# Tuneable asymmetric copper-catalysed allylic amination and oxidation reactions†

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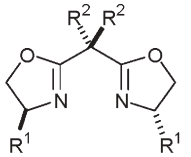
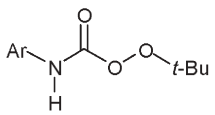
**Asymmetric allylic amination or oxidation can be achieved by reaction of an alkene with a peroxycarbamate catalysed by a chiral copper *bis*-oxazoline complex, and the reaction can be tuned to give either the amination or oxidation product by reagent choice.**

The discovery of new catalytic asymmetric allylic oxidation reactions has been the objective of much research over the past decade.[1,2] 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.[3,4] Other groups have since reported examples of asymmetric copper-catalysed Kharasch–Sosnovsky reactions,[5] but the levels of induction have usually been modest. Recently, Andrus and Zhou reported the highly enantioselective (ee > 94%) allylic oxidation of cyclic alkenes, but reaction rates were low and reaction times of several days were required.[6]

Allylic amination is a well known transformation, but catalytic asymmetric variants of the reaction are rare.[7] 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.[8] 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,[9] but an asymmetric version of this reaction has not been reported.



**1a** $R^1$ = Ph, $R^2$ = H
**1b** $R^1$ = Ph, $R^2$ = Me
**1c** $R^1$ = *t*-Bu, $R^2$ = Me
**1d** $R^1$ = Ph, $R^2$ = $(CH_2)_2$
**1e** $R^1$ = Ph, $R^2$ = $(CH_2)_4$
**1f** $R^1$ = Ph, $R^2$ = $(CH_2)_5$



**2a** Ar = *p*-$MeC_6H_4SO_2$
**2b** Ar = $C_6H_5$
**2c** Ar = *p*-$BrC_6H_4$
**2d** Ar = *m*-$O_2NC_6H_4$
**2e** Ar = *p*-$O_2NC_6H_4$

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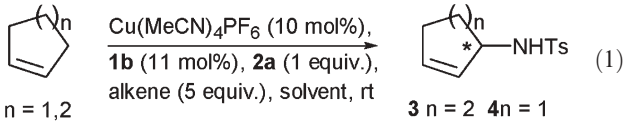
We were intrigued by the possibility of performing direct asymmetric allylic amination of unfunctionalised alkenes using a variant of the Kharasch–Sosnovsky reaction. In preliminary investigations, we performed copper-catalysed allylic amination reactions of cyclohexene and cyclopentene at room temperature in a variety of solvents (reaction times 12–40 h), using the peroxycarbamate **2a** as the nitrogen donor (eqn. 1, Table 1). The ligands **1a–f** were screened and the complex generated from the ligand **1b** and $Cu(MeCN)_4PF_6$ was found to be the best catalyst.[5e]




(1)

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

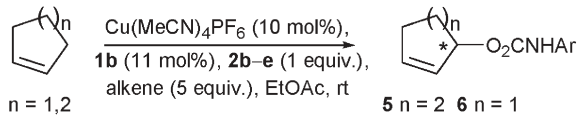
| Entry | Substrate | Solvent | Yield **3/4** (%)[a] | Ee **3/4** (%)[b] |
|---|---|---|---|---|
| 1 | Cyclohexene | PhMe | 22 | 25 (+)(*R*)[c,d] |
| 2 | Cyclohexene | MeCN | 20 | 31 (+)(*R*)[c,d] |
| 3 | Cyclohexene | EtOAc | 26 | 51 (+)(*R*)[c,d] |
| 4 | Cyclohexene | $CH_2Cl_2$ | 44 | 51 (−)(*S*)[d] |
| 5 | Cyclohexene | $Me_2CO$ | 14 | 70 (+)(*R*)[c,d] |
| 6 | Cyclopentene | $CH_2Cl_2$ | 30 | 46 (−)(*S*)[d,e] |

[a] Isolated yield based on the amount of oxidant used. [b] Determined using chiral HPLC. [c] Reaction performed with (*R,R*)-**1b**. [d] Configuration established by comparison of $[\alpha]_D$ values to literature data.[10] [e] Ee determined by chiral HPLC using the corresponding *N*-benzylated 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 acetone 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.[11,12] 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**.[13] 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 or weeks.[6]



(2)

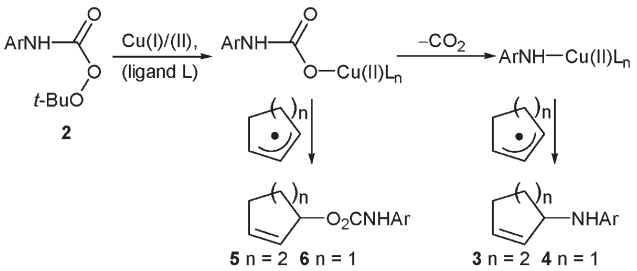
**Table 2** Allylic oxidation of cyclohexene and cyclopentene with the peroxycarbamates **2b–e** and the copper complex of ligand **1b**

| Entry | Substrate | Oxidant | Product | Yield (%)[a] | Ee (%)[b] |
|---|---|---|---|---|---|
| 1 | Cyclohexene | **2b** | **5b** | 37 | 61 (+)(*R*)[c,d] |
| 2 | Cyclohexene | **2c** | **5c** | 29 | 67 (−) |
| 3 | Cyclohexene | **2d** | **5d** | 57 | 65 (+)[c] |
| 4 | Cyclohexene | **2e** | **5e** | 65 | 72 (+)[c] |
| 5 | Cyclopentene | **2b** | **6b** | 34 | 76 (+)[c] |
| 6 | Cyclopentene | **2c** | **6c** | 26 | 70 (+)[c] |
| 7 | Cyclopentene | **2d** | **6d** | 40 | 81 (+)[c] |
| 8 | Cyclopentene | **2e** | **6e** | 48 | 85 (+)[c] |

[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.[13]

Copper-catalysed reactions of the cyclic alkenes performed in the absence of a ligand gave very interesting results. Reactions of the alkenes 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 alkenes 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,[14] our results suggest that the ligand either

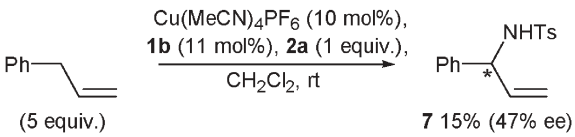



**Scheme 1** Competing allylic amination and oxidation pathways.

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 p$K_a$ of the corresponding sulfonamide or aniline.[15] The use of the peroxycarbamate **2a** always leads to amination (*p*-$MeC_6H_4SO_2NH_2$ has the lowest p$K_a$) whereas use of the peroxycarbamate **2b** leads to oxidation ($PhNH_2$ has the highest p$K_a$).[15] The amines corresponding to the peroxycarbamates **2b–e** have intermediate p$K_a$ 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.



(3)

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,[13] so conversion of the oxidation products into amination products is feasible.

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## 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.

¶ Mixtures of the enantiomerically enriched and racemic products were prepared and analysed by chiral HPLC. Consistent results were obtained confirming the accuracy of ee determination by this method.

‖ Precautions 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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