Tuneable asymmetric copper-catalysed allylic amination and oxidation reactions

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Received (in Cambridge, UK) 8th July 2005, Accepted 15th September 2005
First published as an Advance Article on the web 29th September 2005
DOI: 10.1039/b509678b

Asymmetric allylic amination or oxidation can be achieved by reaction of an alkene with a peroxycarbamate catalysed by a chiral copper bis-oxazoline complex, and the reaction can be tuned to give either the amination or oxidation product by reagent choice.

The discovery of new catalytic asymmetric allylic oxidation reactions has been the objective of much research over the past decade. In 1995, the groups of Pfaltz and Andrus reported the enantioselective allylic oxidation of alkenes using a copper bis-oxazoline complex as the catalyst and a perester as the stoichiometric oxidant. Other groups have since reported examples of asymmetric copper-catalysed Kharasch–Sosnovsky reactions, but the levels of induction have usually been modest. Recently, Andrus and Zhou reported the highly enantioselective asymmetric allylic oxidation of cyclic alkenes, but reaction rates were low and reaction times of several days were required.

Allylic amination is a well known transformation, but catalytic asymmetric variants of the reaction are rare. Kohmura and Katsuki have reported two examples of enantioselective allylic amination by C–H insertion of a metal nitrene generated using a chiral manganese complex. However, in spite of the encouraging levels of asymmetric induction obtained in these cases, further examples of enantioselective allylic amination have not appeared. Katsuki and co-workers have also performed amination by copper-catalysed reaction of an alkene with a peroxycarbamate, but an asymmetric version of this reaction has not been reported.

We were intrigued by the possibility of performing direct asymmetric allylic amination of unfunctionalised alkenes using a variant of the Kharasch–Sosnovsky reaction. In preliminary investigations, we performed copper-catalysed allylic amination reactions of cyclohexene and cyclopentene at room temperature in a variety of solvents (reaction times 12–40 h), using the peroxycarbamate as the nitrogen donor (eqn. 1, Table 1). The ligands 1a–f were screened and the complex generated from the ligand 1b and Cu(MeCN)_2PF_6 was found to be the best catalyst.

![Image](Image)

**Table 1** Allylic amination of cyclohexene and cyclopentene with the peroxycarbamate 2a and the copper complex of ligand 1b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Yield 3/4 (%)</th>
<th>Ec 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclohexene</td>
<td>PhMe</td>
<td>22</td>
<td>25 (+)R/7ad</td>
</tr>
<tr>
<td>2</td>
<td>Cyclohexene</td>
<td>MeCN</td>
<td>20</td>
<td>31 (+)R/7ad</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexene</td>
<td>EtOAc</td>
<td>26</td>
<td>51 (+)R/7ad</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexene</td>
<td>CH₂Cl₂</td>
<td>44</td>
<td>51 (−)S/7ad</td>
</tr>
<tr>
<td>5</td>
<td>Cyclohexene</td>
<td>Me₂CO</td>
<td>14</td>
<td>70 (+)R/7ad</td>
</tr>
<tr>
<td>6</td>
<td>Cyclopentene</td>
<td>CH₂Cl₂</td>
<td>30</td>
<td>46 (−)S/7ad</td>
</tr>
</tbody>
</table>

* Isolated yield based on the amount of oxidant used. † Determined using chiral HPLC. ‡ Reaction performed with (R,R)-1b. § Configuration established by comparison of [α]D values to literature data. ‡ Ec determined by chiral HPLC using the corresponding N-benzylation amine.

The results of our initial experiments indicated that choice of solvent was crucial, with reactions in both ethyl acetate and dichloromethane delivering the allylic amines 3 and 4 with reasonable levels of induction (entries 3 and 4, Table 1). The reaction performed in acetonitrile gave the product 3 with the highest ee (entry 5), but the yield was low. Reducing the reaction temperature to 0 °C had little effect on the level of induction but resulted in a lower reaction rate and poor conversion. The use of other copper(I) salts led to inferior yields and lower levels of asymmetric induction.‡

The influence of the peroxycarbamate on the outcome of the reaction was explored in an attempt to increase the yield and level of asymmetric induction (eqn. 2, Table 2). The tert-butyl N-arylperoxycarbamates 2b–e were prepared from the corresponding isocyanate using literature procedures. Copper-catalysed amination reactions of cyclohexene and cyclopentene using the peroxycarbamates 2b–e in the presence and the absence of a chiral ligand were then investigated. Remarkably, the reaction
of cyclohexene and cyclopentene with the peroxycarbamates 2b–2e in ethyl acetate and in the presence of the copper complex of ligand 1b gave allylic oxidation products 5 and 6 rather than the expected protected allylic amines, with good levels of asymmetric induction in some cases (eqn. 2, Table 2). In contrast to the reactions in which peroxycarbamate 2a was employed as the nitrogen donor, decarboxylation did not occur. However, the stereochemical relationship between the absolute configuration of the product and that of the ligand was the same in both the amination and oxidation reactions e.g. the reaction of cyclohexene performed with (R,R)-1b and peroxycarbamate 2b delivered the oxidation product (R)-5b. The best results (entries 4 and 8, Table 2) were obtained using the peroxycarbamate 2e, and reactions were complete within 16–24 hours at room temperature. The levels of asymmetric induction are the highest obtained for allylic oxidation reactions performed at room temperature and in a reasonable time. Higher levels of induction have been achieved by Andrus and co-workers, but only by performing oxidation reactions at low temperature (usually −20 °C) and extending the reaction times to several days.

\[
\text{Cu(MeCN)}_2PF_6 (10 \text{ mol%), 1b (11 mol%), 2b–e (1 equiv.), alkene (5 equiv.), EtOAc, rt} \quad \text{n = 1, 2}
\]

\[
\text{5 n = 2 \quad 6 n = 1}
\]

Table 2 Allylic oxidation of cyclohexene and cyclopentene with the peroxycarbamates 2b–e and the copper complex of ligand 1b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Oxidant</th>
<th>Product</th>
<th>Yield (%) ( a )</th>
<th>Ee (%) ( b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclohexene 2b</td>
<td>5b</td>
<td>37</td>
<td>61 (+)/(R) ( c )</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cyclohexene 2c</td>
<td>5c</td>
<td>29</td>
<td>67 (−)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexene 2d</td>
<td>5d</td>
<td>57</td>
<td>65 (+)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexene 2e</td>
<td>5e</td>
<td>65</td>
<td>72 (+)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cyclopentene 2b</td>
<td>6b</td>
<td>34</td>
<td>76 (+)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Cyclopentene 2c</td>
<td>6c</td>
<td>26</td>
<td>70 (+)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cyclopentene 2d</td>
<td>6d</td>
<td>40</td>
<td>81 (+)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Cyclopentene 2e</td>
<td>6e</td>
<td>48</td>
<td>85 (+)</td>
<td></td>
</tr>
</tbody>
</table>

\( a \) Isolated yield based on the amount of oxidant used. \( b \) Determined by HPLC. \( c \) Reaction performed with (R,R)-1b. \( d \) Configuration established by comparison of \([\alpha]_D\) values to literature data.

Copper-catalysed reactions of the cyclic amines in the absence of a ligand gave very interesting results. Reactions of the amines with the peroxycarbamate 2a gave amination products 3 and 4 exclusively, whereas reactions with the peroxycarbamate 2b gave oxidation products 5b and 6b. Ligand-free reactions involving the peroxycarbamates 2c–e usually afforded mixtures of the oxidation and amination products in varying amounts, but the outcome depended on the alkene used. For example, the reactions of cyclopentene with the peroxycarbamates 2d and 2e resulted in amination whereas mixtures of oxidation and amination products were obtained when cyclohexene was used as a substrate.

The fact that different outcomes are obtained from the copper-catalysed reactions of cyclic amines with the peroxycarbamates 2 in the presence and absence of a chiral ligand is remarkable. It is clear that the presence of a bis-oxazoline ligand biases the reaction towards oxidation rather than amination when the peroxycarbamates 2b–e are used, and that the two reaction manifolds are finely balanced in the absence of a ligand. Assuming that amination proceeds by a mechanism similar to that proposed for the allylic oxidation reaction, our results suggest that the ligand either

\[
\text{ArN=O \xrightarrow{Cu(I)/(II)\_{1b}} ArN=O \xrightarrow{-CO_2} ArN=O -Cu(I)L_n \quad (5 \text{ equiv.})}
\]

\[
\text{1b (11 mol%), 2a (1 equiv.), Ph}_2\text{C}_2\text{Cl}_2, \text{rt} \quad \text{7 n = 2 \quad 8 n = 1}
\]

\[
\text{Ph} \xrightarrow{Cu(MeCN)_2PF_6 (10 \text{ mol%), 1b (11 mol%), 2a (1 equiv.)}} \text{Ph} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt}} \text{NHTs}
\]

\[
\text{5 n = 2 \quad 6 n = 1}
\]

Scheme 1 Competing allylic amination and oxidation pathways.

Increases the reactivity of the initial copper-carbamate complex or stabilises this intermediate so that decarboxylation does not occur prior to reaction with the alkene (Scheme 1).

The tendency of the peroxycarbamates 2b–e to decarboxylate prior to product formation correlates with the stability of the resulting anions and hence the \( pK_a \) of the corresponding sulfonamide or aniline. The use of the peroxycarbamate 2a always leads to amination (\( p\)-MeC\( _6\)H\( _4\)SO\( _2\)N\( _2\)H\( _2 \)) whereas use of the peroxycarbamate 2b leads to oxidation (PhNH\( _3 \)) which has the highest \( pK_a \). The amines corresponding to the peroxycarbamates 2b–e have intermediate \( pK_a \) values and so the outcome of each reaction is delicately poised and depends on the substrate and the presence or absence of a ligand.

In a final study, we explored the allylic amination of the acyclic alkene allylbenzene (eqn. 3). Although the yield was low, the allylic amine 7 was obtained with a 47% ee, confirming that the asymmetric allylic amination reaction is not restricted to simple cyclic alkenes.

In summary, selective catalytic asymmetric allylic amination or oxidation of alkenes can be performed using the same copper bis-oxazoline catalyst simply by varying oxidant and solvent. Our preliminary results suggest that it may be possible to develop a highly asymmetric version of the amination reaction. The oxidation reactions of cyclohexene and cyclopentene using the peroxycarbamate 2e deliver products with the highest ee levels recorded for copper-catalysed asymmetric allylic oxidation reactions performed at room temperature. Aryl carbamates of allylic alcohols can be rearranged to give allylic amines with substantial chirality transfer, so conversion of the oxidation products into amination products is feasible.

Financial support from the EPSRC (Grant no. GR/R94923/01) is gratefully acknowledged.

Notes and references

† The amount of copper salt and ligand can be reduced, but reaction rates fall as a consequence.
§ The peroxycarbamates 2 are rather unstable and were prepared on a small scale (≤ 1 g) and then stored at −20 °C.
¶ The precesses to exclude moisture or oxygen were not required, but it was essential to use a ligand, copper salt and peroxycarbamate of high purity in order to obtain consistent results.

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15 The pKₐ (DMSO) values for the amides are as follows: 