Scheme 11](image)

Treatment of compounds 3b,c with sulphonamide derivatives 27 in ethoxide gave ketene N,S-acetals 28. Compounds 28 were refluxed with hydrazine derivatives 29a,d,f to give the substituted 5-amino-3-arylsulfonylaminopyrazoles 30 (Scheme 12).\textsuperscript{138}

![Scheme 12](image)

Ketene-S,S-acetal 3l reacted with aniline derivatives 31 to give ketene-N,S-acetals 32, which were treated with hydrazine to yield compounds 33. The latters were cyclized with ethyl cyano(ethoxymethylene)acetate 34 to afford the corresponding 1-(2-nitrovinyl)pyrazole derivatives 35 (Scheme 13).\textsuperscript{139}

It has been found that the 5-amino-3-(methylthio)pyrazoles 36 were synthesized through the reaction of ketene dithioacetals 3a,d with hydrazine derivatives 29a-d in refluxing methanol (Scheme 14).\textsuperscript{140-144}

The furfurylaminopyrazole carboxylic acid ester 39 was prepared by treating 3c with furfurylmethylamine 37 to give compound 38, which cyclocondensed with hydrazine (Scheme 15).\textsuperscript{145}
Treatment of ketene dithioacetals 3b,c with furancarbohydrazides 40 formed compounds 41, which were cyclized with hydrazine to yield the corresponding pyrazole derivatives 42 (Scheme 16). 40

The alkylhydrazinocarbonyl(thiocarbonyl)pyrazolecarboxylates 45 were prepared by the reaction of 2-cyano-3-(2-cyanoethylthio)-3-methylthioacrylic acid esters 43 with either carbonohydrazides or thiocarbonohydrazides 44 (Scheme 17). 41

The 2-substituted 3-amino-3-(methylthio)acrylonitriles cyanoketene 46 were converted into its imino esters hydrochloride salts 47 when treated with dry ethereal hydrogen chloride, then compounds 47 reacted with phenylhydrazine to yield the 4-substituted 3,5-diaminopyrazoles 48 (Scheme 18). 42

When compound 3a was stirred in ethanol with trifluoromethylbenzylhydrazine 49 the pyrazole derivative 50 was produced (Scheme 19). 43

It has been reported that ketene-S,S-acetals 3a,d reacted with 1-ribofuranosylhydrazine 51 to give the interesting pyrazole nucleosides 52 (Scheme 20). 44

The reaction of ketene dithioacetals 3b,c with coumarins 53 has been extensively utilized for the synthesis of the pyrazolecarboxylate derivatives 54 (Scheme 21). 45

The 3-arylsulfonylaminoypyrazoles 56 were synthesized from the reaction of 3-arylsulfonylamino-3-methylthiocyanocrylates 55 with hydrazine derivatives 29b,e (Scheme 22). 46
The 5-amino-1-benzoyl-3-(methylthio)pyrazole derivatives 58 were obtained by the reaction of ketene-\(S, S\)-acetals 3c,d with hydrazides 57 (Scheme 23).\textsuperscript{156,157}
Recently, it has been reported that when compounds 3q-u were subjected to react with hydrazine derivatives 29a,b in refluxing ethanol containing catalytic amount of piperidine, the 5-amino-3-(methylthio)pyrazoles 59 were produced (Scheme 24).\textsuperscript{123}

\[
\begin{align*}
\text{H}_3\text{CS} \quad \text{CN} & \quad + \quad \text{H}_2\text{N-NHR} \quad \xrightarrow{\text{EtOH/pip.} \Delta} \quad \text{R} \quad \text{SCH}_3 \\
\text{3q-u} & \quad 29a,b \\
59 & \quad \begin{array}{cccc}
R & R^1 & Z & 59 \\
\text{a} & \text{C}_6\text{H}_5 & \text{H} & \text{O} & \text{C}_6\text{H}_5 & \text{O} \\
\text{b} & 4-\text{ClC}_6\text{H}_4 & \text{H} & \text{O} & 4-\text{ClC}_6\text{H}_4 & \text{C}_6\text{H}_5 & \text{O} \\
\text{c} & 4-\text{CH}_3\text{C}_6\text{H}_4 & \text{H} & \text{O} & 4-\text{CH}_3\text{C}_6\text{H}_4 & \text{C}_6\text{H}_5 & \text{O} \\
\text{d} & 4-\text{OCH}_3\text{C}_6\text{H}_4 & \text{H} & \text{O} & 4-\text{OCH}_3\text{C}_6\text{H}_4 & \text{C}_6\text{H}_5 & \text{O} \\
\text{e} & \text{H} & \text{H} & \text{S} & \text{H} & \text{C}_6\text{H}_5 & \text{S}
\end{array}
\end{align*}
\]

Scheme 24

Compound 3a reacted with 4-aminoantipyrine 60 to give antipyrine derivative 61; when the latter compound was treated with hydrazine, the 5-amino-3-(p-antipyrylamino)pyrazole-4-carbonitrile 62 was afforded (Scheme 25).\textsuperscript{158}

Recently, it has been shown that the substituted pyrazoles 64 were synthesized by the reaction of ketene-N,S-acetals 63 with hydrazine derivatives 29a,b (Scheme 26).\textsuperscript{159}

The condensation of 3a with hydrazine hydrate yielded the 5-amino-3-(methylthio)pyrazole-4-carbonitrile 65. Treatment of compound 65 with nitrous acid and then coupling with diethylamine yielded the 5-(3,3-diethyl-1-triazeno)pyrazole-4-carbonitriles 66 (Scheme 27).\textsuperscript{160}
The isoxazole derivative 67 was produced by the reaction of compound 3a with hydroxylamine hydrochloride (Scheme 28).161

Treatment of 3a with ammonia afforded 2-amino-2-(methylthio)methylene malononitrile 68. The latter reacted with N,N-dimethylaniline and hydrogen sulfide to give compound 69, which was cyclized oxidatively to give the 5-amino-3-dimethylaminoisothiazole-4-carbonitrile 70 (Scheme 29).99

The cyclization of 3-alkylthio-3-mercapto-2-cyanoacrylamides 71, by using sulphonyl chloride yielded the corresponding 5-alkylthio-3-oxoisothiazole-4-carbonitriles 72 (Scheme 30).162
It has been reported that ketene dithioacetal 3k reacted with diamine to give the cyclic heteroacetales 73 (Scheme 31).\(^{163}\)

The cyano-substituted heterocyclic ketene amidinals 75 were synthesized by the reaction of cyano-substituted ketene mercaptals 3a,b with diamines 74 (Scheme 32).\(^{164}\)

\[
\begin{align*}
\text{H}_3\text{CS} & \text{CN} \quad \text{H}_3\text{CS} \\
\text{Y} & \quad \text{H}_2\text{N}-\text{R} \quad \text{R} \\
^3a & \text{Y=CN} \\
b & \text{Y=CO}_2\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 32}
\end{align*}
\]

The reaction of ketene dithioacetals 3g-i with aliphatic diamine compounds 76 afforded the acetyl-substituted heterocyclic ketene amidinals 77 (Scheme 33).\(^{165}\)

\[
\begin{align*}
\text{H}_3\text{CS} & \text{COCH}_3 \quad \text{H}_3\text{CS} \\
\text{Y} & \quad \text{H}_2\text{N-(CH}_2\text{n}-\text{R} \quad \text{(CH}_2\text{n})_n \times \\
3g-i & 76 \quad a, n=2 \\
b, n=3 \\
77 & Y \quad R \\
a & \text{COCH}_3 \quad \text{H} \\
b, e & \text{CO}_2\text{CH}_3 \quad \text{CH}_3 \\
c & \text{CO}_2\text{C}_2\text{H}_5 \quad \text{CH}_3 \\
d & \text{COCH}_3 \quad \text{COCH}_3
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 33}
\end{align*}
\]

The imidazolidine derivatives 79 were prepared by the reaction of ketene-\(S, S\)-acetals 3a,c,l,g with diethylene triamine or 2-(2-aminoethylamino)ethanol 78 in tetrahydrofuran (Scheme 34).\(^{166,167}\)

\[
\begin{align*}
\text{H}_3\text{CS} & \text{X} \quad \text{H}_3\text{CS} \\
\text{Y} & \quad \text{H}_2\text{N-(Z)-H} \quad \text{THF} \\
3a,c,l,g & 78 \\
79 & X \quad Y \quad Z \\
a & \text{CN} \quad \text{CN} \quad \text{NH} \\
b & \text{CN} \quad \text{CN} \quad \text{O} \\
c & \text{CN} \quad \text{CO}_2\text{C}_2\text{H}_5 \quad \text{O} \\
d & \text{H} \quad \text{NO}_2 \quad \text{O} \\
e & \text{COCH}_3 \quad \text{COCH}_3 \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 34}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{CS} & \text{CN} \quad \text{H}_3\text{CS} \\
\text{Y} & \quad \text{H}_2\text{N}-(\text{Z})-\text{H} \quad \text{Y} \\
3a-c & 80 \\
81 & X \quad Y \quad Z \\
a & \text{Y=CN} \\
b & \text{Y=CO}_2\text{CH}_3 \\
c & \text{Y=CO}_2\text{C}_2\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 35}
\end{align*}
\]
The synthesis of the previously unknown spiro heterocyclic ketene aminals, 3,9-bis(substituted-methylene)-2,4,8,10-tetraazaspiro[5.5]undecane 81 by the cyclocondensation reaction of ketene dithioacetals 3a-c with tetrakis(aminomethyl)methane 80 was carried out (Scheme 35). 168

The cyclic heteroacetale derivative 82 was prepared by the reaction of compound 3k with α-phenylenediamine (Scheme 36). 163

\[
\text{H}_3\text{CS} \quad \text{COC}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5\text{NH}_2 \quad \rightarrow \quad \text{H}_3\text{CS} \quad \text{COC}_6\text{H}_5
\]

Scheme 36

The synthesis of acyclic C-nucleosides 84 were obtained through the reaction of ketene dithioacetals 3a,c with 1-deoxy-1-(methylamino)-D-hexitols 83 (Scheme 37). 169

\[
\text{H}_3\text{CS} \quad \text{COC}_6\text{H}_5 \quad + \quad \text{CH}_2\text{NHCH}_3, \text{EtOH} \rightarrow 30 \text{min.} \quad \left[ \begin{array}{c}
\text{CH}_2\text{OH} \\
\text{N} \\
\text{CH}_3
\end{array} \right] \quad \text{H}_3\text{CS} \quad \text{COC}_6\text{H}_5 \quad \left[ \begin{array}{c}
\text{CH}_2\text{OH} \\
\text{N} \\
\text{CH}_3
\end{array} \right]
\]

Scheme 37

It has been reported that the reaction of compounds 3a,c,d with 2-amino-1-aryl-propane-1,3-diols 85 afforded the 1,3-oxazolidines 86 (Scheme 38). 170,171

\[
\text{H}_3\text{CS} \quad \text{COC}_6\text{H}_5 \quad + \quad \text{H}_2\text{NCH}_2\text{OH} \quad \rightarrow \quad \text{H}_3\text{CS} \quad \text{COC}_6\text{H}_5
\]

Scheme 38

Huang and Zhang have found that ketene dithioacetals 3g,p reacted with 2-aminoethanol or 1-amino-2-propanol 87 to yield the substituted 2-methyleneoxazolidines 88 (Scheme 39). 172
They have also reported that the reaction of ketene dithioacetals $3g,n,p$ with aminohydroxy compounds $89$ gave the corresponding substituted oxazolidine derivatives $90$ (Scheme 40).  

**Scheme 40**

The reaction of ketene dithioacetals $3a-d$ with trimethylsilylmethylamine $91$ in methanol yielded the corresponding $N,S$-acetals $92$. $N$-Alkylation of compounds $92$ with alkyl halides in the presence of potassium carbonate in acetone at room temperature, gave the $N$-alkylated derivatives $93$. The latters reacted with
carbonyl compounds or thiketones 95a,b in the presence of cesium fluoride to afford the corresponding oxazolidines and thiazolidines 96, respectively (Scheme 41). 174

The heterocyclic ketene N,O- and N,S-acetals with an ester substituent in heterocyclic ring 98 were synthesized by the reaction of ketene S,S-acetals 3c,i with serine or cysteine esters hydrochloride 97 in the presence of a base (Scheme 42). 175

Scheme 42

Ketene dithioacetals 3a-c,g-i,l-n reacted with 2-amino-1-ethanethiol in boiling ethanol to give the substituted 2-methylenethiazolidine derivatives 99 (Scheme 43). 176

Scheme 43

The reaction of ketene S,S-acetals 3a-p with α-substituted anilines 100a-c produced the corresponding benzazole derivatives 101 (Scheme 44). 117,177-180

Scheme 44

Scheme 45
The salt of 2,2-dioxoketene-\(S,S\)-acetal 102 was cyclized with 1,2-dibromoethane to give the dithiolanes 103 (Scheme 45).

### 3.1.3. Five-membered rings with three hetero-atoms

Treatment of compounds 47 with carboxylic acid hydrazides 104 in boiling ethanol formed the 2,5-disubstituted 1,3,4-oxadiazole derivatives 105 (Scheme 46).

![Scheme 46](image)

### 3.2. Six-membered rings

#### 3.2.1. Six-membered rings with one hetero-atom

The pyridine-2(1\(H\))-one derivatives 107 were synthesized by the reaction of compound 3a with \(N\)-alkylcyanoacetamides 106a-c in the presence of sodium isopropoxide (Scheme 47).

![Scheme 47](image)

The sulphonylketene dithioacetals 108 were condensed with malononitrile to give the 3-cyano-6-methyl-4-(methylthio)-5-phenylsulphonyl-2-pyridones 109 (Scheme 48).

![Scheme 48](image)

It has been reported that the substituted 6-amino-1-(fur-2-ylmethyleneamino)-1,2-dihydro-4-(methylthio)-2-oxopyridine-3,5-dicarbonitrile 111 was prepared by cyclization of 3a with furan derivative 110 (Scheme 49).

The reaction of 3d with substituted ketones 112 afforded the corresponding 3-cyano-4-(methylthio)-2-oxopyridine-3-carbonitriles 113 (Scheme 50).
The cyclocondensation of compound 3a with cyanoselenoacetamide 114 has been utilized for the synthesis of the 6-amino-3,5-dicyano-(methylthio)-2(1H)-pyridineselenone 115 (Scheme 51).\(^{187}\)

Peseke et al. have shown that the reaction of ketene dithioacetal 116 with N-furfurylcyanooacetamide 117 gave the pyridonecarboxamide derivative 118 (Scheme 52).\(^{188-191}\)

Ketene SS-acetales 3a,g,h reacted with 2-cyanothioacetamide 119 in basic condition to form the corresponding pyridinethiones 120 (Scheme 53).\(^{192,193}\)

Elgemeie et al. have found that 3a,c reacted with 1-cyanoacetyl-4-substituted thiosemicarbazides 121 at r.t. in the presence of potassium hydroxide in dioxan to give the corresponding N-(4-methylthio-2-oxo-1-
pyridyl)thiourea derivatives 122. In a typical experiment, when 3a,c reacted with cyanoacetohydrazide at r. t. in the presence of potassium hydroxide in dioxane, the N-amino-4-methylthio-2-pyridones 123 were produced. In related work Peseke et al.\textsuperscript{194} have reported the synthesis of compound 124 by the reaction of 3c with cyanoacetohydrazide in ethanol under reflux. Reaction of ketene dithioacetals 3a,c with Schiff bases was also examined. Thus, when 3a,c were reacted with 1-cyanoacetyl-4-aryldienesemicarbazides 125 in the presence of potassium hydroxide in dioxane, the Schiff bases 126 were obtained (Scheme 54).\textsuperscript{195}

\[ \text{Scheme 53} \]

\[
\begin{array}{c}
\text{H}_3\text{CS} \quad \text{X} \\
\text{H}_3\text{CS} \quad \text{Y} \\
\text{3a,g,h}
\end{array}
\quad + 
\begin{array}{c}
\text{NC} \quad \text{S} \quad \text{NH}_2 \\
\text{119}
\end{array}
\quad \xrightarrow{\text{base}}
\begin{array}{c}
\text{X} \\
\text{Z} \\
\text{N} \\
\text{SCH}_3
\end{array}
\]

\text{Scheme 53}

<table>
<thead>
<tr>
<th>122</th>
<th>Z</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>NH\textsubscript{2}</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
</tr>
<tr>
<td>b</td>
<td>OH</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
</tr>
<tr>
<td>c</td>
<td>NH\textsubscript{2}</td>
<td>COC\textsubscript{6}H\textsubscript{5}</td>
</tr>
<tr>
<td>d</td>
<td>OH</td>
<td>COC\textsubscript{6}H\textsubscript{5}</td>
</tr>
</tbody>
</table>

\text{Scheme 54}

\[
\begin{array}{c}
\text{KOH/dioxan} \\
\text{3c}\quad \text{Y}=\text{CN} \quad \text{or} \quad \text{CO}_2\text{C}_2\text{H}_5
\end{array}
\]

\text{in case of 3c}

<table>
<thead>
<tr>
<th>126</th>
<th>Z</th>
<th>Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>NH\textsubscript{2}</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
</tr>
<tr>
<td>b</td>
<td>NH\textsubscript{2}</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
</tr>
<tr>
<td>c</td>
<td>NH\textsubscript{2}</td>
<td>4-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
</tr>
<tr>
<td>d</td>
<td>NH\textsubscript{2}</td>
<td>4-OCH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
</tr>
<tr>
<td>e</td>
<td>OH</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
</tr>
<tr>
<td>f</td>
<td>OH</td>
<td>4-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
</tr>
</tbody>
</table>
They have also reported that ketene-S,S-acetals 3a,c,q reacted with N-cyanoarylsulphonylhydrazides 127 in dioxane containing a catalytic amount of potassium hydroxide to yield the corresponding 4-(methylthio)-N-arylsulphonylamino-2-pyridone derivatives 129 (Scheme 55).196

![Scheme 55](image)

Recently, they have been shown that both 3a and 3c reacted with substituted acetanilides 130 in a solution of sodium ethoxide or potassium hydroxide in dioxane to give the corresponding N-aryl-4-(methylthio)-2-pyridones 132. Compounds 132 reacted with aromatic amines 133 in fusion to afford the corresponding 4-amino-2-pyridone derivatives 134 (Scheme 56).197

![Scheme 56](image)

The reaction of ketene-S,S-acetal 3b with aromatic amines 135 gave ketene-N,S-acetals 136, which were cyclized to yield the quinoline derivatives 137 (Scheme 57).198

When compound 3b reacted with dimesone, coumarin derivative 138 was formed. The latter compound 138 was cyclized with hydrochloric acid or methylamine to give the corresponding quinolone derivative 139 or 140, respectively (Scheme 58).199
It has been found that the pyran-2-one derivatives 142 were synthesized through the reaction of 3b with substituted ketones 141 (Scheme 59).200-204

Ketene dithioacetal 3a reacted with cyclopentanone when the reaction was conducted in the presence of potassium hydroxide in dioxane: the expected cycloalkane ring fused 4-methylsulfanyl-2(1H)-pyridone 144 was obtained. In contrast to the behavior of 3a toward cyclopentanone in potassium hydroxide in dioxane, ketene dithioacetal 3a reacted with dimedone under the same condition to give the cyclocondensed 2-pyran derivative 145 and not the expected 2(1H)-pyridone derivative. On the other hand, the dimedone anhydride derivative 146 was obtained by the reaction of 3a with dimedone in refluxing pyridine (Scheme 60).205
3.2.2. Six-membered rings with two hetero-atoms

It has been reported that ketene dithioacetals 3a-c reacted with compound 147 to produce the 1-methyl-2-azathiabenzene-1-oxide derivatives 148 (Scheme 61).

The syntheses of the pyrimidines 150 were generally attained by the condensation reaction of ketene dithioacetals 3a,b,f with amidine derivatives 149a-d in the presence of an appropriate base (Scheme 62).
The 4-(3-indolyl)pyrimidine derivatives 153 were obtained by the reaction of ketene dithioacetals 3a-c with indolylmagnesium bromide 151 to give 3-indoleacrylate derivatives 152. The latter smoothly condensed with amidines 149a,d in the presence of a base (Scheme 63).\(^{214}\)

![Scheme 63]

The reaction of 3a with guanidine 149d in the presence of ethanol containing ethoxide gave the 2,4-diamine-6-ethoxypyrimidine-5-carbonitrile 154 (Scheme 64).\(^{210}\)

![Scheme 64]

![Scheme 65]

<table>
<thead>
<tr>
<th>153</th>
<th>R</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₃</td>
<td>OH</td>
</tr>
<tr>
<td>b</td>
<td>NH₂</td>
<td>OH</td>
</tr>
<tr>
<td>c</td>
<td>NH₂</td>
<td>NH₂</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>157</th>
<th>R¹</th>
<th>R²</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₃</td>
<td>CH₃</td>
<td>NHCH₃</td>
</tr>
<tr>
<td>b</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>NHC₆H₅</td>
</tr>
<tr>
<td>c</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>SCH₃</td>
</tr>
<tr>
<td>d</td>
<td>4-OCH₃C₆H₄</td>
<td>CH₃C₆H₅</td>
<td>SCH₃</td>
</tr>
<tr>
<td>e</td>
<td>CH₂C₆H₅</td>
<td>CH₂C₆H₅</td>
<td>NHCH₂C₆H₅</td>
</tr>
</tbody>
</table>

345
Compound 3l reacted with amines to yield nitroamine derivatives 155, 156; each of them was reacted with formaldehyde and primary amine to give the 1,2,3,6-tetrahydropyrimidine derivatives 157 (Scheme 65). Compound 158 also reacted with amidine derivatives 149a-d in the presence of potassium carbonate to give the corresponding pyrimidine derivatives 159 (Scheme 66).

![Scheme 66](image)

The cyclocondensation of ketene-\(N,S\)-acetal 160 with carboxylic acid derivatives 161a-d gave the 1,4-dihydro-4-oxo-6-(methylthio)pyrimidine-5-carbonitriles 162, 163 (Scheme 67).

![Scheme 67](image)

Tominaga et al. have found that the polarized ethylenes 164 were smoothly reacted with guanidine carbonate 149d to yield the corresponding 2,4-diaminopyrimidine-5-carbonitrile derivatives 165 (Scheme 68).

![Scheme 68](image)
The reaction of ketene dithioacetals 3a,b with carboxamides 166 in sodium hydride/benzene mixture yielded compounds 167. The latters were cyclized in refluxing methanol to give the pyrimidine derivatives 168 (Scheme 69).\(^{211}\)

![Scheme 69](image)

Ketene dithioacetal 3c reacted with thiobenzamide 169 in AcOH/HClO\(_4\) to afford the thiazine derivative 170. The resulting compound 170 was refluxed in ethanol with morpholine to produce the 6-(methylthio)-2-phenyl-4-thioxopyrimidine-5-carboxylate 171 (Scheme 70).\(^{219}\)

![Scheme 70](image)

The reaction of 3b with thioacetamide formed the methyl 2-cyano-3-(methylthio)-3-[[1-(methylthio)ethylidene]amino]propenoate 172, 5-(methoxycarbonyl)-2-methyl-6-(methylthio)-4-thioxo-3,4-dihydropyrimidine 173 and bis[5-(methoxycarbonyl)-2-methyl-6-(methylthio)-4-pyrimidinyl]disulfide 174 (Scheme 71).\(^{211,220}\)

![Scheme 71](image)
Compound 3b also reacted with urea derivatives 175a,b in sodium hydride/benzene mixture to afford the corresponding 6-methylthiouracil-5-carbonitriles 176a,b (Scheme 72). 211

\[
\begin{align*}
\text{Scheme 72}
\end{align*}
\]

The condensation of compound 3a with cyanamide in ethoxide yielded compound 177, which was cyclized in the presence of hydrochloric acid to give the 4-amino-2-chloro-6-(methylthio)pyrimidine-5-carbonitrile 178 (Scheme 73). 221

\[
\begin{align*}
\text{Scheme 73}
\end{align*}
\]

Recently, it has been found that ketene dithioacetals 3q-u reacted with thiosemicarbazide 22b in sodium isopropoxide, to form the corresponding 6-(methylthio)-N-amino-2-pyrimidinethione derivatives 179 (Scheme 74). 123

\[
\begin{align*}
\text{Scheme 74}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 75}
\end{align*}
\]
The 3-aryl-2,4-dioxo-6-(methylthio)pyrimidine-5-carbonitriles 180 were prepared by the reaction of compound 3c with arylureas 172a-c (Scheme 75).\textsuperscript{222,223} 

The benzopyrimidine derivative 182 was synthesized by the reaction of 3a with aminophenylbenzylamines 181 in refluxing ethanol (Scheme 76).\textsuperscript{224,225}

![Scheme 76](image)

It has been found that 2-[bis(methylthio)methylene]indane-1,3-dione 183 reacted with amidine derivatives 149a-d in the presence of potassium carbonate in dimethylformamide to give the 2-substituted-4-methylthioindeno[1,2-d]pyrimidine-5-ones 184 (Scheme 77).\textsuperscript{102,226}

![Scheme 77](image)

When ketene O,S-acetal 185 reacted with carboxylic acid derivatives 161a-d the corresponding oxazinones 186 were produced (Scheme 78).\textsuperscript{220}

![Scheme 78](image)

The alkylideneoxazine derivatives 188 were synthesized by cyclization of ketene S,S-acetals 3b,e,j with 3-aminoneopentanol 187 (Scheme 79).\textsuperscript{173}

![Scheme 79](image)
3.2.3. Six-membered rings with three hetero-atoms

The reaction of ketene dithioacetals 3a,b with dialkylsulfurdiimides 189 afforded the corresponding 2,6-thiadiazine derivatives 190-193 (Scheme 80).²²⁷,²²⁸

\[
\begin{align*}
\text{R}^2\text{NH} & \quad \text{R}^1\text{S} \quad \text{CN} \\
\text{S} \quad \text{N} \quad \text{S} \quad \text{CN} & \quad \text{R}^2\text{S} \quad \text{NH} \\
\text{R}^1\text{S} & \quad \text{N} \quad \text{S} \quad \text{CN} \\
\text{S} & \quad \text{N} \quad \text{S} \quad \text{CN} \\[-2pt]
\text{R}^2 & \quad \text{S} \quad \text{N} \quad \text{S} \quad \text{CN} & \quad \text{R}^1 \\
\text{a Y=CN} & \quad \text{b Y=CO}_2\text{CH}_3
\end{align*}
\]

Scheme 80

3.3. Seven-membered rings

Treatment of compound 3d with α-amino acid derivative 194 in ethanol containing triethylamine formed the tetrahydro-1,4-diazepine-2,7-diones 195 (Scheme 81).¹²⁷

\[
\begin{align*}
\text{H}_3\text{CS} & \quad \text{CN} \\
\text{H}_3\text{CS} & \quad \text{CONH}_2 \\
\text{H}_3\text{CS} & \quad \text{CN} \quad \text{H}_3\text{C} & \quad \text{N} \quad \text{CO}_2\text{C}_2\text{H}_5 & \quad \text{EtOH/Et}_3\text{N} \quad \text{ref. 4 h} \\
\text{3d} & \quad \text{194} & \quad \text{195}
\end{align*}
\]

Scheme 81

\[
\begin{align*}
\text{H}_3\text{CS} & \quad \text{CN} \\
\text{H}_3\text{CS} & \quad \text{Y} \\
\text{H}_3\text{CS} & \quad \text{Y} \quad \text{NH}_2 \quad \text{NH}_2 & \quad \text{ref. 4 h} \\
\text{3} & \quad \text{a Y=CN} & \quad \text{c Y=CO}_2\text{C}_2\text{H}_5 & \quad \text{196} & \quad \text{197}
\end{align*}
\]

Scheme 82
Ketene dithioacetals 3a,c reacted with 1-(2-aminophenyl)-2-aminoethane 196 to afford the 2-substituted hydrogenated 1,3-benzodiazepines 197 (Scheme 82). 229

3.4. Fused heterocyclic compounds

The reaction of compounds 3a or 198 with N-pyrrolylmagnesium bromide 199 in non-polar solvent yielded dinitriles 200, which were cyclized in the presence of amine as a catalyst to give the pyrrolizine derivatives 201 (Scheme 83). 230-231

It has been found that ketene dithioacetals 3a,c and 202 reacted with 2-thiohydantoin derivatives 203 in refluxing ethanol containing catalytic amounts of piperidine to give the corresponding 4-alkylsulfanylpyrrolo[1,2-c]imidazoles 206 (Scheme 84). 232

Ketene dithioacetals 3a,b,f reacted with benzimidazolium salt 207 to give the benzimidazolium N-allylides 208. The latters in refluxing xylene formed the 1,5-dipolar cyclization products the benzopyrroloimidazoles 209 (Scheme 85). 233

The heterocyclic ketene dithioacetals 211a,b were chosen as the key intermediate and were prepared by the reaction of pyrazolin-5-ones 210a,b with sodium ethoxide and carbon disulphide followed by methyl iodide treatment in a one-pot reaction.
Compounds 211a,b reacted with hydrazine derivatives 29a,b in refluxing ethanol containing catalytic amount of piperidine to give the corresponding 4-methylthiopyrazolo[3,4-c]pyrazoles 212 (Scheme 86).\textsuperscript{234}

\textbf{Scheme 86}

It has been reported that 3l reacted with pyridinium \textit{N}-allylides 213 in the presence of a base to produce the indolizine derivative 214 (Scheme 87).\textsuperscript{235,236}

\textbf{Scheme 87}

\textbf{Scheme 88}
The reaction of ketene dithioacetals \(3a,c\) with 2,6-dimethyl-1-ethoxycarbonylmethylpyridinium bromide \(215\) in the presence of potassium carbonate gave the corresponding 3-ethoxycarbonylindolizines \(216\) and 3-vinylindolizines \(217\) (Scheme 88).\(^{237}\)

Both pyridinium-3-cyano-2-(methylthio)allyides \(218\) and isoquinolinium-3-cyano-2-(methylthio)allyides \(220\) were treated with sodium hydroxide 10\% to give the indolizines \(219\) and the pyrrolo[2,1-\(a\)]isoquinolines \(221\), respectively (Scheme 89).\(^{238-240}\)

![Scheme 89](image)

The reaction of compound \(108a\) with 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline \(222\) yielded the pyrroloisoquinolines \(223\) (Scheme 90).\(^{184}\)

![Scheme 90](image)

When \(3a,c\) were treated with 2-amino-6-methyl-1-ethoxycarbonylmethylpyridinium bromide \(224\) in the presence of potassium carbonate the 3-vinylimidazo[1,2-\(a\)]pyridines \(225\), were produced (Scheme 91).\(^{237}\)

![Scheme 91](image)
The reaction of nitroketene dithioacetal 31 with imidazolium salt 226 in the presence of potassium carbonate in dimethylsulfoxide resulted in 1,5-dipolar cyclization to produce the pyrrolo[1,2-a]imidazoles 227 and pyrrolo[1,2-α]pyrazines 228 (Scheme 92).241

![Scheme 92](image_url)

Treatment of imidazolium N-allylides 229 in refluxing 1,2,4-trimethylbenzene resulted in 1,6-cyclization to give the mesomeric betaine, 7-iminoimidazo[1,2-α]pyridiniumide derivative 230 (Scheme 93).241

![Scheme 93](image_url)

The reaction of ketene dithioacetals 3a,b with isoquinolinium imine 231 yielded the corresponding pyrazoloisoquinolines 232. Similarly, 31 reacted with pyridinium imines 233 to yield the pyrazolopyridines 234 (Scheme 94).239,242-244

![Scheme 94](image_url)

Ketene-S,S-acetals 3a,b reacted with 2-benzoylmethylimidazoles 235 to form the corresponding imidazolo[1,2-α]pyridine derivatives 236 (Scheme 95).245
Scheme 95

The cyclocondensation of 3b with 2-benzoymethylimidazole 237 in the presence of potassium carbonate in dimethylformamide produced the 8-benzyol-7-(methylthio)-5-oxo-5H-imidazo[1,2-a]pyridine-6-carbonitrile 238, which was refluxed with POCl₃ to give the imidazo[1,2-a]pyridine derivative 239 (Scheme 96).

Scheme 96

The reaction of compounds 3a,b with benzimidazole derivatives 240 gave the corresponding benzo[4,5]imidazo[1,2-a]pyridines 241 (Scheme 97).

Scheme 97

Matsuda et al. have reported that the reaction of ketene-S,S-acetals 3a,c with 4-methylthiazole derivative 242 yielded the corresponding thiazolo[3,2-a]pyridines 243 (Scheme 98).

The reaction of compound 3b with substituted indoles 244 afforded compounds 245, which were cyclized to form the pyrano[2,3-b]indole derivatives 246 (Scheme 99).

Ketene dithioacetal 247 reacted with 3-iodoindole 248 to give the intermediate 249, which was cyclized in the presence of hydrochloric acid 10% to yield the indole derivative 250. The latter was rearranged in refluxing methanol to give the thieno[3,2-b]indoles 251 (Scheme 100).

355
It has been reported that the pyrazolo[3,4-\(b\)]pyridones 253 was produced through the reaction of compound 3b with 3-aminopyrazoles 252 (Scheme 101).\textsuperscript{256}
Elgemeie et al. have reported that the reaction of 3a,c with 5-aminopyrazoles 254 afforded the 7-methylthiopyrazolo[1,5-a]pyrimidines 256. The latters reacted with hydrazine to give the 1H-dipyrazolo[1,5-a-4',3'-e] pyrimidines 257 (Scheme 102).54,257

They have also shown that the heterocyclic ketene dithioacetals 211a,b reacted with cyanoacetohydrazide or cyanothioacetamide 258 in refluxing ethanol containing catalytic amount of piperidine to obtain the corresponding 4-methylthiopyrazolo[3,4-b]pyridines 259 (Scheme 103).234

Compound 3a reacted with 3-methyl-2-pyrazolin-5-ones 260 in dioxane containing an equivalent amount of potassium hydroxide to give the corresponding 4-methylthiopyrazolo[3,4-b]pyridines 263 through the intermediates 262. Also, 3a reacted with 3-amino-2-pyrazolin-5-ones 261 to yield the corresponding 6-methylthiopyrazolo[3,4-c]pyridines 264.

The behavior of ketene dithioacetal 3a towards other active methylene heterocycles has been also investigated. Thus, compound 3a reacted with 5-thiazoline-4-one derivative 265 in refluxing dimethylformamide containing an equivalent amount of potassium carbonate to yield the 7-methylthiothiazolo[3,2-a] pyridines 266 (Scheme 104).205
Ketene-\textit{S,S}-acetal 3c reacted with \textit{n}-butylamine to form ketene-\textit{N,S}-acetal 267, which was cyclocondensed with hydrazine to afford 3-\textit{n}-butylamino-1\textit{H}-pyrazole-4-carboxlate derivative 268. The latter reacted with ethyl acetoacetate in glacial acetic acid to yield the ethyl 2-(\textit{n}-butylamino)-7-hydroxy-5-methylpyrazolo[1,5-\textit{a}]pyrimidine-3-carboxlate 269 (Scheme 105).
The cyclocondensation of compound 3a with 2-aminobenzoimidazole 270 yielded the benzoimidazopyrimidine derivative 271 (Scheme 106).259

\[
\begin{array}{c}
\text{H}_3\text{CS} \equiv \text{CN} \\
\text{H}_3\text{CS} \equiv \text{CN}
\end{array}
\quad +
\begin{array}{c}
\text{H}_2\text{N} \quad \text{N} \\
\text{H}_2\text{N}
\end{array}
\rightarrow
\begin{array}{c}
\text{H}_2\text{N} \\
\text{H}_2\text{N}
\end{array}
\]

Scheme 106

The thienopyrimidinone derivatives 273 were prepared from the reaction of ketene dithioacetals 3a,b with 2-aminothiophene-3-carboxylic acid derivatives 272 (Scheme 107).260

\[
\begin{array}{c}
\text{H}_3\text{CS} \equiv \text{CN} \\
\text{H}_3\text{CS} \equiv \text{CN}
\end{array}
\quad +
\begin{array}{c}
\text{H}_2\text{N} \quad \text{N} \\
\text{H}_2\text{N}
\end{array}
\rightarrow
\begin{array}{c}
\text{H}_2\text{N} \\
\text{H}_2\text{N}
\end{array}
\]

Scheme 107

The reaction of [bis(methylthio)methylene]substituted heterocyclic compounds 274, 276 with amidine derivatives 149a,d has been extensively utilized for the synthesis of benzo[4,5]thieno[3,2-d]pyrimidines 275 and benzo[4,5]thieno[3,2-d]pyrimidine-5,5-dioxides 277, respectively (Scheme 108).184,261-263

\[
\begin{array}{c}
\text{H}_3\text{CS} \equiv \text{CN} \\
\text{H}_3\text{CS} \equiv \text{CN}
\end{array}
\quad +
\begin{array}{c}
\text{H}_2\text{N} \quad \text{N} \\
\text{H}_2\text{N}
\end{array}
\rightarrow
\begin{array}{c}
\text{H}_2\text{N} \\
\text{H}_2\text{N}
\end{array}
\]

Scheme 108

It has been reported that the cyclocondensation reaction of 3b with triazolamine 278 yielded the triazolopyrimidine derivative 279 (Scheme 109).264
The amination of ketene $\text{S,S}$-acetal 3a with benzylamine afforded ketene $\text{N,S}$-acetal 280, which was cyclocondensed with hydrazine to give the 5-amino-3-benzylamino-$1H$-pyrazole-4-carbonitrile 281. The latter was cyclized with 3-chloroaniline to prepare the pyrazolo[3,4-$d$]pyrimidines 282 (Scheme 110).

It has been found that the corresponding 4-methylthio[3,4-$d$]pyrimidine derivatives 284 were synthesized by the reaction of compounds 211a,b with guanidine, urea and thiourea 283 (Scheme 111).

The reaction of 3a with 2-pyridineacetonitrile 285 afforded the 1,3-dicyano-4-imino-2-methylthio-$4H$-quinolizine 286 (Scheme 112).

The cyclocondensation of compounds 3a-c with 2-aminopyridine 287 gave the corresponding 2-methylthiopyrido[1,2-$a$]pyrimidine derivatives 288 (Scheme 113).
The 2-N-substituted pyranooisoquinolines 290 were synthesized by the reaction of 3b with 1,3-dioxoisoquinoline derivatives 289 (Scheme 114).  

**Scheme 113**

**Scheme 114**

**References**

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RECENT DEVELOPMENT IN THE CHEMISTRY OF 
4,5-DIHALO-3(2H)-PYRIDAZINONES

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Abstract. 4,5-Dihalo-3(2H)-pyridazinones have gained increasing importance in the synthetic chemistry of pyridazines over the last decade. In particular, new examples of nucleophilic displacement of halogens, novel types of N-protection leading to a more efficient functionalization, and the introduction of C-C coupling reactions by palladium catalysts illustrate the significant development in the field. All these aspects are covered by this review.

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   2.1. Alkylated derivatives
   2.2. Sulfonylation
   2.3. Acylation
3. Halogen exchange reactions
   3.1. Nucleophilic substitution reactions
   3.2. Palladium catalysed C-C coupling reactions
4. Concluding remarks
Acknowledgements
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1. Introduction

1. 4,5-Dihalo-3(2H)-pyridazinones attracted much attention over the last three decades due to their easy availability, and efficient functionalization with electrophiles at the lactam moiety and/or 6-position, and with nucleophiles at the 4- and/or 5-position(s). These properties make them particularly attractive starting materials for the synthesis of 4- and/or 5-substituted monocyclic and 4,5-annelated polycyclic pyridazine derivatives. In the last decade too, considerable advance has been made in the synthetic chemistry of this class compounds. In this review, the most significant progresses from 1993, the date of publication of our first comprehensive review on the field will be covered.¹

2. Substitution at the lactam moiety

The most convenient source of 4,5-dichloro- and dibromo-3(2H)-pyridazinones is the condensation reaction of the respective mucohalic acid (2,3-dichloromalealdehydic acid) with hydrazine hydrate. The N-substituted compounds could be obtained either by application of the properly substituted hydrazine for the condensation or, to avoid the highly toxic substituted hydrazines, by functionalization of the parent 4,5-
dihalo compounds. Alkylation, sulfonylation and acylation have been thoroughly studied over the last years, particularly a Korean group headed by Yoon has significantly contributed to this field.

Although, in these reactions either N- or O-substituted derivatives may a priori be formed, in the most cases, N-substitution has been found to occur, whereas formation of the O-substituted derivatives has only been detected under special conditions.

2.1. Alkylated derivatives

Pyridazine nucleosides with potential biological activity are of continuous interest.

Pyridazinones 2 and 3 containing a 4-oxybutyl moiety, as analogues of nucleosides, were prepared via alkylation of 4,5-dichloro-3(2H)-pyridazinone (1a) with 4-iodobutyl acetate and 4-iodobutyl benzoate in dimethyl sulfoxide in the presence of sodium hydride. Synthesis of 2-(2-oxopropyl)pyridazinones without or with a nitro group, compounds 5 and 6, respectively, was carried out by using either 4-bromoacetoacetic acid or chloroacetone (Scheme 1). With the latter procedure higher yields were achieved.

![Scheme 1]

Pyridazine N-nucleosides such as 7 were also prepared. Compound 7 could be conveniently obtained by ribosylation of 1a with 1-O-acetyl-2,3,5-tri-O-benzoyl β-D-ribofuranose in the presence of ammonium sulfate, hexamethyldisilazane and stannic chloride (Scheme 2).

The N-substituent of the pyridazinone may also serve as a protecting group needed for or facilitating further transformations. As protecting groups at the 2-position, benzyloxymethyl and benzyl are amongst the most popular ones. Improved methods for N-benzylation have more recently been reported. Treatment of 1a or 1b with benzyl bromide in the presence of potassium carbonate and tetrabutylammonium bromide in acetonitrile, or in the presence of 8N potassium hydroxide as a base in dimethyl sulfoxide, respectively, afforded 2-benzyl derivatives 8 in good yields.
The tetrahydropyranyl group could also be attached to the lactam nitrogen. Synthesis of \( \text{N}-\text{tetrahydropyranyl derivative} \) 9 was accomplished from 1a with an excess of dihydropyran and \( p \)-toluenesulfonic acid (or pyridinium tosylate) in refluxing tetrahydrofuran (Scheme 3). 8

\[
\text{Scheme 2}
\]

Sometimes, alkylation reactions of the parent dihalopyridazinones could be sluggish due to the low solubility of these compounds. Apparently, this problem could be solved by introduction of a labile functionality to the 2-position. It has been recently reported that 4,5-dichloro-2-hydroxymethyl-3(2\( H \))-pyridazinone (10a), which itself was prepared from 1a in hot 35\% formalin, can be \( \text{N} \)-alkylated, and with this compound reasonable reaction rates as well as good yields can be achieved. The method is highly versatile, and the conditions are mild. The following examples are provided for illustration.

Treatment of 10a with various alkyl halides in the presence of potassium carbonate in acetone (or in acetonitrile) at reflux temperature gave the corresponding 2-alkyl derivatives 12 with no formation of 2-alkoxymethyl derivatives 13. Higher yields of 12 were generally obtained when the synthesis started from compound 10a. 9

\[
\text{Scheme 3}
\]
Synthesis of 4,5-dichloro-2-(ω-phtalimido)- and (ω-saccharin-2'-yl)-3(2H)-pyridazinones (14) was also studied starting from both 1a and 10a. In these cases too, rate of the alkylation reaction of 10a was higher than that of 1a.$^{10}$

A plausible mechanism of these transformations involves two steps. In the first step, compound 10a may undergo a retro-ene type fragmentation with a C-N bond cleavage (it may be facilitated a hydrogen-bonding formed between OH and the pyridazine-carbonyl) to liberate formaldehyde as a leaving enophile; then, in the subsequent step formation of the new C-N bond occurs.

It is noteworthy that acylation of the hydroxymethyl derivative 10a, takes a different pathway from the route shown for alkylation. Treatment of 10a with acyl chlorides in the presence of potassium carbonate in refluxing acetone or acetonitrile led smoothly to the formation of the corresponding esters 15, i.e. O-acylation of the hydroxymethyl group took place. Formation of 2-acylpyridazinone derivatives 16 could not be observed (Scheme 4).

\[
\begin{align*}
1a: & \ Y=H \\
7a: & \ Y= \text{NO}_2 \\
10a: & \ Y=H (59\%) \\
11: & \ Y=\text{NO}_2 (76\%) \\
12 \ a & \ b \ c \ d \\
& \ R^1 \text{Me Et Pr Bu} \\
& \ ii) R^1X; \text{K}_2\text{CO}_3; \text{acetone; reflux; 2-4 h; (82-95\%)} \\
13 & \\
15 \ a & \ b \ c \ d \\
& \ R^2 \text{Me Et ClCH}_2 \text{Bu} \\
& \ v) R^2\text{COCl; K}_2\text{CO}_3; \text{acetone or MeCN; rt or reflux;} \\
& \text{6-10 h; (73-88\%); X= I, Br, Cl} \\
\end{align*}
\]

\[\text{Scheme 4}\]
A further application of 10a for alkylation was provided by reactions with dibromoalkanes. Again, for comparison, the same reactions were also carried with 1a. The reaction of 1a with α,ω–dibromoalkanes gave different types of products; seemingly, the chain length (n) of the alkylating agent and the reaction conditions directed the reaction.\(^{11}\) When 1a was reacted with dibromomethane (n=1), a N,N-methylene bridged bis(pyridazinyl) derivative 18 was obtained as the only product using either potassium carbonate in acetonitrile at 82 °C (Method A, Table 1) or potassium hydroxide and tetrabutylammonium bromide in benzene at 56 °C (Method B).

### Scheme 5

![Scheme 5](image)

**Table 1. Alkylation of 1a with dibromoalkenes**

<table>
<thead>
<tr>
<th>n</th>
<th>Method</th>
<th>Starting from 1a</th>
<th>Isolated yields</th>
<th>Starting from 10a</th>
<th>Isolated yields</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>17 18 19</td>
<td>17 18 19</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>-</td>
<td>96</td>
<td>-</td>
<td>90</td>
</tr>
<tr>
<td>1</td>
<td>B</td>
<td>-</td>
<td>97</td>
<td>-</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>30</td>
<td>* 59</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>90</td>
<td>*</td>
<td>91</td>
<td>*</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>76</td>
<td>16</td>
<td>96</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>96</td>
<td>*</td>
<td>94</td>
<td>*</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>95</td>
<td>*</td>
<td>93</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>92</td>
<td>*</td>
<td>90</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>94</td>
<td>*</td>
<td>94</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>61</td>
<td>31</td>
<td>60</td>
<td>29</td>
</tr>
</tbody>
</table>

*Product was detected by gas chromatography but not isolated

Reactions of 1a with 1,3-dibromopropane, 1,4-dibromobutane and 1,6-dibromohexane afforded the corresponding N-(α-bromoalkyl) derivative 17 as the major product, and 18 as the minor product. The reaction with 1,2-dibromoethane under the conditions of Method A, afforded as major product, a third type
of products, the \( O,N \)-ethylene bridged \( bis \)(pyridazinyl) compound 19 (Table 1). All these alkylation reactions were also carried out starting from the hydroxymethylpyridazinone 10a. The product ratio obtained with 1,2-dibromoethane was slightly different from the above results. In this case, compound 19 was again the major product, but 18 was also obtained, as the minor product (Scheme 5).

For the mechanism of \( N \)- and \( O \)-alkylation reactions of 1a with 1,2-dibromoethane, transition states of I and II, respectively, were considered. Being the structure II more favorable in the presence of potassium carbonate, \( O \)-alkylation may occur predominantly. On the other hand, alkylation in the presence of tetrabutylammonium bromide and potassium hydroxide affords selectively the \( N \)-alkylated product since formation of II is unfavorable due to the steric hindrance exhibited by the tetrabutylammonium ion (Scheme 6).

![Scheme 6](image)

**Scheme 6**

The final example of alkylation relates to a convenient one-pot procedure for the preparation of \( N \)-alkyl-4-halo-5-methoxypyridazinones 20. In this process, compounds 1 were treated with various alkyl halides and 2 equivalents of potassium carbonate in refluxing methanol to obtain compounds 20. However, using potassium carbonate in a different molar ratio in refluxing methanol, a side product was also detected:
either 4,5-dimethoxy-3(2H)-pyridazinone (in the presence of more than 2 equivalents of potassium carbonate) or 2-alkyl-4,5-dihalo-3(2H)-pyridazinone (12) (in the presence of less than 2 equivalents of potassium carbonate) was formed. For comparison, compounds 20 were also synthesized in two steps: i) alkylations of pyridazinones 1 with alkyl halides using potassium carbonate in dimethyl formamide, and ii) nucleophilic substitution with sodium methoxide in methanol.

For preparation of 5-hydroxy derivatives 21, the 5-methoxy derivatives 20 were O-demethylated by hydrolysis in aqueous potassium hydroxide (Scheme 7).

2.2. Sulfonylation

Sulfonylation reactions of 1a with various sulfonyl chlorides have been studied. In all cases, 2-N-sulfonylpyridazinones 22 were obtained (Scheme 8). Effect of the base on the rate and yield of the reaction of 1a with 4-nitrobenzenesulfonyl chloride was investigated in tetrahydrofuran (Table 2). High rate and excellent yield were obtained by using 4-(N,N-dimethylamino)pyridine at room temperature.

![Scheme 8](image)

**Table 2. Reaction of 1a with 4-nitrobenzenesulfonyl chloride**

<table>
<thead>
<tr>
<th>Base</th>
<th>Time (h)</th>
<th>Temp.</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>K₂CO₃</td>
<td>4</td>
<td>Reflux</td>
<td>77</td>
</tr>
<tr>
<td>Cs₂CO₃</td>
<td>5</td>
<td>R.t.</td>
<td>75</td>
</tr>
<tr>
<td>NaH</td>
<td>50</td>
<td>R.t.</td>
<td>65</td>
</tr>
<tr>
<td>Et₃N</td>
<td>2</td>
<td>R.t.</td>
<td>92</td>
</tr>
<tr>
<td>DMAP*</td>
<td>0.17</td>
<td>R.t.</td>
<td>92</td>
</tr>
<tr>
<td>Pyridine</td>
<td>59</td>
<td>Reflux</td>
<td>63</td>
</tr>
<tr>
<td>BuLi</td>
<td>0.33</td>
<td>0 °C</td>
<td>82</td>
</tr>
</tbody>
</table>

*4-(N,N-dimethylamino)pyridine

2.3. Acylation

Acylation of pyridazinone 1a with various acyl chlorides also afforded N-acyl derivatives: compounds 23 were obtained in good yields in the presence of triethylamine in dichloromethane. The synthetic utility of these compounds for N-acyl transfer reactions has been investigated. Treatment of various primary amines including amino acids or aminocarboxylic acids with 1 equivalent of 23 in tetrahydrofuran...
under the conditions listed in Table 3 afforded the corresponding amides (24) chemoselectively, and in excellent yields (Scheme 9).

![Scheme 9](image)

**Scheme 9**

<table>
<thead>
<tr>
<th>R</th>
<th>R^1</th>
<th>Conditions</th>
<th>Yield of 24 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td>0.5 h; reflux</td>
<td>95</td>
</tr>
<tr>
<td>Me</td>
<td>4-HO(CH_2)_2C_6H_4</td>
<td>0.2 h; 17 °C</td>
<td>94</td>
</tr>
<tr>
<td>Me</td>
<td>HOOCCH_2</td>
<td>4 h; reflux</td>
<td>84</td>
</tr>
<tr>
<td>Me</td>
<td>2-HOOC_6H_4</td>
<td>14 h; reflux</td>
<td>94</td>
</tr>
<tr>
<td>Me</td>
<td>4-HOC_6H_4</td>
<td>0.2 h; 17 °C</td>
<td>95</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>4 h; reflux</td>
<td>98</td>
</tr>
<tr>
<td>Ph</td>
<td>4-HO(CH_2)_2C_6H_4</td>
<td>18 h; 18 °C</td>
<td>97</td>
</tr>
<tr>
<td>Ph</td>
<td>HOOCCH_2</td>
<td>24 h; reflux</td>
<td>98</td>
</tr>
<tr>
<td>Ph</td>
<td>2-HOOC_6H_4</td>
<td>34 h; reflux</td>
<td>84</td>
</tr>
<tr>
<td>Ph</td>
<td>4-HOC_6H_4</td>
<td>12 h; 18 °C</td>
<td>94</td>
</tr>
<tr>
<td>4-MeOC_6H_4</td>
<td>Ph</td>
<td>3 h; reflux</td>
<td>99</td>
</tr>
<tr>
<td>4-MeOC_6H_4</td>
<td>4-HO(CH_2)_2C_6H_4</td>
<td>7 h; 18 °C</td>
<td>93</td>
</tr>
<tr>
<td>4-MeOC_6H_4</td>
<td>HOOCCH_2</td>
<td>42 h; reflux</td>
<td>72</td>
</tr>
<tr>
<td>4-MeOC_6H_4</td>
<td>2-HOOC_6H_4</td>
<td>14 h; reflux</td>
<td>87</td>
</tr>
<tr>
<td>4-MeOC_6H_4</td>
<td>4-HOC_6H_4</td>
<td>5 h; 18 °C</td>
<td>99</td>
</tr>
</tbody>
</table>

**Table 4.** Study of steric influences on acyl-transfer reactions of acylpyridazinones

<table>
<thead>
<tr>
<th>Mixture of starting amines</th>
<th>Amide product (R=4-MeOC_6H_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtNH_2 + Et_2NH</td>
<td>EtNHCOR (85%)+Et_2NCOR (14%)</td>
</tr>
<tr>
<td>C_6H_5NH_2 + (C_6H_5)_2NH</td>
<td>C_6H_5NHCOR (97%)</td>
</tr>
<tr>
<td>PhCH_2NH_2 + PhCH_2NHMe</td>
<td>PhCH_2NHCOR (99%)</td>
</tr>
<tr>
<td>PhCH_2NH_2 + PhCH(Me)NH_2</td>
<td>PhCH_2NHCOR (75%)+PhCH(Me)NHCOR (21%)</td>
</tr>
<tr>
<td>PhCH(Me)NH_2 + PhCH_2NHMe</td>
<td>PhCH(Me)NHCOR (9%)+PhCH_2N(Me)COR (89%)</td>
</tr>
<tr>
<td>PhCH_2NHMe + PhCH_2NH(i-Pr)</td>
<td>PhCH_2N(Me)COR (98%)</td>
</tr>
</tbody>
</table>
Sensitivity of the acyl transfer to steric effect was studied by the reaction of 4,5-dichloro-2-(4-methoxybenzoyl)-3(2H)-pyridazinone with a 1:1 mixture of two sterically different amines (Table 4). The results suggest that primary amines (vs. secondary) react preferably, and α-branching is still tolerated for reaction.

3. Halogen exchange reactions

The most characteristic and important reactions of 4,5-dihalo-3(2H)-pyridazinones are nucleophilic displacement reactions of halogens. These reactions allow the introduction of a wide variety of nucleophiles, including N-, O- and C-nucleophiles, onto the pyridazine ring, and provide simple synthetic routes to many polycyclic ring systems, too. One of the key issues of these transformations is the regiochemistry of the substitution. A considerable body of experimental evidence and theoretical studies indicate that the reaction follows an addition-elimination pathway, and the regiochemistry might be significantly influenced by the reaction conditions; polar solvent is generally favorable for the 5-substitution. The regiochemistry is more complicated in the presence of 6-nitro group.  

The other type of efficient halogen-displacement reactions is represented by C-C coupling reactions catalysed by palladium. These methodologies have currently been explored for pyridazine chemistry.

3.1. Nucleophilic substitution reactions

Pyridazine nucleoside analogues 3 were functionalised at the 5-position with a variety of nucleophiles.

For preparation of amino derivatives, the nucleophilic displacement of 5-chloro was carried out with sodium azide to obtain 25.

![Scheme 10]
Debenzylation and subsequent reduction of the 5-azido function to amino group led to the target compound 27. Nucleophilic substitution reaction of 3 with methylamine resulted in the 5-methylamine derivative 30 which was used to prepare the 5-N-methylamino analogues of 27, 29 i.e. compounds 31, 32 (Scheme 10).\(^2\)

Chloroacetamide proved to be a suitable nucleophile for the preparation of 5-chloroacetamido derivatives 33, which was then transformed into 35 in two steps via debenzyolated compound 34.\(^2\) Compound 35 also could be obtained directly from 33 by hydrogenolysis under basic conditions. Hydrazine hydrate is a fairly reactive nucleophile towards dihalopyridazinones. Treatment of 3 with hydrazine hydrate in dimethyl sulfoxide in the presence of potassium carbonate led smoothly to 4-chloro-5-hydrazone derivative 36. Debenzyolation and subsequent dehalogenation resulted in the formation of 38 (Scheme 11).\(^2\)

![Scheme 11](image)

The relatively easy replacement of halogens with amines is illustrated by the reactions of 4,5-dihalo-3(2H)-pyridazinones containing a reactive oxo group in the N-substituent.\(^3\) Reaction of 5b with methylamine or cyclopropylamine in the presence of triethylamine in methanol gave regioselectively the corresponding 5-alkyliminopropyl derivatives 39, without concomitant formation of the 2-(2-alkyliminopropyl) derivatives. Hydroxylamine hydrochloride was the only exception. Its reaction with 5b afforded 4,5-dibromo-2-(2-hydroxyiminopropyl)-3(2H)-pyridazinone 40 as a mixture of the syn and anti forms of the oxime.

Reaction of 5 with phenols has also been investigated. Dichloro and dibromo compounds 5a and 5b with 4-amino-2,6-dichlorophenol in the presence of potassium fluoride and potassium carbonate in acetonitrile gave compounds 41a,b, respectively, regio- and chemoselectively. However, when 5 was treated with 4-amino-2,6-dichlorophenol in the presence of potassium fluoride or potassium carbonate, two products, the phenoxy derivative 41 and the respective anilino compound, 5-(3,5-dichloro-4-hydroxyphenylamino)-4-halo-2-(2-oxopropyl)-3(2H)-pyridazinone (not shown) were obtained (Scheme 12).

The influences of N-protecting groups on the nucleophilic displacement reactions have been studied systematically. A comparison with unprotected derivatives was also made. In the first type of protecting
groups dibromooxopropyl, acyloxymethyl, and hydroxymethyl are included, all of which, under the conditions of nucleophilic substitution, undergo easily a retro-ene type C-N bond fission, whereas in the second type, the moderately stable sulfonyl, and the more stable tetrahydropyranly and benzyl are typical examples.

Scheme 12

Scheme 13

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Introduction and removal of the 1,1-dibromo-2-oxopropyl protecting group could be carried out easily, under mild conditions.\textsuperscript{17} 4,5-Dihalo compounds 42 were prepared by bromination of 5 at the side chain in the presence of sodium acetate in a mixture of acetic acid and chloroform. The subsequent nucleophilic substitution and deprotection were carried out in a one-pot reaction. Thus, treatment of 42a or 42b in methanol with potassium carbonate, with sodium azide or with methylene hydrochloride in the presence of triethylamine resulted in the formation of 5-substituted-4-halo-3(2\textit{H})-pyrazinones 43a-f, respectively (Scheme 13).

![Chemical structure](image)

**Scheme 14**
The reaction took also place with phenol: the N-protected-5-substituted derivatives were formed first, which could be deprotected with potassium carbonate in water to yield 43g or 43h. Reactions of compounds 42 with para-substituted phenols 44 afforded the 2-unsubstituted-5-phenoxypyridazinones 46 in two steps (Scheme 13). In the case of 2-acetoxymethyl group (pyridazinones 15a, 47), the methoxylation, azidation or amination took also place. The nucleophilic substitution at C-5 and deprotection at N-2 by a retro-ene type mechanism were again carried out in a one-pot reaction (Scheme 14).

Reaction of 15a or 47 with 1 equivalent of phenol in the presence of 1 equivalent of potassium carbonate gave the respective acetoxymethyl derivative 48a, 48b, which could be deprotected to 43g and 43h, respectively. Interestingly, reaction of the same starting compounds 15a and 47 with 2 equivalents of reagents led to a mixture of compounds 43 and a 2-phenoxymethyl derivative 49. Formation of the latter type was explained by a nucleophilic substitution at C-5 followed by Mannich condensation with phenol.

To complete the studies with phenols, 15a or 47 was treated with 2 equivalents of substituted phenols 44 in the presence of 2 equivalents of potassium carbonate to afford 50 and/or 46 5-phenoxypyridazinones with or without 2-acetoxoy substituent (Scheme 14). Electron-withdrawing substituents on the phenol ring favored the formation of 5-substituted-2-acetoxymethyl derivatives, whereas electron-releasing substituents were preferable for the formation of 5-substituted-2-deprotected products. This observation reveals that the electron-releasing group enhances the rate of retro-ene fragmentation.

Another type of nucleophilic substitution, consisting of functionalization and retro-ene type deprotection, is represented by transformations of 4,5-dihalo-2-hydroxymethyl-3(2H)-pyridazinones (10) as starting compounds. Treatment of 10 with various nucleophilic reagents resulted in the correspondingly 5-substituted, at the lactam moiety unprotected 43. However, when using 2 equivalents of phenol and potassium carbonate instead of one equivalent, a mixture of the 43g or 43h and the Mannich product 49a or 49b was obtained, respectively (Scheme 15).

Scheme 15

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It seems to be interesting to compare the results of nucleophilic displacement reactions of the parent compound, 4,5-dichloro-3(2H)-pyridazinone (1a) with those obtained with the N-protected derivatives. Four nucleophiles, methoxide, ethylamine, phenols and azide, in different solvents (Table 5) were investigated.\textsuperscript{20} Methoxyla
tion of 1a gave 43a in moderate to high yield in a mixture of tetrahydrofuran-water, methanol or water, whereas no reaction proceeded in the other four solvent systems.

On the contrary, reaction of 1a with azide anion in each solvent system afforded the azido derivative 43c in good yield.

Reaction of 1a with ethylamine afforded the 5-ethyamino derivative 43i in moderate yields, except for reactions in methanol or ethanol. In this cases, a mixture of the 5-ethyamino derivative 43i and the corresponding 5-alkoxy compound 43a or 43k were obtained.

Reaction of 1a with 2 equivalents of phenol in THF-water, acetonitrile-water or water solvents gave the 5-phenoxy derivative 43g, whereas a mixture of 43k and 43g was formed in ethanol. Fairly unexpectedly, performing the reaction in methanol, the 5-methoxy derivative 43a could only be obtained (Scheme 16).

\begin{center}
\textbf{Scheme 16}
\end{center}

\begin{center}
\begin{table}
\caption{Product distribution in the reaction of 1a with nucleophiles in various solvents (s. Scheme 16)}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Conditions} & \textbf{Product} & \textbf{THF} & \textbf{THF/H2O} & \textbf{MeOH} & \textbf{EtOH} & \textbf{MeCN} & \textbf{MeCN/H2O} & \textbf{H2O} \\
\hline
a) & 43a (%) & 0 & 62 & 91 & 0 & 0 & 0 & 90 \\
\hline
b) & 43c (%) & 71 & 92 & 64 & 70 & 69 & 82 & 75 \\
\hline
c) & 43i (%) & 56 & 58 & 19 & 46 & 52 & 76 & 48 \\
& 43a (%) & 0 & 0 & 52 & 0 & 0 & 0 & 0 \\
& 43k (%) & 0 & 0 & 0 & 23 & 0 & 0 & 0 \\
\hline
d) & 43a (%) & 0 & 0 & 98 & 0 & 0 & 0 & 0 \\
& 43k (%) & 0 & 0 & 0 & 14 & 0 & 0 & 0 \\
& 43g (%) & 0 & 90 & 0 & 52 & 0 & 87 & 82 \\
\hline
\end{tabular}
\end{table}
\end{center}
The second type of protecting groups exhibited also a facilitating effect on the nucleophilic substitution. The 2-(arylsulfonyl)-4,5-dichloro-3(2H)-pyridazinones (22) with or without ortho substituent at the arylsulfonyl moiety, in a reaction with amines such as ethylamine, diethylamine, cyclohexylamine and piperidine, gave a mixture of 5-alkylamino-2-arylsulfonyl derivatives 51 and N-alkylsulfonamides 52 as the major products (Scheme 17). On the contrary, compounds 51 were obtained as main products in good yields from arylsulfonyl compounds containing an ortho-substituent.

![Scheme 17](image)

The tetrahydropyranyl protecting group was completely intact during the nucleophilic displacement reaction. It was applied for the large scale synthesis of 3-chloro-5-methoxypyridazine (56) which is an important intermediate for synthesis of pyridazine herbicides. Reaction of 9 with sodium-methoxide in methanol afforded 53 in good yield. Two subsequent transformations, reductive dehalogenation and deprotection, gave 55 which was then treated with phosphorous oxychloride to afford the target compound 56 (Scheme 18).

![Scheme 18](image)

Behavior of the 2-benzyl group was similar to that of the methyl group. Regioselective reactions of 2-benzyl- and 2-methyl-4,5-dichloro-3(2H)-pyridazinone could be performed with sodium methoxide: in anhydrous dioxane 5-chloro-4-methoxy derivatives (57\textsuperscript{1}; 58\textsuperscript{2}) were obtained, whereas in methanol the 4-chloro-5-methoxy isomer 59 was formed (Scheme 19).
The regiochemical outcome and solvent dependence are less predictable in the case of 4,5-dichloro-2-methyl-6-nitro-3(2H)-pyridazinone (60). For instance, with potassium carbonate in methanol, different product ratios of 4- and 5-substituted derivatives have been obtained depending on the temperature and the stochiometry of potassium carbonate to the substrate. A lower base/substrate ratio and lower temperature were favorable for formations of both the 4- and 5-monomethoxy products 61, 62, whereas a higher base/substrate ratio and higher temperature were preferable for the formations of disubstituted products 64-66; the 6-methoxy derivative 63 was only a minor product (Table 6).

The 6-amino derivative 67 obtained by the reduction of 6-nitro derivative 60 behaved however differently. Its methoxylation took place regioselectively to afford the 5-methoxy derivative 68 in good yield (Scheme 20).

Scheme 19

\[
\begin{align*}
8a: R &= \text{PhCH}_2 \\
12a: R &= \text{Me} \\
57: R &= \text{PhCH}_2 \\
58: R &= \text{Me} \\
59: R &= \text{Me}
\end{align*}
\]

i) NaOMe; dioxane; 1 h; rt; (57: 74%; 58: 70-80%)
ii) NaOMe; MeOH; 1 h; rt; (85%)

Scheme 20

\[
\begin{align*}
a)-g): & \text{K}_2\text{CO}_3; \text{MeOH} \\
h): & \text{Fe}; \text{NH}_4\text{Cl}; \text{H}_2\text{O}; \text{CHCl}_3; \text{rt}; 21 \text{ h} \\
i): & 1.3 \text{ equiv. K}_2\text{CO}_3; \text{MeOH}; \text{reflux}; 2 \text{ h}
\end{align*}
\]
The synthesis and selective α₁-adrenoceptor activity of (4-chloro-5-methoxyphenylethyl)-piperazinylpyridazinones were recently reported. These compounds were also obtained by nucleophilic displacement reaction of 4,5-dichloropyridazinones; alkylene-bridged bis(pyridazinyl) derivatives were also prepared.²³

### Table 6. Conversion of the 6-nitro derivative 60 into methoxy-substituted derivatives

<table>
<thead>
<tr>
<th>Method</th>
<th>60 : K₂CO₃ ratio</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product distribution (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1:0.5</td>
<td>Reflux</td>
<td>1</td>
<td>61 62 63 64 65 66</td>
</tr>
<tr>
<td>B</td>
<td>1:1</td>
<td>Reflux</td>
<td>1.5</td>
<td>- 62 4 22 39 -</td>
</tr>
<tr>
<td>C</td>
<td>1:1</td>
<td>35</td>
<td>2</td>
<td>- 52 - - 4</td>
</tr>
<tr>
<td>D</td>
<td>1:1.3</td>
<td>Reflux</td>
<td>1</td>
<td>- - - 18 52 -</td>
</tr>
<tr>
<td>E</td>
<td>1:2</td>
<td>35</td>
<td>4</td>
<td>- - - 30 62 -</td>
</tr>
<tr>
<td>F</td>
<td>1:2</td>
<td>Reflux</td>
<td>0.5</td>
<td>- - - 32 66 -</td>
</tr>
<tr>
<td>G</td>
<td>1:3.4</td>
<td>Reflux</td>
<td>24</td>
<td>- - - - - 92</td>
</tr>
</tbody>
</table>

Reactions of 4,5-dihalopyridazinones with bifunctional nucleophiles can be utilized for the preparations of fused pyridazines.

Malonitrile possessing two proper functionalities for consecutive inter- and intramolecular nucleophilic reactions was employed for the synthesis of pyrrolo[2,3-c]pyridazines. This reagent also illustrates the high reactivity of a C-nucleophile towards the 5-position of 4,5-dichloropyridazinones.

Pyrrolo[2,3-c]pyridazines with hydroxyalkyl substituent as analogues of acyclonucleosides having antiproliferative and/or antiviral activity were prepared from the N-alkylated-6-amino-4,5-dichloropyridazinones 67.²⁴ On reacting these compounds with the anion of malonitrile, obtained by in situ deprotonation, bicyclic compounds 69 were formed regioselectively. Subsequently, further functionalization of the fused system was accomplished in two steps.

![Scheme 21](image_url)

The methyl derivative 69a was acetylated with acetic anhydride in the presence of potassium carbonate to give the 2-acetylamino bicyclic derivative 70; alkylation of which, interestingly, with 4-
iodobutyl benzoate in the presence of potassium carbonate in dimethyl formamide failed to yield the desired N-benzyloxybutyl derivative. N-Alkylation could be however performed smoothly with 2-unsubstituted compounds 71, and compounds 72a-c were obtained (Scheme 21).

Malonitrile was also reacted with 4,5-dichloro- and 4,5-dichloro-6-nitropyridazinones.

Pyridazine-nucleosides containing a monocyclic pyridazine ring with a malonitrile moiety were prepared from dichloropyridazinone nucleoside 7 with malonitrile in the presence of sodium hydride in dimethyl sulfoxide. Thus, the 5-pyrazidinylmalonitrile 73 obtained in this way was then debenzoylated to the desired compound 74. Pyrrolo[2,3-c]pyridazine nucleoside 80 was prepared from 4,5-dichloro-6-nitropyridazinone nucleoside 75. In the first step, on treatment with malonitrile, each of the possible monosubstituted three regioisomers 76, 77, 78 were isolated. Of them, 78 formed as the main product in the previous step, was transformed to the pyrrolopyridazine 79 with sodium borohydride in the presence of stannous chloride dihydrate. Subsequent debenzoylation afforded the nucleoside 80 (Scheme 22).

![Scheme 22](image-url)

Aminoethanols and aminopropanols were already successfully reacted with 4,5-dichloropyridazinones to obtain pyridazinoxazines, pyridazinoxazepines, and their thiazine and thiazepine analogues. The extension of these reactions to the 4,5-dichloro-2-methyl-6-nitro-3(2H)-pyridazinone (Schemes 23-25), has recently been studied experimentally and theoretically as well. Reactions with aminoethanols, aminopropanols and aminobutanol in refluxing ethanol or butanol afforded separable mixtures of 4- and 5-hydroxyalkylaminopyridazinones, the latter being generally the main products.
\[ \begin{array}{cccccc}
R^1 & R^2 & R^3 & m \\
81: & 
82: & 
83: & 
84: & 
85: & 
86: & H - CH_2 -cis/ 1 
87: & H - CH_2 -trans/ 1 
88: & H - CHCH_2CH_2 -/diendo/ 1 
89: & H - CHCH_2CH_2 -/dixol/ 1 
90: & H - CH_2 -cis/ 0 
91: & H - CH_2 -cis/ 0 
\end{array} \]

Scheme 23

\[ \begin{array}{cc}
& 82 \\
& 93b \\
81 \rightarrow 84, 86 \rightarrow 91 : (i): \text{NaOEt/EtOH, reflux} \\
& 84, 85 \\
& 92a, 93a, 94a, 95a, 96a, 96b, 97a, 97b, 98a, 98b \\
& 92a, 94a, 94c, 98a, 98b:m = 0 \\
& 93a, 95a, 95c, 96a, 96b, 97a, 97b:m = 1 \\
& 94c, 95c \\
\end{array} \]

Scheme 24

\[ \begin{array}{cc}
& 104, 105 \\
102, 103 : (i): \text{Fe/AcOH, rt} (ii): \text{NaOEt/EtOH, reflux} \\
& 104, 105 \\
& 106, 107 \\
99a, 99b, 100, 102, 104, 106 : m = 0 \\
99b, 99d, 103, 105, 107 : m = 1 \\
& 100, 101 \\
\end{array} \]

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The ring closure reactions of the 5-isomers 81-91 with sodium ethoxide took place with the involvement of C-6 to afford 3,4-annelated products 92-98, and, in a few cases only, a 4,5-annelated system and/or monocyclic compounds formed by intermolecular nucleophilic substitution (93b; 94c, 95c) (Scheme 23).

Ring closure of the 4-isomers with an N-benzyl substituent 99a, b led to the formation of bicyclic products, whereas 4-isomers with no substituent at the nitrogen, compounds 99c, d gave the 6-ethoxy monocyclic derivatives 100, 101. A further support for the constitution of the fused system was provided by chemical transformations too. The 6-amino bicyclic 106 and 107 were prepared in two independent ways: either by ring closure of 102, and 103 or by reduction of the nitro of 104 and 105 (Scheme 24).

The regioisomerically annelated system of 106, 107, i.e. compounds 109-111, were transformed via 112 and 113 into novel ortho- and peri-fused ring systems 114-117 (Scheme 25).

The preparative results were consistent with theoretical considerations based on the FMO theory.

\[
\begin{align*}
\text{81, 82, 88} & \xrightarrow{i} \text{81, 82, 88}^* \\
\text{108} & \xrightarrow{ii} \text{108}^* \\
\text{109, 110, 111} & \xrightarrow{iii} \text{109, 110}^* \\
\text{112, 113} & \xrightarrow{iv} \text{112, 113}^* \\
\text{81, 108, 97, 112} & \xrightarrow{5} \text{81, 108, 97, 112}^* \\
\end{align*}
\]

(i): Fe/NaOAc, rt; (ii): NaOEt/EtOH, reflux; (iii): Pd/C, cyclohexene, EtOH, reflux; (iv): HC(OEt)3, EtOH, reflux; (v): (EtOCO)2O, CH2Cl2, reflux; (vi): CH2C(OEt)3, EtOH, reflux

\[
\text{Scheme 25}
\]

3.2. Palladium catalysed C-C coupling reactions

Carboaromatic as well as heterocyclic compounds, with trifluorosulfonyloxy-, iodo- and bromo-substituents are generally excellent substrates for C-C coupling reactions. The earliest examples of Pd-catalysed C-C coupling reactions of pyridazines were also carried out with such substituents. The reactivity of a chloro-substituent of carboaromatic compounds, is usually very low in Pd-catalysed reactions. Unlike these compounds, however, chloro substituents of pyridazines may be expected to be sufficiently reactive for Pd-catalysed coupling reactions, due to the electrondeficient nature of the heterocyclic
Although, in many cases, better yields could be obtained with bromo-, iodo- or triflate-substituents.

4,5-Dibromo and dichloro-3(2H)-pyridazinones and their derivatives have more recently been utilized for Suzuki arylation and Sonogashira coupling reactions. Scope and limitation of these methodologies, and their possible applications for the synthesis of polycyclic ring systems have been much investigated by Belgian and Hungarian groups headed by Lemière, Maes, Hajós and Mátýus. In these reactions too, selective displacement of halogens is of much concern, and it represents an important issue of further synthetic application, too.

The synthesis of 4,5-diaryl-3(2H)-pyridazinones with different aryl groups could be achieved via consecutive Suzuki cross-coupling reactions of pyridazines possessing different leaving groups. In this approach, selectivity could be obtained. Thus, 4,5-dibromo-2-benzyl-3(2H)-pyridazinone (8b) was hydrolyzed with potassium hydroxide to afford the 5-hydroxy derivative 119, which was next treated with trifluoromethansulfonic anhydride to obtain the corresponding triflate 122. The Suzuki reaction of 122 was carried out with 4-methylthiophenylboronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) as the catalyst in a mixture of 2M aqueous sodium carbonate and tetrahydrofuran. As expected, trifluoromethansulfonyloxy group proved to be much more reactive, than the bromo, and as a result, 4-bromo-5-methylthiophenylpyridazinone 123 was obtained in acceptable overall yield for the last two steps. Oxidation of compound 123 with magnesium monoperoxiphtalate led to the methylsulfonyl derivative 124. It was subjected to the next Suzuki coupling reaction with lithium tri(2-propoxy)-3-pyridylboronate in dimethylformamide using [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) as catalyst to obtain diaryl substituted pyridazinone 125 exhibiting cyclooxygenase-2 inhibitory properties (Scheme 26).

Attempts have also been made to perform selective arylations of N-substituted 4,5-dichloro-3(2H)-pyridazinones 126. The reaction however failed with 1 equivalent of boronic acid (Table 7). When using 3 equivalents of boronic acid in the presence of palladium-tetrakis(triphenylphosphine) and 2M aqueous sodium carbonate in toluene at reflux temperature, in turn, the 4,5-diaryl derivatives (127-132) were obtained in excellent yields. Another catalyst, an air-stable oxime derivative in the presence of potassium
carbonate and tetrabutylammonium bromide in refluxing water was also effective for the diarylation to prepare 2-methyl-4,5-diphenyl-3(2H)-pyridazinone (132) (Scheme 27).31

Scheme 27

Table 7. Pyridazinones disubstituted with the same aryl groups

<table>
<thead>
<tr>
<th></th>
<th>R^1</th>
<th>R^2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>127</td>
<td>Me</td>
<td>Ph</td>
<td>98</td>
</tr>
<tr>
<td>128</td>
<td>Me</td>
<td>4-MeOC_6H_4</td>
<td>97</td>
</tr>
<tr>
<td>129</td>
<td>Me</td>
<td>4-FC_6H_4</td>
<td>100</td>
</tr>
<tr>
<td>130</td>
<td>Ph</td>
<td>Ph</td>
<td>97</td>
</tr>
<tr>
<td>131</td>
<td>Ph</td>
<td>4-MeOC_6H_4</td>
<td>87</td>
</tr>
<tr>
<td>132</td>
<td>Ph</td>
<td>4-FC_6H_4</td>
<td>100</td>
</tr>
</tbody>
</table>

Scheme 28

It could therefore be concluded that reactivity difference of 4- and 5-positions of dichloropyridazinones is not high enough to obtain selective arylations in Suzuki coupling reactions. For efficient utilization of dichloropyridazinones for the preparation of non-identically diarylated pyridazinones
like compound 125, required a series of steps: i) the temporary blocking of one of the 4- and 5-positions ii) a coupling reaction, iii) re-functionalization of the blocked position for the second Suzuki-reaction, and then iv) the second arylation. A successful realization of this strategy was based on the application of 4-chloro-5-methoxypyridazinones 133 and their 5-chloro-4-methoxy regioisomers 144, both of these methoxy derivatives were easily and in high yields available by selective nucleophilic displacement reactions of 4,5-dichloropyridazinones. Therefore, the ways were open to both regioisomeric products too. The monoaryl-monomethoxypyridazinone intermediates offered a further application to obtain polycyclic pyridazines in a straightforward way. The key event of this approach is the ring closure with the involvement of the methoxy substituent and a substituent of the aryl group. Both these pathways have been investigated and are next illustrated.

Treatment of 133, and 144 with boronic acids resulted smoothly in the monoarylated products 134-143 and 155-162, respectively (Scheme 28).

| Table 8. 4-Aryl-5-methoxy-3(2H)-pyridazinones |
|------------------------|------------------------|------------------------|
| **R¹** | **R²** | **Yield (%)** |
| 134 Me | Ph | 100 |
| 135 Me | 4-MeOC₆H₄ | 100 |
| 136 Me | 4-MeSC₆H₄ | 100 |
| 137 Me | 4-FC₆H₄ | 100 |
| 138 Me | 3-CF₃C₆H₄ | 97 |
| 139 Me | 3-MeOC₆H₄ | 100 |
| 140 Me | 2-MeC₆H₄ | 100 |
| 141 Me | 2,4-Cl₂C₆H₄* | 90 |
| 142 Ph | Ph | 100 |
| 143 Ph | 4-CH₃OC₆H₄ | 94 |

*2.5 equivalents of boronic acid were used

| Table 9. 5-Aryl-4-methoxy-3(2H)-pyridazinones |
|------------------------|------------------------|------------------------|
| **R¹** | **R²** | **Yield (%)** |
| 155 Me | Ph | 100 |
| 156 Me | 4-CH₃OC₆H₄ | 100 |
| 157 Me | 4-FC₆H₄ | 100 |
| 158 Me | 3-CF₃C₆H₄ | 100 |
| 159 Me | 3-thienyl | 85 |
| 160 Ph | Ph | 100 |
| 161 Ph | 4-CH₃OC₆H₄ | 100 |
| 162 Ph | 3-thienyl | 100 |

Suzuki reaction of 4-chloro-5-methoxy-3(2H)-pyridazinones 133 with ortho-formylphenylboronic acid, an arylboronic acid containing the ortho-functionality for further transformations, was used for
preparation of 4-(2-formylphenyl)-5-methoxy derivatives 163. However, this reaction was particularly sensitive for reaction conditions, presumably due to a steric hindrance exhibited by two ortho-substituents of the substrate and reagent as well as to the enhanced hydrolytic deboronation of boronic acid by the presence of the electron-withdrawing formyl group. Yet, the reaction could be completed successfully by using a large excess of boronic acid. The synthesis of the other regioisomers 166 required a smaller excess of boronic acid. Both regioisomers could be transformed to two different tricyclic fused systems.

Scheme 29

In the first route, the ring closure was accomplished by the formation of a bond between carbon and nitrogen atoms. Upon treatment of compounds 163 or 166 with aqueous ammonia in methanol, ring closure reaction occurred surprisingly smoothly to give the respective isomers of pyrazidino[4,5-c]isoquinolinone system (164, 167). The N-unsubstituted compounds 165 and 168, respectively, could also be obtained from 164b, and 167b, respectively, by removal of the benzyl group with aluminium trichloride in toluene (Scheme 29).

In the second route, transformation of 163b, 166b into another tricyclic ring system was achieved by formation of a carbon-oxygen bond via lactonization. The first step was the O-demethylation by refluxing the methoxy derivatives in aqueous potassium carbonate solution. The subsequent oxidation of the formyl group with potassium permanganate, then acidification of the reaction mixture led directly to the 2-benzyl-1H-isochromeno[3,4-d]pyrazidine-1,6(2H)-dione (169) in a one-pot reaction. In the case of the regioisomeric 166b, the intermediate benzoic acid derivative 170 was cyclized with a catalytic amount of sulfuric acid in dimethoxyethane to obtain 3-benzyl-3H-isochromeno[3,4-d]pyrazidine-4,6-dione (171) (Scheme 30).

Utilization of 4(5)-aryl-5(4)-methoxypyridazinones for the synthesis of 4,5-diaryl-3(2H)-pyridazinones with different aryl groups involved the hydrolytic demethylation of the 4-aryl-5-methoxy-(134-143, 172) as well as 5-aryl-4-methoxy-3(2H)-pyridazinones (155-162).
The hydroxy compounds could be converted into triflates using trifluoromethanesulfonic anhydride and triethylamine. Subsequent Suzuki reaction indeed yielded 186-190 diaryl derivatives with different aryl rests (Scheme 31, Tables 10, 11).32

For introduction of alkynyl substituents, the Sonogashira reaction has been widely applied. Sonogashira cross-coupling reactions of 4,5-dichloro-3(2H)-pyridazinones resulted in the formations of disubstituted or a mixture of mono- and disubstituted derivatives.33 Thus, treatment of 126 with 3 equivalents of phenylacetylene or trimethylsilylacetylene in the presence of PdCl2(PPh3)2, CuI and triethylamine in refluxing tetrahydrofuran yielded the corresponding dialkynyl derivatives (191-194) in good yields, whereas reaction of 126a with pent-1-yne resulted in the mixture of disubstituted and monosubstituted products 195, and 196, respectively (Scheme 32, Table 12).
Table 10. 4-Aryl-5-hydroxy-3(2H)-pyridazinones

<table>
<thead>
<tr>
<th>St. comp</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>Me</td>
<td>2-MeC₆H₄</td>
<td>173</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>134</td>
<td>Me</td>
<td>Ph</td>
<td>174</td>
<td>8</td>
<td>84</td>
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<tr>
<td>135</td>
<td>Me</td>
<td>4-CH₃OC₆H₄</td>
<td>175</td>
<td>7</td>
<td>89</td>
</tr>
<tr>
<td>136</td>
<td>Me</td>
<td>4-CH₃SC₆H₄</td>
<td>176</td>
<td>12</td>
<td>99</td>
</tr>
<tr>
<td>138</td>
<td>Me</td>
<td>3-CF₃C₆H₄</td>
<td>177</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>141</td>
<td>Me</td>
<td>2,4-Cl₂C₆H₄</td>
<td>178</td>
<td>7.5</td>
<td>99</td>
</tr>
<tr>
<td>143</td>
<td>Ph</td>
<td>4-CH₃OC₆H₄</td>
<td>179</td>
<td>24</td>
<td>93</td>
</tr>
<tr>
<td>172</td>
<td>PhCH₂</td>
<td>4-CH₃SC₆H₄</td>
<td>180</td>
<td>29</td>
<td>79</td>
</tr>
</tbody>
</table>

¹ 1 mmol of pyridazinone; 35 ml of 0.57 M KOH solution
² 1 mmol of pyridazinone; 85 ml of 0.57 M KOH solution
³ 1 mmol of pyridazinone; 206 ml of 0.57 M KOH solution
⁴ 1 mmol of pyridazinone; 175 ml of 0.57 M KOH solution

Table 11. 4,5-Diaryl-3(2H)-pyridazinones

<table>
<thead>
<tr>
<th>St. Comp</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>173</td>
<td>Me</td>
<td>2-MeC₆H₄</td>
<td>4-FC₆H₄</td>
<td>186</td>
<td>8</td>
<td>72*</td>
</tr>
<tr>
<td>176</td>
<td>Me</td>
<td>4-CH₃SC₆H₄</td>
<td>4-FC₆H₄</td>
<td>187</td>
<td>4</td>
<td>73</td>
</tr>
<tr>
<td>176</td>
<td>Me</td>
<td>4-CH₃SC₆H₄</td>
<td>Ph</td>
<td>188</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>180</td>
<td>PhCH₂</td>
<td>4-CH₃SC₆H₄</td>
<td>4-FC₆H₄</td>
<td>189</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>180</td>
<td>PhCH₂</td>
<td>4-CH₃SC₆H₄</td>
<td>4-CF₃C₆H₄</td>
<td>190</td>
<td>3</td>
<td>54</td>
</tr>
</tbody>
</table>

*3 equivalents of boronic acid were used

Attempts to perform selective Sonogashira reaction of 4,5-dichloro-3(2H)-pyridazinones failed. On the other hand, 4-chloro-5-methoxy-2-methyl-3(2H)-pyridazinone (133a) could be transformed easily to the corresponding triflate 198 by hydrolysis and subsequent triflation reaction. In the next step, selective Sonogashira reaction was achieved by the treatment of the triflate 198 with alkyynes at room temperature.

![Scheme 32](image)

\[
\text{i) 3 equiv. alkyne; 3 mol% PdCl}_2(\text{PPh}_3)_2; 3 \text{ mol% CuI; TEA; THF; 80 °C}
\]

Scheme 32

The monoalkynyl compounds obtained 199-201 were subjected to a further Sonogashira reaction with another terminal alkyne to give the 4,5-dialkynyl-3(2H)-pyridazinones (Scheme 33, Table 13). In a
similar way, the regiosomeric products were also prepared starting from 5-chloro-4-methoxy-2-methyl-3(2H)-pyridazinone.

**Table 12. Mono- and dialkynyl-3(2H)-pyridazinones**

<table>
<thead>
<tr>
<th>Pdz</th>
<th>Alkyne</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>R2</td>
<td>191-195</td>
<td>196</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>16</td>
<td>75</td>
</tr>
<tr>
<td>Me</td>
<td>Me3Si</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Ph</td>
<td>Me3Si</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>Me</td>
<td>Pr</td>
<td>72</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>

**Scheme 33**

Suzuki reaction of the 5-alkynyl-4-chloro compound 199 with phenylboronic acid and also with 3-trifluoromethylphenylboronic acid was also successfully carried out to afford the corresponding aryl-alkynyl derivatives 205, 206 (Scheme 34, Table 14). The 4-alkynyl-5-chloro derivatives also underwent the same transformations.

Although, 5-iodo-2-methyl-3(2H)-pyridazinone (207), as being a 5-monosubstituted pyridazinone, is not within the scope of this article, its origin from 4,5-dichloro-2-methyl-3(2H)-pyridazinone and high synthetic value34 prompted us to provide one example of its possible application for the synthesis of tricyclic pyridazinones.

The Suzuki arylation reactions of 207 with phenyl- and 2-pivaloylaminophenyl boronic acids afforded 208 or 209, respectively.35 After deprotection, the amines 210 were diazotated to the corresponding diazonium salts, which were subjected in situ to an azidation reaction to give the azides 211. Heating of the
latter compounds resulted in the formation of the 3-methylpyridazino[4,5-\textit{b}]indol-4(3\textit{H})-one and its chloro derivative (212); the reaction takes place most probably through a nitrene intermediate (Scheme 35).

\[
\begin{align*}
\text{O} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\text{i)} 1.5 equiv. RB(OH)$_2$; Pd(PPh$_3$)$_4$; 2M Na$_2$CO$_3$; toluene; reflux

**Scheme 34**

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>205</td>
<td>Ph</td>
<td>15</td>
<td>86</td>
</tr>
<tr>
<td>206</td>
<td>3-CF$_3$C$_6$H$_4$</td>
<td>16</td>
<td>78</td>
</tr>
</tbody>
</table>

**Table 14. 5-Aryl-4-alkynylpyridazinones**

4. Concluding remarks

4,5-Dihalo-3(2\textit{H})-pyridazinones represent an important class of pyridazines from both synthetic and theoretical points of view. Recent results illustrate their usefulness in the preparation of novel types of mono- and polycyclic pyridazines with possible practical applications. We hope that this review, demonstrating many aspects of the progress, will stimulate further interest in this field.
Acknowledgements

We are grateful to our colleagues, B. Dajka-Halász, O. Éliás, L. Károlyházy, G. Krajoovszky, B. Podányi, A. Schwartz, K. Szabó at the Department of Organic Chemistry, Semmelweis University, for their enthusiasm and valuable contribution as well as to our excellent friends Gy. Hajós, Zs. Riedl, G. Lemière, B. Maes, N. Haider for the fruitful and stimulating collaboration.

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References

SYNTHESIS OF HETEROCYCLES FROM ALLENES
BY INTRAMOLECULAR RING CLOSURE

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Abstract. This review is devoted to the synthesis of heterocycles by intramolecular ring closure starting from allenic compounds.

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1. Introduction

The allene chemistry is of great interest in organic synthesis. Many books or accounts published on this subject attest that.\cite{1-5}

Starting from allenes a lot of heterocycles has been synthesised.

In this paper our purpose is to review, for about the ten past years and size by size, the synthesis of heterocycles by intramolecular reactions involving the allenes. So, reactions like epoxidation\cite{6} or other examples of reactions in which at least the allene participation is intermolecular\cite{7-9} are ruled out.
Five-membered rings are the most important kind of cyclic compounds obtained from allenes. In a less extent, six and other-membered rings have been gotten also. In 1999, Banert published a report on the “synthesis of five-membered heterocycles from novel functionalized allenes”. So the papers we quote here in the field of the synthesis of five-membered heterocycles from intramolecular ring closure of allenic compounds are essentially additional papers compared with those quoted by Banert.

About the heteroatoms, the most widely used are oxygen and nitrogen but sulphur, phosphorus and others are sometime used.

2. Heterocycles with three-membered rings

2.1. Epoxidation

Epoxides may be gotten from α-allenic alcohols in two manners using palladium catalysis. With iodonium salts and palladium acetate, the α-allenic alcohol 1 led to the trans- epoxide 2 (R² = Ph) when Cs₂CO₃ was used as base (Scheme 1). Nevertheless, in the same conditions, but with K₂CO₃ this reaction led to the formation of the syn-diol cyclic carbonate 3.

\[ \text{Scheme 1} \]

With Pd(PPh₃)₄ as catalyst the same kind of alcohol gave a mixture of trans and cis epoxides with a high diastereoselectivity for the trans isomer. Depending on the reaction conditions the trans/cis ratio was varying from 14:1 to 30:1 when R¹ was a n-C₄H₉ group and R² a phenyl. Starting from the chiral allene 1b the trans epoxyde 2b is obtained with high enantiomeric excess (Scheme 2).

\[ \text{Scheme 2} \]

2.2. Aziridination

Similar results have been gotten with α-amino allenes 4 (Scheme 3). Dioxane was found to be the best solvent for this reaction.

The reaction was highly stereoselective. Starting from a (S, aS) amino allene, the major product was a 2,3-cis-2-alkenylaziridine 5 while from the (S, aR) isomer, the major product was the 2,3-trans-2-alkenylaziridine 6. In this case a few amount of the 3-pyrroline 7 was observed as by-product.

The base-mediated intramolecular amination of bromoallenes led to a chiral 2,3-cis-ethynylaziridines. Starting from the (S, aS) or the (S, aR) isomer, the cis-aziridine was the major product (Scheme 4). However, the best stereoselectivity was obtained from the (S, aR) isomer.

400
3. Heterocycles with four-membered rings

The palladium-catalysed heteroannulation of allene-tethered amines 11 was reported. The reaction provided azacyclobutane 12 or/and tetrahydropyridine 13 (Scheme 5). Starting from 11c only 12c was obtained in enantiomerically pure form.15

Starting from 11a,b the ratio 12:13 depends on the substituents R and P but also on the reaction times and R1–X.16 With R = CO2Me (11b) both 12b and 13b were obtained in enantiomerically pure form. To favour the formation of 12 the best is to use short reaction times and vinylic triflates as R1–X.

4. Heterocycles with five-membered rings

4.1. Oxygen heterocycles

In this heading we found furanic compounds and furanones or butenolides. The first ones are generally produced from allenylalcohols or ketones while the others are usually coming from allene-tethered carboxylic acids.
4.1.1. Saturated oxygen heterocycles (tetrahydrofurans)

Palladium catalysis allows to add a coupling reaction to the ring closure. Starting from \( \gamma \)-allenyl alcohols 14, the reaction led to 2-vinyl tetrahydrofurans 15 (Scheme 6).

The \( R^2 \) group may be brought by an aryl or vinyl halide\(^{17} \) or by hypervalent iodonium salts.\(^{18} \) Acylation-cyclisation (\( R^2=RC=O \)) is possible using acyltetracarbonylcobalt complexes.\(^{19} \)

![Scheme 6](image)

Also compound 15 (\( R^2=Ts \)) may be simply obtained from 14 by radical addition of \( p \)-toluenesulfonyl bromine or iodide.\(^{20} \) Actually, in this case, the ring closure occurs in an intramolecular nucleophilic substitution second step.

Starting from the bis(allene) 16, similar reaction using the radical addition of TsBr or TsSePh afforded the tetrahydrofuran 17 bearing a vinyl sulfone and a \( trans \) vinyl bromide or selenide (Scheme 7).\(^{21} \)

![Scheme 7](image)

Tetrahydrofurans bearing a vinyl bromide may be gotten from \( \gamma \)-allenyl alcohols 14 by Pd (II) catalysis in the presence of LiBr (Scheme 8).\(^{22} \)

![Scheme 8](image)

4.1.2. Unsaturated oxygen heterocycles

4.1.2.1. Dihydrofurans
The older way to get dihydrofurans from allenes is probably the silver (I) mediated ring closure of \( \alpha \)-allenylalcohols.\(^{23}\) However HCl gas in chloroform\(^{24}\) (\( R^5 = \text{COOEt} \)) or \( \text{AuCl}_3 \)\(^{25}\) in \( \text{CH}_2\text{Cl}_2 \) gave similar results (Scheme 9). In all cases the reaction proceeded with complete axis to centre chirality transfer.

Furanomycin, a Streptomyces metabolite, was synthesised in a few steps using the Ag(I) promoted ring closure of the allenic compound \( 21 \) as key step (Scheme 10).\(^{26}\)

![Scheme 10](image)

The Ag (I)-promoted ring closure of 2,3-pentadiene-1,5-diols has been investigated.\(^{27}\) Generally the cyclisation occurs through the more hindered hydroxyl group (Scheme 11).

![Scheme 11](image)

Cyclisation affording 2,5-dihydrofurans has been also done with coupling using catalytic \( \text{PdCl}_2 \) (Scheme 12).\(^{28,120}\)

![Scheme 12](image)
2,3-Dihydrofurans have been synthesised by Pd(0) promoted ring closure involving a coupling reaction (Scheme 13). It is possible to start the cyclisation from a $\beta$-allenyl alcohol$^{29}$ (phenyl, or more generally, aryl iodide was then used) or a 1-allenylxy-2-iodobenzene$^{30}$ with sodium azide. In the latter case, the organic azides so formed were then trapped with dimethylacetynedicarboxylate to afford the corresponding triazoles.

Although oxaphospholes are not only oxygen heterocycles, one can classify here the formation of 2,5-dihydro oxaphospholes from phosphorylated allenes because it is the oxygen atom which acts as a nucleophile in the ring closure (Scheme 14).$^{31}$

4.1.2.2. Furans

These compounds may be prepared from $\alpha$-allenyl ketones by silver catalysis$^{32}$ as well as Pd(II) catalysis$^{33}$ (Scheme 15). In the latter case the ring closure provided mainly the dimer$^{36}$.

With palladium(0) catalysis the ring closure of the $\alpha$-allenyl ketone can be associated with a coupling reaction introducing in this way a substituent at the 3- or 4- position of the corresponding unsubstituted furan (Scheme 16).$^{34,35}$
Deprotection of the $\beta$-allenyl silyl ether 39 afforded the furan derivative 40 in good yield (Scheme 17). Actually, the expected diol underwent a 5-\textit{exo}-dig ring closure; dehydration of the so-formed dihydrofuranol derivative led to 40.

### 4.1.2.3. Furanones

The most general way to get furanones involves the use of allene-tethered carboxylic acids as starting material. Direct cycloisomerisation of an $\alpha$-allenylacid directed by metal salts acting as Lewis acids like CuCl$_3$ or AgNO$_3$ afforded $\beta$-unsubstituted butenolides (Scheme 18). The $\beta$-halobutenolides 43 were prepared by the ring closure of the $\alpha$-allenylacids$^{40-43}$ 41 ($R^4=H$) using halogens, NBS or CuX$_2$ (Scheme 19).

![Scheme 18](image)

The Pd(II)/LiBr-mediated cyclisation of the $\gamma$-allenylacids 44 afforded the 5-(1-bromoalkenyl) dihydrofuran-2-one 45 (Scheme 19)$^{22,44}$ Moreover, starting from the $\alpha$-allenoates 41 ($R^4=\text{alkyl}$), the compounds 43 were also produced using halogens$^{45}$ or CuX$_2$ in aqueous ethanol$^{46}$

![Scheme 19](image)

Palladium(0) catalyses the coupling cyclisation of $\gamma$-allenylacids$^{17,18}$ to lead 5-vinyl-dihydro furan-2-ones 46 as well as $\alpha$-allenylacids$^{47,48}$ to afford 4-substituted-$5H$-furanones 47 (Scheme 20).

![Scheme 20](image)

Compounds 47 have been obtained with medium to high enantiomeric excess using a chiral ligand in the Pd(0) catalysed coupling cyclisation$^{49}$ of 41 or by chirality transfer from 1:1 salts of optically active $\alpha$-allenylacid–base.$^{50}$

If the allene-tethered carboxylic acids or esters are the main sources of cyclisation to furanones, other methods have been used. For example, several methylene-3-oxabicyclo[3.1.0]hexan-2-ones were obtained by Cu$^{2+}$ induced intramolecular carbene addition from diazooacetates derived from $\alpha$-allenyl alcohols.$^{51}$
Radical cyclisation of allene-tethered bromoacetal has also been used.\textsuperscript{52} This method has nicely been applied as key step to the synthesis of Botryodiplodin.\textsuperscript{53} Lithiation and carbonylation of 1-alkyl-1-methoxyallene provided 5-alkyl-5-methoxy-5\texttextit{H}-furan-2-ones.\textsuperscript{54} The ruthenium-catalysed cyclic carbonylation of \textit{\alpha}-allenylalcohol afforded also substituted 5\texttextit{H}-furan-2-ones.\textsuperscript{55}

4.2. Nitrogen heterocycles

Many papers talking about five-membered nitrogen heterocycles from allenes talk also about oxygen heterocycles.\textsuperscript{18–22} Moreover, the “nucleophilic transition metal based cyclisation of allenes” was recently reviewed.\textsuperscript{56}

4.2.1. Saturated nitrogen heterocycles

The toluene-\textit{p}-sulfonyl-mediated radical cyclisation of bis(allenes) linked together with an heteroatom was early mentioned in the 4.1.1. section about the tetrahydrofurans.\textsuperscript{21} Similar results were obtained for the synthesis of nitrogen heterocycles \textsuperscript{49} starting from \textsuperscript{48}. Compounds \textsuperscript{48} were also carbocyclised using palladium catalysis (Scheme 21).\textsuperscript{57}

\begin{equation}
\text{Scheme 21}
\end{equation}

Palladium-catalysed carbocyclisation was also performed starting from \textit{\delta}-allenylaldehydes or ketones (Scheme 22).\textsuperscript{58,59}

\begin{equation}
\text{Scheme 22}
\end{equation}

Very similar results were also obtained using the palladium–indium-mediated arylative ring closure of the same starting material (Scheme 23).\textsuperscript{60}

A very nice carbocyclisation was used to build the pyrrolidine unit of (-)-\textit{\alpha}-kainic acid.\textsuperscript{61} The cyclo-isomerisation of \textit{\gamma}-aminoallenes is another efficient way to access to 2-vinyl-pyrrolidines (Scheme 24). The hydroamination ring closure was carried out as well by silver catalysis,\textsuperscript{62} palladium catalysis\textsuperscript{63} or organolanthanide catalysis.\textsuperscript{64} The last-mentioned method was nicely used as key step in the synthesis of the pyrrolizidine alkaloid (+)-xenovenine.\textsuperscript{65}

The pyrrolidines \textsuperscript{56} were obtained from \textit{\gamma}-aminoallenes \textsuperscript{54} in several manners (Scheme 25). As we have early seen for oxygen heterocycles, the radical addition of \textit{p}-tosyl bromide or iodide to \textsuperscript{54} followed by an intramolecular nucleophilic substitution led to the compound \textsuperscript{56} with a \textit{p}-toluenesulfonyl group as X.\textsuperscript{20}
The palladium catalysis allowed to introduce several others substituents like bromine, aryl, alkenyl or, by a carbonylation–coupling cyclisation with aryl iodides and carbon monoxide, benzoyl. Similar compounds \( [X = RC(O)] \) were also nicely gotten using the cobalt-mediated acylation-cyclisation method.

4.2.2. Unsaturated nitrogen heterocycles

Pyrrolidinones were prepared from \( \alpha \)-allenylsulfonamides by oxidative cyclisation using dimethyloxirane.

The Scheme 26 shows a palladium-catalysed ring closure providing the oxazolidinones 58 from the allenyl \( N \)-tosylcarbamates 57.
Depending on the reaction conditions, the X group introduced on the 1-alkenyl position in 58 was a bromine atom\(^\text{22}\) when the reaction was performed in the presence of LiBr with palladium acetate as the catalyst or a CH\(_2\)CH\(_2\)CHO group by a conjugate addition with acrolein.\(^\text{70}\) It was also an allylic group;\(^\text{71}\) an aromatic one\(^\text{72}\) with hypervalent iodonium salts or a methoxycarbonyl group.\(^\text{73}\)

The reaction of \(\alpha\)-allenyl hydrazines with \(n\)-BuLi in THF was investigated.\(^\text{74}\) In this way, 3-pyrrolines were obtained in good yields and high enantiomeric purity when SAMP-hydrazines were used. Starting from allene-tethered dithiosemicarbazides, a tin hydride-mediated cyclisation led to both 3\(H\)-pyrroles and alkylidene pyrrolines.\(^\text{75}\) Thermal isomerisation of the former to the latter occurred in some cases.

Silver-mediated ring closure of \(\beta\)-allenylamines afforded 3,4-dihydro-2\(H\)-pyrroles.\(^\text{76-78}\) While, starting from \(\alpha\)-allenylamines 59, the 2,5-dihydro-1\(H\)-pyrroles 60 have been gotten in two ways (Scheme 27).

![Scheme 27](image)

Firstly, the silver-mediated ring closure afforded a compound resulting in just a cycloisomerisation of the starting material (X=H).\(^\text{79-81}\) Very recently, compounds like 60 (X=H) were also obtained by the Ru-catalysed ring closure of allene-tethered alkenes.\(^\text{121}\) Secondly, the palladium-catalysed ring closure permitted to introduce a carbon-containing group as X. Aryl groups were easily introduced using Pd(PPh\(_3\))\(_4\) with an aromatic halide at room temperature,\(^\text{80}\) increasing the temperature resulted in the formation of the corresponding pyrrole. A carbonylative cyclisation under CO provided the compound 60 with a benzoyl group as X.\(^\text{67}\)

Similarly bicyclic heterocycles have been gotten starting from allenyl or homoallenyl pyrrolidin or oxazolidin-2-ones (Scheme 28).

![Scheme 28](image)

The 4-allenyl oxazolidinones 61 (X = O) were cycloisomerised to the compound 63 (R\(^3\) = G = H) using silver catalysis involving a 5-endo-trig ring closure.\(^\text{82}\) On the other hand, the palladium-mediated coupling-cyclisation reaction of the same kind of starting materials afforded the oxazolidinones 63 and their corresponding pyrrolidinones (G = allylic group).\(^\text{83}\) The compounds 63 (R\(^2\) =H, G = benzylic group) were also mainly obtained from the homoallenyl oxazolidinones or pyrrolidinones 62 by a palladium-catalysed cyclisation-coupling reaction involving now a 5-exo-dig ring closure.\(^\text{84,85}\)
In the field of the bicyclos heterocycles, it had been reported the synthesis of \( N \)-alkyl-2-vinylindoles from \( N \)-alkyl-\( N \)-homoallenylanilines by a tandem process involving an oxydation at the nitrogen and then a set of three rearrangements. \(^{86}\)

The compound \( 65 \) with an indole skeleton was directly constructed by intramolecular carboxypalladation of the allene \( 64 \). \(^{87}\) The reaction was proposed to proceed via the intermediate \( 66 \) (Scheme 29).

![Scheme 29](image)

Dihydropyrrolones and alkylidenedihydropyrrolones were gotten respectively from \( \alpha \)-allenylamines through carbonylative cyclisation by ruthenium catalysis, \(^{88}\) from \( \alpha \)-allenylamides \(^{89}\) with \( \text{CuX}_2 \) and from \( \alpha \)-allenylimines through carbonylative ring closure by iron catalysis. \(^{90}\)

Sometimes the same starting material is able to lead to a nitrogen heterocycle or to an oxygen one. To illustrate this purpose and before going to the next point, let us consider a very interesting recent work (Figure 1) showing that the \( \text{Pd}(0) \)-catalysed coupling-cyclisation of 2,3-allenamides may lead to \( \gamma \)-hydroxy-\( \gamma \)-lactams or iminolactones depending on some steric hindrance factors. \(^{122}\)

![Figure 1](image)

4.3. Other heterocycles

As it is pointed out above, in the overwhelming majority of cases the heterocycles coming from allenes are oxygen or nitrogen heterocycles. However, in some scarce cases other heterocycles were synthesised. It is perhaps useful to recall here the case of the oxaphospholes mentioned above at the paragraph 4.1.2.1. \(^{31}\)

Very recently a silicon-tethered allenic intramolecular Pauson-Khand reaction was reported. \(^{91}\) This reaction led to five or six-membered silicon heterocycles.

5. Heterocycles with six-membered rings

5.1. Oxygen heterocycles
As we have already seen in the case of the five-membered heterocycles, the ring closure may be generated by the formation of a C–C bond inside an allenic ether or ester. In this field, cyclic ethers were obtained using the palladium-mediated intramolecular hydrocarbonation of alkoxyallenes or o-iodobenzyloxyallenes. The palladium-catalysed cyclisation-coupling reaction of buta-2,3-dienyloxyaldehydes or ketones has already been reported about the formation of five-membered rings as well as the intramolecular cyclopropanation of allenic diazoacetates.

Of course, six-membered cyclic ethers or esters were also prepared by the intramolecular formation of a C–O bond starting from an allene-tethered alcohol or acid. The radical addition of p-toluenesulfonyl bromide or iodide to allene-tethered alcohols has been reported above. Substituted tetrahydropyrans were obtained in this way when TsI was used. It is to be noticed that, with the same starting material, eight-membered ether was the product of the reaction when TsBr was used. The Pd(II)-catalysed oxybromination of allenic alcohols and allenic acids as well as the ruthenium-catalysed cyclic-carbonylation of allenic alcohols were also reported above. Substituted tetrahydropyrans and δ-lactones were obtained in this way.

The p-toluenesulfonic acid-mediated cyclisation of benzenesulfinic β-allenylalcohols afforded benzenesulfanyl-dihydro-2H-pyrans. While the PdCl₂-mediated methoxycarbonylation of a conveniently allene-tethered alcohol was used as the key step in the synthesis of (+) rhopaloic acid A.

At last, it should be noted that hydroxy-methoxyallenylphthalans (Scheme 30) were isomerised to isochromanes with palladium(0) catalysis.

The reaction took place through a Pd(0)-catalysed ring expansion of the α-allenyl cyclic hemiketal. A mechanism involving a cascade hydropalladation-ring expansion has been suggested.

5.2. Nitrogen heterocycles

Piperidines have been prepared from allenic compounds by carbocyclisation or by amino cyclisation using silver catalysis, palladium catalysis or lanthanide catalysis. The silver-mediated ring closure of δ-allenylamines has been used as the key step in the synthesis of the clavepictine A and B.

Compounds like 3-hydroxy-piperidin-4-ones were obtained from β-allenylsulfonamides by oxidative cyclisation with dimethylidioxirane.
The Pd(II)-catalysed oxydative aminocarbonylation\textsuperscript{73} and the Pd(0)-catalysed coupling reaction with hypervalent iodonium salts\textsuperscript{72} of allene-tethered N-tosylcarbamates provided 4-alkenyl-N-tosyl-[1,3]oxazinan-2-ones.

The free-radical addition of the tosylbromide on δ-allenylsulfonamides led to 2-alkenyl-N-tosylpiperidines while, starting from β-allenylsulfonamides, the same reaction led to 1,5-ditosyl-1,2,3,6-tetrahydropyridines.\textsuperscript{20} Other 1,2,3,6-tetrahydropyridines have also been obtained from silver-mediated 6-endo-trig ring closure of β-allenylamines.\textsuperscript{76} On the other hand, 2,3,4,5-tetrahydropyridines were gotten by titanium-mediated cyclisation of β-allenylamines.\textsuperscript{100} Starting from gem-difluoroallenic propargylamines, a novel Mo-catalysed [2+2] cycloaddition afforded gem-difluoro-3-azabicyclo[4.2.0]octa-1[8],5-dienes including a 1,2,3,6-tetrahydropyridine unit.\textsuperscript{101}

The tandem hydropalladation-ring expansion reaction early seen about the formation of six-membered oxygen heterocycles allowed also to get 2,3-dihydro-isoquinoline-1,4-dione.\textsuperscript{97}

Similarly, the tandem intramolecular carbopalladation-heterocyclic ring expansion reaction permitted the access to the tetracyclic quinolitidine derivatives 70 (Scheme 31).\textsuperscript{102}

The Ru-mediated cyclocarbonylation of β-allenyl sulfonamides under CO pressure afforded some derivatives of the 5,6-dihydro-1H-piperidin-2-one.\textsuperscript{88}

The cascade palladium-catalysed cyclisation-anion capture furnished a good access to 2H-isoquinolin-1-ones 72.\textsuperscript{30,103,104} Depending on the reaction conditions, the exo-methylene isomer 73 was sometimes produced (Scheme 32).

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Depending on the substitution pattern, the silver-mediated cyclisation of phosphonylated \( \beta \)-allenylamines may lead to 2,5-dihydropyridines.\(^{77}\) These compounds, substituted at the 3-position by a tributylstannanyl group, have also been obtained by the tin-mediated free radical cyclisation of \( \beta \)-allenyl benzoyloximes, oxime ethers or hydrazones. Actually, the main product of the addition of the tin radical on the allenyl moiety results generally in a five membered carbocycle \( 76 \) coming from a 5-\( \text{exo} \)-dig ring closure process (Scheme 33). But, depending mainly on the size and the polarity of the \( R^3 \) substituent, and, in a lesser extent, on the nature of the \( Z \) substituent, a rearranged compound \( 77 \) or a dihydropyridine \( 75 \) coming from a six-\( \text{endo} \)-trig ring closure on the nitrogen have been obtained.

With a bulky and electron-withdrawing \( R^3 \) group the dihydropyridine \( 75 \) was the main or the sole product of the reaction.\(^{105,106}\)

To finish, let us consider the tandem cyclisation-oxidation reaction of allene-tethered hydrazones leading to pyridazinones derivatives.\(^{107}\)

6. Heterocycles with larger rings

Contrary to the case of five or six-membered heterocycles, there is only a few papers related to the formation of seven and larger-membered heterocycles coming from intramolecular ring closure of allenic compounds.

Concerning the formation of seven-membered rings, let us mention the synthesis of dihydro[c] benzazepin-3-ones from allene-tethered nitrones precursors,\(^{108}\) the synthesis of 2-vinyloxepanes by Pd(II)-catalysed intramolecular hydrocarbonation of alkoxyallenes\(^ {92}\) and the formation of seven-membered lactones by ruthenium-catalysed cyclocarbonylation of allenylalcohols.\(^ {109}\) In this latter case, eight-membered lactones were also prepared in the same way.

The thermal isomerisation of 1-morpholino-3-phenylallenes \( 78 \) had also been reported.\(^ {110}\)

The formation of the seven-membered nitrogen heterocycle in the oxazinobenzazepine derivative \( 79 \) was explained in three steps: firstly, a 1,4-shift of a proton affording an unsaturated azomethine ylide; secondly, a conrotatory 1,7-electrocyclisation and thirdly, a rearomatisation by a 1,5-suprafacial hydrogen shift.

About the eight-membered rings, it should be noticed that 2\( H \)-oxocines have been gotten from allenylalcohols by the tosylbromide radical addition.\(^ {20}\) The Pd(II)-catalysed cyclisation of \( \omega \)-haloallenes have permitted the access to benzo[c]oxepine, benzo[c]oxocine derivatives and similar nine-membered heterocycles \textit{via} a cyclic carbopalladation.\(^ {111}\) The formation of medium (7–11) ring azacycles by a tandem iodination-cyclisation process starting from allene-tethered sulfonamides has been investigated.\(^ {112,113}\)
As shown in the case of five-membered heterocycles, the Pd(0)-catalysed coupling of allene-tethered N-tosylcarbamates with hypervalent iodonium salts is a good way to provide cyclic carbamates. In this way, oxazonin-2-one and oxazecin-2-one derivatives were synthesised in moderate yields.72

7. Miscellaneous

Under this heading we shall consider either reactions involving the formation of more than one cycle (one by one or at the same time) or the formation of bridged polycyclic compounds or else the formation of other heterocycles: sulphur heterocycles for instance. As expected, unlike the case of five and six-membered heterocycles, we only found a few papers talking about that.

In the synthesis of 81 (Figure 2) from 80, two fused heterocycles were formed by Pd(0) cascade carbo and heteroannulation of allenic compounds.114 In the enantioselective allene-enone photocycloaddition (82 → 83) the cyclobutane ring and the five-membered one were closed at the same time.115 As for it, the tetracyclic compound 85 was arising from 84 by an intramolecular azide "criss-cross" addition.116 The reaction of o-(1,2-propadienyloxy)benzaldehyde 86 with phenylhydroxylamine led to the dioxa azabicyclo[3.2.1]octene 87.117 The nitrone formed in a first step underwent an intramolecular dipolar cycloaddition reaction with the allenic moiety to give 87.

![Figure 2](image)

In the total synthesis of ent-gelsedine the key step was the formation of the bridged bicyclic compound 90 from the allenylpyrrolidinone 88 coming itself from (S)-malic acid.118 The ring closure was generated by a very nice iodide-promoted allene N-acyliminium ion cyclisation (Scheme 35).119

8. Conclusion

This short survey shows that the intramolecular ring closure of allenic compounds may be a powerful method for the synthesis of various heterocycles. Most of the papers are talking about the formation of five-membered heterocycles; then, is coming the formation of six-membered heterocycles and, in a less extent the seven and medium-membered rings. The synthesis of three and four-membered heterocycles by intramolecular cyclisation of allenic compounds has not much been investigated.
The heteroatoms used in these syntheses are mainly oxygen and nitrogen but sulphur, phosphorus and silicium also have been used. Two methods were used to make the heterocycle: either bind together two carbons in a compound with a heteroatom in a convenient position inside the molecule, or directly make a link between the heteroatom and one of the allenic carbons.

A great variety of chemical reactions were used to make the cyclisation. Among these tools, the most widely used are probably the Lewis acid-promoted ring closure and the palladium-catalysed cyclisation; but other methods have been used. The free radical ring closure or the cyclisation promoted by a nucleophilic addition on the allenic moiety as well as the use of other transition metals than palladium as catalyst are some good examples of that.

References