

Enantioselective allylic acyloxylation catalysed by copper–oxazoline† complexes

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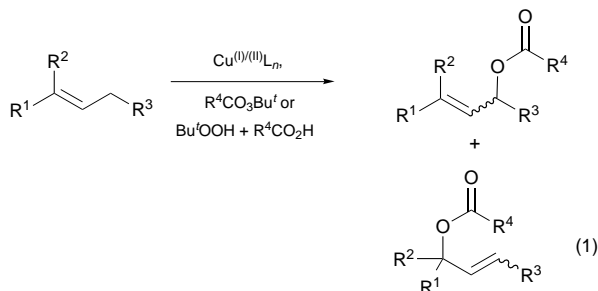
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The oxidation of cyclic alkenes with peresters catalysed by copper complexes of bis-oxazolines, prepared from (1*S*,2*R*)-aminoindanol, affords acylated allylic alcohols in good yield and with good levels of enantiocontrol.

The discovery of reactions for the enantioselective oxidation of alkenes has been a fertile area of research in recent years, and there are now several general and reliable catalytic methods for the enantioselective epoxidation¹ and dihydroxylation of alkenes.^{1,6,2} The discovery of new reactions for the direct asymmetric synthesis of allylic alcohols from alkenes would complement these oxidation reactions in which unsaturation is lost. With this objective in mind, we have recently become interested in the enantioselective allylic oxidation of alkenes using the Kharasch–Sosnovsky reaction.³

During the Kharasch–Sosnovsky reaction, an alkene is converted into an acylated allylic alcohol by a copper-catalysed reaction with a perester or a peroxide in the presence of a carboxylic acid [eqn. (1)].^{3,4} Many years ago, Denney reported that it



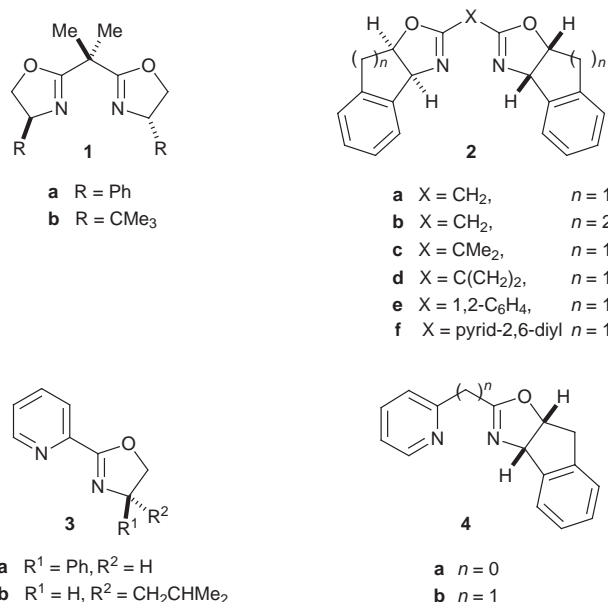
was possible to oxidise cyclic alkenes to give non-racemic allylic alcohol derivatives of low optical purity using stoichiometric amounts of a chiral copper carboxylate complex to promote the reaction.⁵ Until recently, this was the only example of an enantioselective variant of the Kharasch–Sosnovsky reaction.

In 1991, Muzart reported that it was possible to perform an enantioselective allylic oxidation of cyclohexene to provide the (*S*)-cyclohex-2-enyl acetate with ~30% ee using a catalytic amount of a complex prepared from copper(I) oxide and (*S*)-proline.^{6a} Muzart subsequently demonstrated that cyclopentene could be oxidised to the acylated allyl alcohol with 59% ee using modified conditions.^{6b,c}

Encouraged by Muzart's original report we embarked on our research in this area. Initially, we selected bidentate oxazolines as candidate ligands because they have been used to good effect in other asymmetric copper-mediated reactions. Shortly after we had commenced our work, Pfaltz⁷ and Andrus⁸ reported the enantioselective acyloxylation of simple alkenes using copper–bis-oxazoline complexes with higher levels of induction

than those obtained by Muzart. These and other recent reports, in which copper complexes of amino acids⁹ or other ligands¹⁰ have been used to catalyse the Kharasch–Sosnovsky reaction, prompted us to disclose results of preliminary studies at this time.

Cyclohexene was chosen as the standard substrate for preliminary studies in order to avoid the issues of regiocontrol and scrambling of the alkene geometry which arise with acyclic alkenes [eqn. (1)].³ A variety of bidentate oxazoline ligands (1–4) was screened and the degree of induction was found to

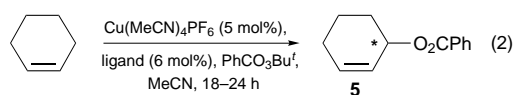


vary considerably depending on the specific ligand used. We elected to perform our reactions at 40 °C in acetonitrile because reactions were complete within 24 hours and good yields of the product **5** were obtained under these conditions [eqn. (2)]. In our experience the bis-oxazoline ligands **2a–e**, derived from (1*S*,2*R*)-aminoindanol,¹¹ were generally superior to those (**1**) used by Pfaltz.¹² Oxidation reactions of cyclohexene catalysed by copper complexes of the bis-oxazolines **2** afforded the ester **5** with significantly higher levels of induction than the conventional bis-oxazoline ligands **1** under identical conditions. § The reaction of cyclohexene catalysed by the complex of ligand **2d** afforded (*S*)-cyclohex-2-enyl benzoate with the highest ee

§ Pfaltz reported that oxidation of cyclohexene using a copper complex of the ligand **1b** at 7 °C in acetonitrile afforded the ester **5** in 64% yield and with an ee of 77%.⁷ However, this reaction required 15 days to proceed to completion. When Pfaltz performed the same reaction using conditions (acetonitrile, 50 °C) similar to our own, the reaction was complete in 1 day but the ester **5** was obtained in lower yield (44%) and with an inferior ee (51%).

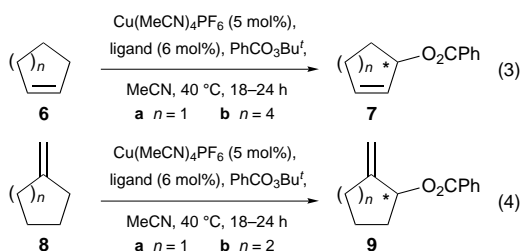
† The correct IUPAC name for oxazoline is 4,5-dihydrooxazole.

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Table 1 Formation of compound **5**

Entry	Ligand	T/°C	Yield 5 (%) ^a	ee 5 (%) ^b	Config.
1	1a	40	71	59	<i>S</i>
2	1b	40	74	40	<i>S</i>
3	2a	40	62	45	<i>S</i>
4	2b	40	69	28	<i>S</i>
5	2c	40	65	69	<i>S</i>
6 ^c	2c	0	48	78	<i>S</i>
7 ^d	2c	40	76	71 ^e	<i>S</i>
8	2d	40	65	74	<i>S</i>
9	2e	40	59	21	<i>S</i>
10	2f	40	66	52	<i>S</i>
11	3a	40	56	17	<i>S</i>
12	3b	40	57	28	<i>R</i>
13	4a	40	63	37	<i>R</i>
14	4b	40	56	35	<i>R</i>

^a Yield of isolated product based on the amount of perester used. ^b Determined by HPLC analysis (Chiralcel OD column, 0.1% isopropanol in hexane). ^c This reaction was performed over 21 days. ^d Activated 4 Å molecular sieves added to the reaction. ^e The ee was determined by comparison of optical rotation data.

Table 2

Entry	Ligand	Substrate	Product	Yield (%) ^a	ee (%) ^b	Config.
1	1a	6a	7a	72	69	<i>S</i>
2	2c	6b	7b	31	10	<i>S</i>
3	2d	8a	9a	51	43 ^c	— ^d
4	2c	8b	9b	43	26	— ^d

^a Yield of isolated product based on the amount of perester used. ^b Determined by HPLC analysis (Chiralcel OD column, 0.1% isopropanol in hexane). ^c The ee was determined by HPLC analysis (Chiralcel OD column, hexane). ^d Absolute configuration was not determined.

(74%) of those reactions performed at 40 °C (entry 8, Table 1). Lowering the reaction temperature to 0 °C resulted in a modest increase in the ee of the product when the copper complex of the ligand **2c** (entries 5 and 6, Table 1) was used as the catalyst, but prolonged reaction times were required and the yields were poor. § Addition of activated 4 Å molecular sieves to the reactions was found to give a modest increase in the yield but had little effect on the level of induction (compare entries 5 and 7, Table 1).^{10b,c}

Reactions catalysed by copper complexes of the pyridyloxazolines **3** and **4** afforded cyclohex-2-enyl benzoate with modest ee (entries 11–14). Interestingly, the relationship between the absolute configuration of the product and the configuration of the ligand was opposite to that encountered for reactions catalysed by copper complexes of the bis-oxazolines **1** and **2**. This suggests that the transition states of the reactions promoted by complexes of the ligands **3** and **4** must differ from those of the reactions promoted by complexes of the ligands **1** and **2**.

At this stage we explored variables such as solvent polarity, nature of the copper salt and choice of oxidant. We established

that acetonitrile was the best solvent † and that the copper salt †† used had little effect on the yield or level of asymmetric induction. We also found that oxidation could be performed using *tert*-butyl hydroperoxide in the presence of a carboxylic acid. When this procedure was employed, the nature of the carboxylic acid had little influence on the level of induction but did have an effect on the yield.**

Having identified the optimum ligand and reaction conditions, we investigated the oxidation of some other substrates [eqn. (3) and (4), and Table 2]. Surprisingly, the oxidation of cyclopentene was catalysed most efficiently by the copper complex of ligand **1a** rather than complexes of the ligands **2**. Pfaltz has reported that the copper complex of bis-oxazoline **1b** is a particularly effective catalyst for this reaction, but we found that the copper complex of the ligand **1a** gave superior results when the reaction was performed at 40 °C. †† Oxidation of cyclooctene resulted in poor yields of the product **7b** with very low ee, the best result being obtained using the catalyst generated from ligand **2b**. Cyclooctene seems to be a remarkably poor substrate for the reaction, a finding which is consistent with results reported by Andrus.⁸

We also examined the oxidation of methylenecyclopentane and the methylenecyclohexane. Exocyclic alkenes of this type has not been investigated as substrates for enantioselective allylic oxidation and we were interested to see if they were suitable substrates for this reaction.¹³ Both substrates underwent oxidation to afford single regioisomeric products in reasonable yield and with modest levels of asymmetric induction when copper complexes derived from the ligands **2c** and **2d** were used as catalysts. The successful enantioselective oxidation of these substrates demonstrates that the formation of a stereogenic centre in the putative organocopper intermediate (as is the case with endocyclic alkenes) is not a requirement for asymmetric induction during oxidation.

On the basis of our results, we conclude that copper complexes of bis-oxazoline ligands are good catalysts for the Kharasch-Sosnovsky allylic oxidation of cyclic alkenes. Although no single ligand is superior for all substrates, we have demonstrated that the aminoindanol-derived bis-oxazoline ligands **2** are usually better than the simple bis-oxazoline ligands **1**.

We are continuing to search for improved catalysts for the allylic oxidation of alkenes and to apply these reactions to more complex substrates. The results of these studies will be reported in due course.

Experimental

General procedure for the enantioselective allylic oxidation of cyclic alkenes

To a stirred solution of Cu(MeCN)₄PF₆ (0.2 mmol) in acetonitrile (12 ml) was added the chiral ligand (**1–4**) (0.24 mmol). The mixture of the copper salt and ligand was stirred for 5 min to give a pale blue solution. The alkene (20 mmol) was then added to the solution followed by dropwise addition of *tert*-butyl peroxybenzoate (4 mmol) over approximately 1 min, whereupon the solution turned dark blue. The reaction was then heated to 40 °C, the colour of the solution changing from blue to green after an initial induction period. The solution was

† Reduced levels of asymmetric induction were observed with most other solvents, although reasonable results were obtained when the reactions were performed in benzene or acetone.

‡ Copper(I) oxide, copper(I) chloride, copper(I) triflate, copper(II) acetate, copper(II) benzoate and copper(II) triflate were also used.

** Yields from the oxidation reactions generally increased as the molecular weight of the carboxylic acid increased.

†† Pfaltz reported that oxidation of cyclopentene using a copper complex of the ligand **1b** at –20 °C in acetonitrile afforded the ester **7a** in 61% yield and with an ee of 84%.⁷ However, this reaction required 22 days to proceed to completion.

heated at 40 °C for 12–18 h and the reaction monitored by TLC [hexane–diethyl ether (1:1)]. Completion of the reaction was indicated by the complete consumption of *tert*-butyl peroxybenzoate (*R*_f 0.65) and the solvent was then removed *in vacuo* to afford a brown liquid. The crude product was purified by flash column chromatography on silica gel [hexane–diethyl ether (25:1)] to give the product as a clear liquid. The enantiomeric excess of the product was determined by HPLC (Chiracel OD column, 0.1% isopropyl alcohol in hexane).

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References

- 1 For leading references concerning the enantioselective epoxidation reactions of alkenes, see (a) R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, ch. 4.1; (b) E. N. Jacobsen, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, ch. 4.2; (c) K. B. Sharpless, *Tetrahedron*, 1994, **50**, 4235; (d) P. Besse and H. Veschambre, *Tetrahedron*, 1994, **50**, 8885; (e) T. Katsuki, *Coord. Chem. Rev.*, 1995, **140**, 189.
- 2 For leading references concerning the enantioselective dihydroxylation reactions of alkenes, see (a) R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, ch. 4.4; (b) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
- 3 D. J. Rawlinson and G. Sosnovsky, *Synthesis*, 1972, 1.
- 4 A. L. J. Beckwith and A. A. Zavitsas, *J. Am. Chem. Soc.*, 1986, **108**, 8230.
- 5 D. B. Denney, R. Napier and A. Cammarata, *J. Org. Chem.*, 1965, **30**, 3151.
- 6 (a) J. Muzart, *J. Mol. Catal.*, 1991, **64**, 381; (b) A. Levina and J. Muzart, *Tetrahedron: Asymmetry*, 1995, **6**, 147; (c) A. Levina and J. Muzart, *Synth. Commun.*, 1995, **25**, 1789.
- 7 A. S. Gokhale, A. B. E. Minidis and A. Pfaltz, *Tetrahedron Lett.*, 1995, **36**, 1831.
- 8 M. A. Andrus, A. B. Argade, X. Chen and M. G. Pamment, *Tetrahedron Lett.*, 1995, **36**, 2945.
- 9 (a) M. T. Rispens, C. Zondervan and B. L. Feringa, *Tetrahedron: Asymmetry*, 1995, **6**, 661; (b) M. J. Södergren and P. G. Andersson, *Tetrahedron Lett.*, 1996, **37**, 7577.
- 10 (a) K. Kawasaki, S. Tsumura and T. Katsuki, *Synlett*, 1995, 1245; (b) K. Kawasaki and T. Katsuki, *Tetrahedron*, 1997, **53**, 6337; (c) A. D. Gupta and V. K. Singh, *Tetrahedron Lett.*, 1996, **37**, 2633.
- 11 (a) I. W. Davies, L. Gerena, D. Cai, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1997, **38**, 1145; (b) I. W. Davies, L. Gerena, N. Lu, R. D. Larsen and P. J. Reider, *J. Org. Chem.*, 1996, **61**, 9629; (c) I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1996, **37**, 1725; (d) I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1996, **37**, 813; (e) I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Chem. Commun.*, 1997, 1753.
- 12 (a) A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 339; (b) C. Bolm, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 542.
- 13 B. Cross and G. H. Whitham, *J. Chem. Soc.*, 1961, 1650.

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