Metal Mediated Nitrene and Carbene Transfer Reactions for the Synthesis of Fine Chemicals.

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The development of metal-catalyzed intermolecular nitrogen atom transfer reactions, such as the amination of hydrocarbons is a topic of high current interest. Very good results have been obtained by using PhI=NSO$_2$Ar as the nitrogen source and metal complexes as catalysts. However the [N($p$-tolylsulfonyl)imino]phenyliodinane compounds can only be obtained from the corresponding sulfonamides, and thus they belong to a limited family of reagents. In addition to that the sulfonyl group is always introduced in the molecule and PhI is formed as side-product.$^1$ In order to develop new methods for the direct and selective synthesis of organonitrogen compounds, in the last years we have explored the use of arylazides as aminating agents in the presence of ruthenium or cobalt porphyrin complexes as catalysts.$^2$

Arylazides are a versatile class of starting materials, they can be easily synthetized from the corresponding substituted anilines, they are stable enough to be safely handled in the laboratory, they allow to introduce a $N$-aryl group in the molecule and last but not least the only by-product of the reaction is molecular nitrogen. The metal complexes are easily synthesized in high yield starting from the differently substituted porphyrin ligands and Ru$_3$(CO)$_{12}$ or CoCl$_2$•(H$_2$O)$_4$ respectively.

Co$^{II}$ (porphyrin) complexes catalyze the reaction of ArN$_3$ with hydrocarbons containing a benzylic group, ArR$_1$R$_2$CH, to give the corresponding amines, ArR$_1$R$_2$C-NHAr. When at least one of the R$_1$-R$_2$ substituents is hydrogen, the catalytic reaction proceeds further to give the imine ArRC=NAr in good yields.$^3$
Both ruthenium and cobalt porphyrin complexes were found to be good catalysts for the synthesis of allyl amines and aziridines from non activated olefins. The amination reaction of olefins is very selective and the formation of amines or aziridines strongly depends on the nature of the unsaturated substrate. It is worth noting that we have never observed the formation of both of them in a single reaction and that the rate and selectivities of ruthenium catalyzed reactions are higher than those of cobalt catalyzed ones.

Terminal olefins like styrene react with arylazides in the presence of ruthenium porphyrin complexes to yield the corresponding aziridines in high yields and short reaction time. It is worth noting that the TON of the amination of α-methylstyrene is 2175, to our knowledge the largest TON reported for this class of reactions. With internal cis or trans di-substituted olefins, the yield of the reaction is determined by the sterically hindrance on the β-carbon. With tri- or tetra-substituted olefins no reaction was observed. On the other hand the reaction between cyclic internal olefins and arylazides afforded allyl amines instead of aziridines. The mechanistic investigations of these two reactions indicate two different intermediates for the two amination reactions, an imido complex (A) for allylic amination and an azido-metal complex (B) for the aziridination.

In order to study the scope of the aziridination reaction we have tested the catalytic activity of Ru(porphyrin)CO complexes in the amination of conjugated dienes by aryl azides.
The reaction yields $N$-aryl-2-vinylaziridines\textsuperscript{5} without thermolytic or photolytic activation of the azides.

\[
\begin{align*}
\text{R}^1\text{C} & \quad \text{R}^4\text{C} \\
\text{R}^2 & \quad \text{R}^5 \\
\text{R}^3 & \quad \text{ArN}_3
\end{align*}
\]

\[
\text{Ru(porphyrin)CO} \rightarrow \frac{\text{R}^1\text{C} \quad \text{R}^4\text{C} \quad \text{R}^2 \quad \text{R}^5 \quad \text{R}^3 \quad \text{ArN}}{\text{N}_2}
\]

\textbf{Scheme 3. Synthesis of }N\text{-aryl-2-vinylaziridines}

Several olefins and azides were tested in the reaction catalyzed by Ru(TPP)CO (I) (TPP = dianion of tetraphenylporphyrin) and the synthetic results are illustrated in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>(2\text{a}, \text{R} = 4\text{-NO}_2)</td>
<td>4</td>
<td>99 (77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2\text{b}, \text{R} = 4\text{-Cl})</td>
<td>4</td>
<td>95 (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2\text{c}, \text{R} = 3,5-(\text{CF}_3)_2)</td>
<td>1.5</td>
<td>99 (66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2\text{d}, \text{R} = 4\text{-Br})</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2\text{e}, \text{R} = 4\text{-OCH}_3)</td>
<td>15</td>
<td>15 (traces)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2\text{f}, \text{R} = 4\text{-CN})</td>
<td>11</td>
<td>99 (70)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>(3)</td>
<td>12</td>
<td>35 (10)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{CH}_2\text{CH}=\text{C} (\text{CH}_3)_2)</td>
<td>(4)</td>
<td>10</td>
<td>61 (20)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Ph}=\text{C} \quad \text{Ph})</td>
<td>(5)</td>
<td>3</td>
<td>40 (25)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>(6)</td>
<td>8</td>
<td>82 (35)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>(7)</td>
<td>15</td>
<td>65 (54)</td>
</tr>
</tbody>
</table>

\textbf{Table 1. Aziridination of conjugated dienes catalyzed by Ru(TPP)CO}

Note that two different yields are reported for each reaction in Table 1. The first was determined by $^1\text{H}$ NMR (1-chloro-4-nitrobenzene as an internal standard) at complete conversion of the starting azide whereas the number in parenthesis is the yield of the isolated
product, purified by flash chromatography on deactivated silica. The reactions between 2,3-dimethyl-1,3-butadiene and different azides (Table 1, entry 1) proceeds with high yields in short reaction times using aryl azides bearing electron-withdrawing groups in the para or meta positions of the aryl group (Table 1, products 2a, 2c). The reaction between 2,3-dimethyl-1,3-butadiene and 4-cyanophenyl azide afforded the corresponding vinylaziridine in a 99% yield but required a longer reaction time (Table 1, product 2f). This can be due to the presence of a coordinating group such as -CN that can compete with the -N₃ moiety for the ruthenium atom, thus partly inhibiting the catalytic reaction. As expected, an electron-donating and coordinating group like -OCH₃ (Table 1, product 2e) resulted in a longer reaction time and a lowering of the yield. When the diene is not symmetric, the aziridine moiety is always formed on the less sterically hindered double bond (Table 1, entries 2, 3). When the diene is 1,3-disubstituted, the aziridine ring is formed on the double bond with the unsubstituted terminal carbon atom (Table 1, entry 5). Lower yields are registered with a sterically encumbered 1,4 disubstituted diene (Table 1, entry 4). However the reaction occurred with a trans selectivity and with retention of the geometry of the unreacted double bond. Our methodology does not allow the preparation of aziridines of unconjugated or cyclic dienes such as 1,5-hexadiene and 1,3-cyclooctadiene. On the other hand, the reaction between 1,3-cyclohexadiene and 4-nitrophenyl azide afforded the allylamine 7 (Table 1, entry 6) instead of the corresponding vinylaziridine. We propose that the formation of 7 could be due to rearrangement of the unstable N-aryl vinylaziridine. In order to optimize the synthetic methodology, in the case of the aziridination of 2,3-dimethyl-1,3-butadiene with 4-nitrophenyl azide, we lowered the amount of the catalyst and we obtained after 9 hours at 65°C a 90% yield of 2a using mol ratios 1/ArN₃/diene = 1:400:2000.

Figure 3. Ruthenium porphyrin complexes used as catalysts
At this stage it was interesting to investigate the influence of the electronic and/or steric behavior of different Ru(porphyrin)CO complexes on the vinylaziridines formation. Therefore we synthesized different catalysts (Fig. 3) tested in the reaction to yield 2a. The analysis of the collected data indicates a small dependence of both reaction rate and selectivity on the electronic and steric nature of the substituents in the porphyrin skeleton.

As reported in Table 1, the purification procedure causes a lowering of the yields due to the ring opening reactions of N-aryl-2-vinylaziridines to 2,5-1H-benzo[b]azepines\(^6\) (Scheme 4).

![Scheme 4. Synthesis of (Z)-2,5-dihydro-3,4-dimethyl-7-nitro-1H-benzo[b]azepine (8)](image)

**Figure 4.** \(^1\)H NMR spectra of the reaction shown in Scheme 4

The \(^1\)H NMR analysis of the reaction between 2,3-dimethyl-1,3-butadiene and 4-nitrophenyl azide revealed that 8 is the only reaction product when the 1/ArN\(_3\)/diene ratio is 1:20:70 and the catalyst is 13 times more concentrated (Fig. 4). Preliminary results show that the same methodology can also be applied to the synthesis of 1H-benzo[b]azepines of myrcene and trans-2-methyl-1,3-pentadiene. A more extensive investigation of this rearrangement reaction is still in progress.

The logical extension of this topic is the use of chiral complexes as catalysts. It is well known that porphyrin metal complexes have been used in enantioselective oxidation reactions with success. Therefore we have synthesized the cobalt and ruthenium complexes of a chiral porphyrin reported some years ago by Marchon\(^7\) in which the meso positions are occupied by four myrthenal groups. These complexes have been used as catalysts for amination reactions.
but, in spite of the good catalytic activity observed, the enantioselectivity of the reactions was poor. However, it should be noted that this is the first example of the use of an arylazide in an enantioselective amination reaction.\(^8\) The synthesis of chiral porphyrins often requires several steps and usually the yields are very low. Therefore we are also studying the use of Schiff base ruthenium and cobalt complexes as catalysts for amination and cyclopropanation reactions.\(^9\) The best synthetic results were obtained in cyclopropanation of \(\alpha\)-methylstyrene employing 17\(^{10}\) as catalyst (Fig. 5).

\[
\begin{align*}
\text{H}_3\text{C} & \quad + \quad \text{N}_2\text{CHCOOEt} \\
\text{Ph} & \quad \text{EtOOC} \quad \text{Ph} + \quad \text{EtOOC} \quad \text{Ph}
\end{align*}
\]

\(\text{trans} / \text{cis} = 1:2\)

Figure 5. The cyclopropanation reaction involving the chiral catalyst 17

Currently, the interest of our research is moving from the classical homogeneous catalysis to the heterogeneous one. Application of new materials in the field of catalysis has been extensively studied in order to prepare catalysts more stable, selective and with the possibility of their easy recovery and recycle. With this idea in mind, we investigated the preparation and characterization of new Hyflon based membranes, entrapping a series of fluorinated ruthenium porphyrins. Preliminary results using the catalytic membrane showed a good activity in the aziridination of styrenes and also the possibility of recycling it.

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