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Gold(I)-Catalyzed Hydroindolylation of Allenyl Ethers†

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The gold (I)-catalyzed reaction/rearrangement of allenyl ethers has been investigated in the presence of indoles. Either hydroindolylation or alkylation of indole with the pendant group of allenyl ether has been observed. The reaction outcome seems to be decided mainly by the nature of the pendant group of the allenyl ether. Control experiments are indicative of an inner sphere mechanism for the hydroindolylation reaction.

Allenes are simple three carbon synthetic building blocks having three consecutive carbons which can be differentially functionalized with equal ease. Arguably, gold catalysts, because of their soft and carbophilic character, have been well explored in recent times for the intermolecular and, more particularly, the intramolecular functionalization of allenes.2,8 The gold-catalyzed hydroalkoxylation and hydroamination of allenes has been well explored by the groups Yamamoto, Hashmi and Widenhoefer.4,8 Comparatively, the gold-catalyzed hydroarylation of allenes is less explored.6,9 The gold-catalyzed conjugate addition of the furans to the electron deficient allenes by Hashmi and co-workers,8 the intermolecular hydroarylation of allenes employing di- and trimethoxybenzene derivatives as nucleophiles by Gagne and co-workers,4 the intra- and intermolecular hydroindolylation of (electronically unbiased) allenes by Widenhoefer and co-workers4b,9c are the only few notable reports documented so far in this area. Keeping in mind the fact that there are very limited examples of the arylation with the allenes and that the functionalized indoles are valuable synthons in the area of total synthesis, we intended to explore the possibility of the hydroindolylation of allenyl ethers under the gold-catalysis.

Figure 1: Gold-catalyzed functionalization of allenyl ethers

We speculated three possible products from the gold(I)-catalyzed reaction of allenyl ethers when there is an external C-nucleophile such as indole is present in the reaction medium. The addition can occur either at C1, like it was observed with the oxygen nucleophiles10 or at C3, which is desired. On the other hand, if the fast [1,3] O→C rearrangement of these allenyl ethers is the first event, it will result in the isolation of the corresponding acryl aldehyde (Figure 1).11

To start in this direction, the four allenyl ethers 1a–1d have been selected as the model allene substrates, considering their increasing ease of stabilization of the intermediate benzyl cation, thereby increasing the possibility of the [1,3]O→C rearrangement. The reactions were conducted by adding a freshly prepared CH2Cl2 solution of AuCl(PPh3) and AgSbF6 (0.1 mol% Au with respect to the indole 2a) to a cooled solution of indole and allene in CH2Cl2 and left over for 1.5 h at rt. The results are surprising and complementary in nature with the allenyl ethers 1a/1b and 1d. As shown in Scheme 1 with the allenes 1a and 1b, the products 4aa and 4ab resulting from the hydroindolylation have been isolated. With 1d, the C3benzylation was the only event giving 5ada as the main product. The possibility of the C1 activation was eliminated with the C3 benzylation of indole.

Scheme 1: The complementary reactivity of the allenyl ethers 1a–1d

Table 1: Catalyst screening for hydroindolylation of allenyl ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuCl(PPh3)</td>
<td>--</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>AuCl(PPh3)</td>
<td>AgSbF6</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td>--</td>
<td>AgSbF6</td>
<td>15%</td>
</tr>
<tr>
<td>4</td>
<td>--</td>
<td>AgOAc</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>--</td>
<td>AgNTf2</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>--</td>
<td>AgBF4</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>AuCl(PPh3)</td>
<td>AgNTf2</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>AuCl or AuBr3</td>
<td>--</td>
<td>~32%</td>
</tr>
</tbody>
</table>

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On the other hand, in case of the reaction of 1c with indole 2a, mixture of 4ac and 5ac were observed. Quite interestingly, no formation of the [1,3] O→C rearrangement product was noticed with any of the four allenyl ethers used. This is very important since the allenyl ethers 1c and 1d undergo instantaneous rearrangement even with 0.05 mol% of the same catalyst in the absence of indole.\textsuperscript{11}

Next, the compatibility of other Au-catalytic systems for the hydroindolylation reaction has been examined by keeping the indole 2a and benzyl allenylether 1b as the representative substrate. As shown in Table 1, the Au(I) complex alone has no influence on the reaction (entry 1). With AgSbF\textsubscript{6} alone, only trace amounts of product was formed and the remaining allenyl ether decomposed. With other additives like AgOAc, AgNTf\textsubscript{2} and AgBF\textsubscript{4} salts, no product formation was observed individually or in combination with AuCl(PPh\textsubscript{3})\textsubscript{3}. Interestingly, in the case of allenamides, the nucleophilic addition was smooth with the AgNTf\textsubscript{2} in combination with gold(I) complex.\textsuperscript{12} With both AuCl\textsubscript{3} and AuBr\textsubscript{3} salts, the hydroindolylation reaction was the major event. However, this resulted only in 32% of the product 4ab.

The generality of these complementary reactions (Table 2) has been explored by employing two sets of allenyl ethers that mainly differ on the ease of the benzylic carbocation formations. All the reactions were carried out by employing 0.1 mol% of the catalyst solution. Initially, various p-(floro/chloro/bromo) benzylallenylethers 1e–1g were screened for the hydroindolylation purpose and delivered the corresponding products 4ae–4ag in 71–73% yield. Not only the simple benzylallenyl ethers but also the allenyl ethers bearing a fused ringlike 2-naphthylmethyl, 1-naphthylmethylallenyl ethers 1i and 1j are also found to be good substrates for this hydroindolylation process. The reactions of the tetrahydrofurfurylallenylether 1k and 2,6-diflorobenzylallenylether 1h were also found to be successful for the hydroindolylation with indole.\textsuperscript{35}

Also employed were various substituted indoles to study the influence of the nucleophilicity on the reaction outcome. The reactions with the 1-Me- (2b) 5-methoxy- (2e) and 5-bromoindole (2d) and 2-methyl-5-methoxy- (2e) indoles with selected allenyl ethers proceeded smoothly with excellent yields.\textsuperscript{35}

On the other hand, the reactions of indole 2a with the electron rich allenyl ethers 1n–1s exclusively provided the benzylaion products 5an–5as respectively.

Quite interestingly, the mechanistic studies on these gold-catalyzed allene functionalization\textsuperscript{4} with the external nucleophiles are scarce. In general, two pathways comprising either an inner sphere or an outer sphere coordination of gold with indole\textsuperscript{15} and/or allene have been postulated. While, an inner sphere pathway has been proposed for the gold(III)-catalyzed intermolecular hydroamination of allenes by Yamamoto,\textsuperscript{5a} for the same reaction, when gold(I) was employed, an outer sphere pathway was suggested by Toste.\textsuperscript{5d} The possibility of both inner and outer sphere pathways has been speculated for intermolecular hydroamination and also for the addition of the furans to allenes respectively by the Widenhoefer and Hashmi groups.\textsuperscript{5b, 4a} Coming to the hydroindolylation of allenes, an outer sphere pathway has been suggested by both the Widenhoefer and Che groups.\textsuperscript{4b, 4d} Thus, the issue of inner vs outer sphere pathways in the gold-catalyzed nucleophilic addition to allenes still remains an open question.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Table 2: Scope of complementary alkylation or benzylation of indoles with allenyl ethers & \\
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\end{tabular}
\end{table}
Given the observed dependence of the reaction outcome on electronic effects associated with the the allene, we conducted some control experiments with the pre-mixed indole gold solution [2b, Au(PPh3)SbF6] as catalyst to examine the feasibility of both [1,3] rearrangement [without any indole in the reaction mixture] and the hydroindolylation [with indole] of alleny l ethers 1b and 1c. As shown in Scheme 2, with this pre-complex [2b, Au(PPh3)SbF6], only a trace amount of hydroindolylation products 4bb and 4bc was observed with the alleny l ethers 1b and 1c. On the other hand, in the presence of 1 eq. N-methylindole (2b), both alleny l ethers 1b and 1c gave the good yields of the corresponding hydroindolylation products.

These observations strongly suggest that an inner sphere coordination path is in operation for the corresponding hydroindolylation reactions (Figure 2). The pattern of 1H NMR of N-methylindole has been completely changed when recorded in the presence of 1 eq. of Au(PPh3)SbF6, indicating possible interaction of gold complex with indole. However, the 31P spectra did not provide any conclusive information (See ESI). Hence, to further understand the involvement of an inner sphere mechanism in these two complementary hydroindolylation/benzylation reactions, an equimolar mixture of the alleny l ether 1b and indole 2a has been treated with 1 eq. of catalyst solution A (prepared from the N-methylindole 2b). The LC-MS analysis of the reaction indicated the formation of 4bb resulting from the hydroindolylation with the N-methylindole 2b that was present with the gold-complex (for complete experimental details see ESI). The product expected from hydroindolylation with externally present indole 2a was not detected. Next, the benzylation reaction was examined with an equimolar mixture of alleny l ether 1s and indole 2a has been treated with 1 eq. of catalyst solution A. Once again, the LCMS analysis clearly indicated the exclusive benzylation of the N-methylindole 2b present on the gold-complex (Scheme 3). Similarly, when added 1 eq. of complex B [indole 2a/AuPPh3/SbF6] to an equimolar solution of N-methylindole and allenes 1b or 1s, in both the instances, the exclusive transfer of indole 2a only was observed.

**Scheme 2:** The reactivity of alleny l ethers 1b and 1c with pre-complex A in the absence and in the presence of indole 2b.

From the above control experiments, it is very clear that the complexation of 2b with the gold-center is the first event and the subsequent transfer of the N-methylindole from the metal complex to the alleny l ethers 1b and 1c was evidenced by the formation of trace amounts of the hydroindolylation products 4ab and 4bc. Notably, the resulting complex is not sufficiently active to bring the rapid [1,3]-rearrangement of the alleny l ether 1c. The plausible mechanism was depicted in the Figure 2.

**Figure 2:** Proposed mechanistic pathway for the gold(I) catalyzed hydroindolylation/benzylation of alleny l ethers.

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**Scheme 3:** Competition experiments in support of the inner sphere mechanism.
These stoichiometric experiments clearly indicated that the indole transfer either to the allene or to the carbocation of the contact ion pair (resulting from the dissociation of the allenyl ether) is occurring intramolecularly.

In conclusion, the gold (I)-catalyzed hydroarylation of allenyles has been investigated. Preliminary control experiments reveal that the key C–C bond formation event, i.e. the nucleophilic addition to allene seems to be proceeding via an inner sphere pathway. However, further studies are warranted to provide conclusive evidence in this regard and also to understand the nature of the intermediates/transition states involved in this process.

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Notes and references

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2) Electronic Supplementary Information (ESI) available: [Characterization data and spectra of all new compounds]. See DOI: 10.1039/b000000x/
Graphical Abstract:

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Nucleophilicity Game: The gold (I)-catalyzed reactions/rearrangement of allenyl ethers has been investigated in the presence of indoles. Either hydroindolylation or alkylation of indole with the pendant group of allenyl ether has been noticed. The reaction outcome seems to be decided mainly by the nature of pendant group of allenyl ether. Control experiments are indicative of an inner sphere mechanism for the hydroindolylation reaction.