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Enantioselective Allylic Oxidation Catalyzed by Chiral Bisoxazoline-Copper Complexes

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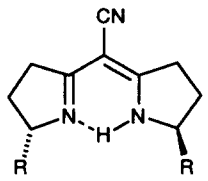
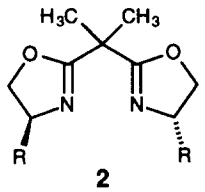
Abstract: *Copper(I) complexes prepared in situ from chiral bisoxazolines and Cu(I)OTf have been studied as catalysts for the allylic oxidation of cycloalkenes. Using 5 mol% of catalyst and tert-butyl perbenzoate as oxidant, optically active 2-cycloalkenyl benzoates were obtained in moderate to good yields. The highest enantiomeric excesses, 74% at 23 °C and up to 84% at lower temperatures, were observed for cyclopentene and cycloheptene, while cyclohexene gave somewhat lower selectivities ranging between 64-77%ee.*

The copper-catalyzed allylic oxidation of olefins with peresters has been the subject of numerous synthetic and mechanistic investigations.[1,2] This useful reaction which allows the preparation of allylic carboxylates from simple alkenes has been shown to proceed by a radical chain mechanism *via* an intermediate allyl radical. There is evidence for copper being directly involved in the formation of the C-O bond, suggesting that the reaction might be rendered enantioselective by complexing the copper ion with a suitable chiral ligand. Indeed, optically active products were obtained in some cases using chiral non-racemic copper complexes as catalysts or stoichiometric reagents.[3-6] However, the enantiomeric excesses reported to date are rather low (≤30% ee).



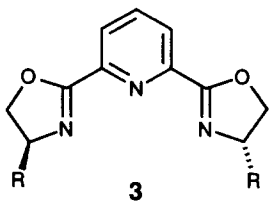
1

R = CH_2OSiMe_2t-Bu



2

a *R* = *i*-Pr
b *R* = *t*-Bu
c *R* = Ph



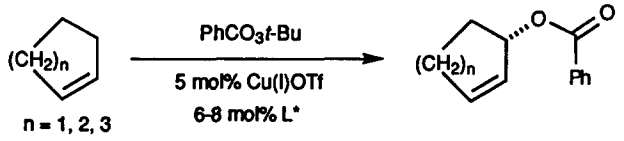
3

R = *i*-Pr

Several years ago, we became interested in this class of reactions in connection with our work on chiral semicorrin-copper complexes which proved to be efficient catalysts for the enantioselective cyclopropanation of olefins.[7] Initial experiments, using the same complexes in the reaction of *tert*-butyl perbenzoate with cyclohexene were encouraging. Enantiomeric excesses of 65-75% could be obtained with a copper(I)

complex of the semicorrin **1** as a stoichiometric reagent.[8] In analogous catalytic reactions, however, the enantioselectivity decreased significantly after 2-3 turnovers. The recent development of new semicorrin-like ligands such as the bisoxazolines **2**[9,10], which within a short time have found a remarkable variety of successful applications in asymmetric catalysis[9-11], prompted us to resume our work on copper-catalyzed allylic oxidation.

Table 1. Enantioselective allylic oxidation of cycloalkenes[12]

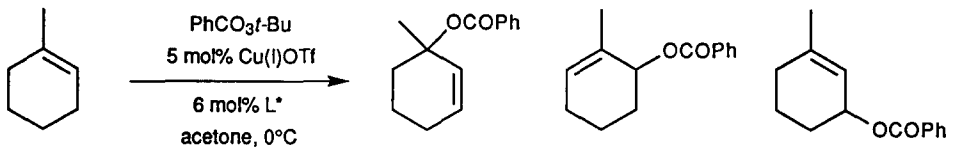


Substrate	L*	Solvent[a]	Time [days]	Temp. [°C]	Conversion [%]	Yield[b] [%]	ee[c] [%]
cyclopentene	**2a**	CH_3CN	4	23	57	74	74
	2a	CH_3CN	12	7	60	81	77
	2a	acetone	14	0	75	76	75
	2a	acetone	22	–20	67	66	82
	2b	CH_3CN	4	23	88	68	74
	2b	CH_3CN	12	7	65	65	79
	2b	CH_3CN	12	0	100	64	80
	2b	CH_3CN	22	–20	68	61	84
	2c	acetone	5	23	99	84	71
cyclohexene	**2a**	acetone	1	50	100	71	58
	2a	acetone	3	23	99	69	64
	2a	CH_3CN	9	23	91	64	61
	2b	CH_3CN	1	50	90	44	51
	2b	CH_3CN	7	23	63	68	60
	2b	CH_3CN	15	7	77	64	77
	2c	acetone	3	23	100	77	67
	3	CH_3CN	3	23	95	80	71
cycloheptene	**2a**	CH_3CN	2	50	87	57	69
	2a	CH_3CN	3	23	78	75	74
	2a	CH_3CN	14	7	63	44	82

[a] $CH_3CN/CHCl_3$ 3:1 or acetone/$CHCl_3$ 3:1. [b] Yield based on consumed perester. [c] Determined by HPLC on a chiral column (hexane/isopropanol 1000:1; 2-cyclohexenyl benzoate: Chiralcel OJ, 2-cyclopentenyl benzoate: Chiralcel OD, 2-cycloheptenyl benzoate: Chiralcel OD-H). All products show negative optical rotation values and, therefore, have (*S*)-configuration.[16]

In initial experiments, various 5-aza-semicorrins[13] and bisoxazolines were tested as ligands in the reaction of cyclohexene with *tert*-butyl perbenzoate. The most promising results were obtained with Cu(I)-complexes prepared *in situ* from copper(I) triflate or $[Cu^{I}(CH_3CN)_4]PF_6$ and bisoxazolines **2a-c** (Table 1). These complexes were found to undergo 10 - 15 turnovers without loss of enantioselectivity. Using 5 mol% of catalyst, based on perester, 2-cyclohexenyl benzoate was formed in moderate to good yield with substantial enantiomeric excess.[12] An analogous catalyst prepared from $Cu^{II}(OTf)_2$ was distinctly less reactive and less selective. Cyclopentene and cycloheptene gave similar results. Depending on the substrate and the specific ligand, either acetonitrile or acetone proved to be the solvent of choice, the reaction in acetone being generally faster than in acetonitrile. The highest enantiomeric excesses, 74% at 23 °C and up to 84% at lower temperatures, were observed for cyclopentene and cycloheptene, while cyclohexene gave somewhat lower selectivities ranging between 64 - 77% ee. Comparable enantioselectivities and yields were obtained using Nishiyama's tridentate bisoxazoline ligand **3**.[9i]

Scheme 1



4 **5** **6**

L*	Composition [%][a]			Enantiomeric Excess [%][b]		
	4		**6**	**4**	**5**	**6**
2a	9	50	42	90	63	13
2b	8	42	50	73	37	42

[a] Determined by GC (5% PhMe silicon). [b] Determined by HPLC (**4** and **5**: Chiralcel OJ, **6**: Chiralcel OD).

As expected, 1-methylcyclohexene was converted to a mixture of regioisomers resulting from hydrogen abstraction at the two allylic methylene groups (Scheme 1). The methyl group was not oxidized under these conditions. The enantiomeric purities of the three products differed substantially, with a remarkably high ee of the minor regioisomer **4** (total yield of **4**, **5**, and **6**: 70-85%; 80-90% conversion). In independent studies, Andrus and coworkers have applied the same catalysts to acyclic olefins and obtained enantioselectivities in the range of 30-50% ee.[14]

The ee's induced by the chiral bisoxazoline ligands **2** and **3** clearly exceed the enantioselectivities reported to date for allylic oxidations of this type. The high levels of enantiocontrol indicate that the chiral catalyst is intimately involved in the formation of the allylic C-O bond, consistent with a mechanism involving coordination of an allyl radical intermediate to a (bisoxazoline)copper carboxylate complex and subsequent transfer of carboxylate to the copper-bound allyl system, possibly by a concerted mechansim as suggested by Beckwith and Zavitsas.[2] Although the enantioselectivity and catalytic efficiency still need to be improved, a first step toward a practical catalyst system for this useful transformation has been taken.

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12. *General procedure.* A solution of ligand **2a**[15] (202mg, 0.75 mmol) in chloroform (2ml) was added to [$Cu^{I}OTf \cdot 0.5\ (C_6H_6)$] (140 mg, 0.5 mmol; Fluka pract., ~90%) under N_2. The solution was stirred at r.t. for 1 h. The catalyst solution was transferred through a Chromafil® disposable filter (pore diameter 0.2 μm) to a Schlenk tube containing cyclopentene (2.7 g, 40 mmol, 4 equiv. based on perester) and acetone (6 ml) under N_2. *tert*-Butyl perbenzoate (2.03g, 9.4 mmol; Fluka pract. ~90%) was slowly added within 10 min and the reaction mixture was then kept at 0 °C for 14 days. After addition of water, the mixture was extracted twice with Et_2O. The organic layers were washed with 2N HCl and with water. Removal of the solvent *in vacuo* and purification by flash chromatography on silica gel (3.5 x 30 cm column, hexane/EtOAc 99:1) gave 1.10g of (*S*)-2-cyclopentenyl benzoate (56% yield, 76% based on consumed perester; 75% ee). The ee was determined by HPLC (t_R = 32.3 min (*S*), 39.8 min (*R*); Chiralcel OD, 0.46x30 cm, hexane/*i*-PrOH 1000:1; 0.5 ml/min). $[\alpha]_D$ = –157 (*c* = 0.77, $CHCl_3$). The spectroscopic data were in accordance with ref. 16a.
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