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Asymmetric allylic oxidation of cycloalkenes using a tridentate tris(oxazoline) ligand as a chiral auxiliary

Yoshinori Kohmura and Tsutomu Katsuki *

Department of Molecular Chemistry, Graduate School of Science, Kyushu University 33, Hakozaki, Higashi-ku,
Fukuoka 812-8581, Japan

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Abstract

A tridentate tris(oxazoline) ligand (**4b**) was found to be an efficient chiral auxiliary for copper-mediated asymmetric allylic oxidation (Kharash–Sosnovsky reaction) of cycloalkenes. Regardless of the ring size of the substrate, the reaction examined showed good enantioselectivity higher than 81% ee. © 2000 Elsevier Science Ltd. All rights reserved.

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Optically active 2-cycloalken-1-ols such as 2-cyclopenten-1-ol and 2-cyclohexen-1-ol or their derivatives are useful building blocks for organic synthesis and several methodologies have been developed for the synthesis of this class of compounds: for example, (i) enantioselective reduction of cycloalkenone[1] and (ii) enantioselective conversion of cycloalkene oxides.[2] As cycloalkenes are readily available, their allylic oxidation to the corresponding 2-cycloalken-1-ols or their derivatives is more desirable from the practical view point. Although several reactions are available for allylic oxidation, the Kharash–Sosnovsky reaction using stoichiometric peroxides and a catalytic amount of a metal ion such as a copper(I) ion is advantageous for the following reasons: (i) the reaction conditions are mild; (ii) the reaction is catalytic and clean if suitable peroxide and metal ion are used.[3] Furthermore, it is expected that the reaction can be enantioselective if the metal ion carries appropriate chiral ligand(s).[4] Actually, the first example of an asymmetric version of the Kharash–Sosnovsky reaction was reported as early as 1965, though the enantioselectivity was not sufficient.[5,6] Recently, optically active bis- and tris-(oxazoline)s have been found to be efficient chiral auxiliaries and high enantioselectivity greater than 80% ee has been achieved with these chiral auxiliaries and *t*-butyl peroxybenzoate as a stoichiometric oxidant.[7] The Kharash–Sosnovsky reaction involves four steps: (i) reductive cleavage of the O–O bond of the peroxyester generating a *t*-butoxy radical and a copper carboxylate; (ii) hydrogen atom abstraction at an allylic carbon by the *t*-butoxy radical; (iii) ligation of the resulting allyl radical to the copper

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* Corresponding author. Fax: +81 92 642 2607; e-mail: katsuscc@mbox.nc.kyushu-u.ac.jp (T. Katsuki)

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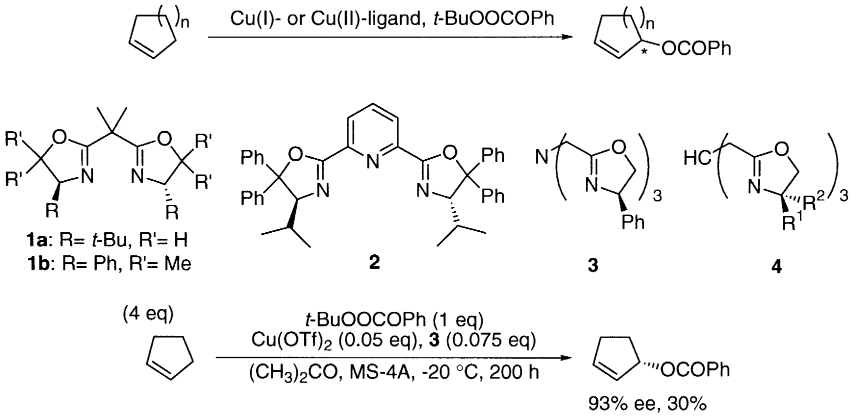
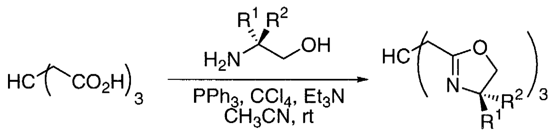
carboxylate; and (iv) reductive elimination of the resulting copper(allyl) carboxylate to give cycloalkenyl benzoate.[3] The face selection of the allyl radical is considered to be mainly performed in the third step, ligation of the allyl radical, and the selection strongly depends on the shape of the chiral ligand and the substrate structure. In accordance with this consideration, each of the reported oxazoline ligands showed a specific feature in the enantioselection. For example, a Cu(I) complex bearing bis(oxazoline) ligand **1** showed high enantioselectivity in the oxidation of cyclo-pentene, -hexene and -heptenes,[7a,b,f] but only modest selectivity in the oxidation of cyclooctene.[7b,f] A Cu(II) complex bearing pyridinebis(oxazoline) ligand **2** exhibited good to high enantioselectivity in the oxidation of the above cycloalkenes except for cyclopentene, the oxidation of which showed modest enantioselectivity.[7d,g] We observed that the Cu(II) complex with tetradentate tris(oxazoline) ligand **3** showed high enantioselectivity in the oxidation of cyclopentene (Scheme 1), while enantioselectivity in the oxidation of other cycloalkenes was moderate.[7c,e] We expected that the copper complexes bearing new C_3-symmetric tris(oxazoline) ligands **4** would have structures different from the previously reported copper–oxazoline complexes and show enantioselectivity different from other complexes in the oxidation of cycloalkenes.[8]



Scheme 1.

Ligands **4** were synthesized from methanetriacetic acid[9] and optically pure β-amino alcohols[†] according to the reported procedure (Scheme 2).[10] Ligands **4** were sensitive to silica gel, and the crude reaction mixtures were quickly chromatographed through a short silica gel column ($CHCl_3$:Et_3N=1:0 to 100:1) to give **4**.



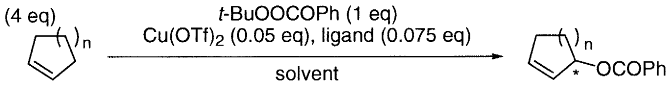
	R^1	R^2	Yield (%)
4a	Ph	H	40
4b	4-MeOC$_6$H$_4$	H	45
4c	H	4-CF$_3$C$_6$H$_4$	36
4d	H	*i*-Pr	20

Scheme 2.

[†] (*R*)-2-Amino-2-phenylethanol and (*S*)-2-amino-3-methyl-1-butanol were obtained by reduction of D-phenylglycine and L-valine, respectively. (*R*)-2-Amino-2-(4-methoxyphenyl)ethanol and (*S*)-2-amino-2-(4-trifluoromethylphenyl)ethanol were prepared from 4-vinylanisol and 4-trifluoromethylstyrene according to the reported procedure and their absolute configurations were assigned on the basis of the empirical rule on asymmetric dihydroxylation: (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Chang, H. T.; Sharpless, K. B. *Tetrahedron Lett.* **1996**, *37*, 3219–3222. (c) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207–1217.

We first examined the oxidation of cyclopentene in the presence of $Cu(OTf)_2$–**4a** using *t*-butyl peroxybenzoate as an oxidant in acetone at room temperature. The reaction was slow and the enantioselectivity was also diminished to a considerable extent, as compared with the reaction with **3** as the chiral auxiliary (Table 1, entries 1 and 2). However, it is noteworthy that, though the structures of the oxazoline units in **3** and **4a** are the same, the sense of enantioselection by **4a** was opposite to that by **3**, suggesting that the geometry of the copper ion ligated by **4a** is different from that ligated by **3**.[8] Furthermore, addition of molecular sieves 4 Å deteriorated enantioselectivity (entry 3), while the oxidation with a Cu(II)–**3** complex was accelerated without adversely affecting enantioselectivity by the addition of sieves.[7e] We next examined the effect of the solvent on enantioselectivity (entries 4–11). Different from the reaction with the Cu(II)–**3** complex which was smoothly effected in a polar solvent such as acetone, the present reaction was better effected in a less polar solvent and the best enantioselectivity was attained by using 1,2-dichloroethane as the solvent (entry 7). Use of aromatic solvents deteriorated enantioselectivity (entries 10 and 11). Under the optimized conditions, the effect of the substituent at the oxazoline unit on enantioselectivity was next examined and the presence of an aryl substituent was found to be essential (entry 16). The enantioselectivity was improved, as the HOMO of the aryl ring rose (entries 7, 12, and 15). Lowering the reaction temperature enhanced enantioselectivity but the reaction rate was decelerated

Table 1
Asymmetric allylic oxidation of cycloalkenes



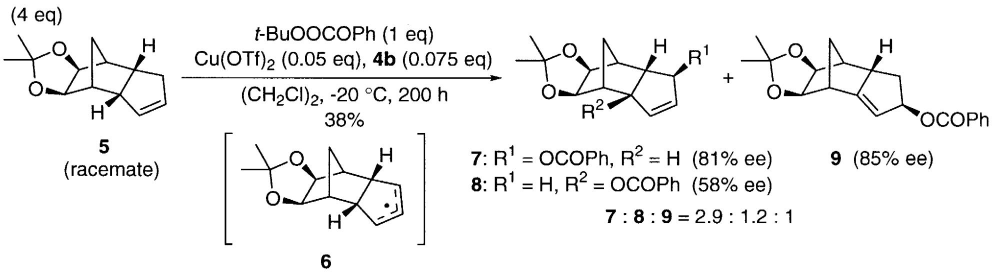
Entry	n	Ligand	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)	Confign.[b]
1	1	**4a**	$(CH_3)_2CO$	rt	10	46	65[c]	*R*
2[d]	1	**3**	$(CH_3)_2CO$	rt	16	83	76[c]	*S*
3[d]	1	**4a**	$(CH_3)_2CO$	rt	46	77	31[c]	*R*
4	1	**4a**	CH_3CN	rt	21	69	63[c]	*R*
5	1	**4a**	$CH_3CO_2C_2H_5$	rt	8	57	45[c]	*R*
6	1	**4a**	CH_2Cl_2	rt	7	77	74[c]	*R*
7	1	**4a**	$(CH_2Cl)_2$	rt	7	78	76[c]	*R*
8	1	**4a**	$(CH_2Cl)_2$	0	48	80	83[c]	*R*
9	1	**4a**	$(CH_2Cl)_2$	-20	210	40[e]	87[c]	*R*
10	1	**4a**	C_6H_6	rt	7	77	34[c]	*R*
11	1	**4a**	C_6H_5Cl	rt	8	71	56[c]	*R*
12	1	**4b**	$(CH_2Cl)_2$	rt	6	71	80[c]	*R*
13	1	**4b**	$(CH_2Cl)_2$	0	48	73	85[c]	*R*
14	1	**4b**	$(CH_2Cl)_2$	-20	200	46[e]	89[c]	*R*
15	1	**4c**	$(CH_2Cl)_2$	0	48	77	51[c]	*S*
16	1	**4d**	CH_2Cl_2	rt	11	43	2[c]	*S*
17	2	**4b**	$(CH_2Cl)_2$	0	48	80	82[c]	*R*
18	2	**4b**	$(CH_2Cl)_2$	-20	200	50[e]	86[c]	*R*
19	3	**4b**	$(CH_2Cl)_2$	0	48	64	88[f]	*R*
20	3	**4b**	$(CH_2Cl)_2$	-20	200	13[e]	92[f]	*R*
21	4	**4b**	$(CH_2Cl)_2$	rt	48	24	81[c]	*R*
22	4	**4b**	$(CH_2Cl)_2$	0	200	25[e]	85[c]	*R*

a) Isolated yield. Yield was calculated based on the amount of *t*-butyl peroxybenzoate used.
b) Determined by comparison of the specific rotation (reference 7e).
c) Determined by HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol=1000:1).
d) Reaction was carried out in the presence of MS-4A.
e) *t*-Butyl peroxybenzoate was not consumed completely.
f) Determined by ^1H NMR analysis (270 MHz) using $Eu(hfc)_3$.

(entries 12, 13, and 14). The reaction using Cu(II)–**4b** complex as the catalyst for 48 h gave the benzoate of 85% ee in 73% (entry 13). The reaction at −20°C showed slightly higher enantioselectivity (89% ee) but the yield decreased (entry 14). These results suggest that the interaction between an allyl radical and the aryl substituents strongly affects the reaction rate and the enantioselectivity. Although Singh et al. reported that the addition of phenylhydrazine improved the reaction rate in the Cu(II)-mediated reaction, it adversely affected the present reaction.[7g]

The oxidation of other cycloalkenes with Cu(II)–**4b** as the catalyst also proceeded with high enantioselectivity, though only the oxidation of cyclooctene was slow (entries 17–22). Lowering the reaction temperature again enhanced enantioselectivity but the reaction rates were decelerated.

We next examined asymmetrization of racemic olefin **5** by using a Cu(OTf)$_2$–**4b** complex as the catalyst (Scheme 3). It is expected that hydrogen atom abstraction at the allylic methylene carbon in **5** provides a *meso*-allyl radical intermediate **6**, desymmetrization of which gives optically active benzoate **7**.[11] Desymmetrization of **6** proceeded with good enantioselectivity to give benzoate **7** of 81% ee. However, the formation of undesired side products (**8** and **9**) was observed due to the low regioselectivity in the hydrogen atom abstraction by the *t*-butoxy radical, which occurred outside the coordination sphere of the copper ion. The allyl radical generated by hydrogen atom abstraction at the methine carbon leads to the formation of **8** and **9**.



Scheme 3.

Typical experimental procedure was exemplified by the oxidation of cyclopentene with a Cu(OTf)$_2$–**4b** complex as the catalyst: A 0.18 M solution of **4b** in dichloromethane (82 μL, 15 μmol) was added to the pre-dried Cu(OTf)$_2$ (3.6 mg, 10 μmol) under nitrogen. The solution was stirred for 1 h at room temperature and the solvent was removed in vacuo. To the residue was added 1,2-dichloroethane (0.50 mL) and cyclopentene (70 μL, 0.8 mmol), successively, and the whole mixture was cooled to 0°C. *t*-Butyl peroxybenzoate (38 μL, 0.2 mmol) was added dropwise. After being stirred for 48 h at 0°C, the reaction mixture was directly subjected to a pad of silica gel (hexane:AcOEt=9:1) to remove the copper complex. The filtrate was concentrated in vacuo and the residue was further purified by column chromatography on silica gel (hexane:AcOEt=100:1) to give (*R*)-2-cyclopentenyl benzoate as a colorless oil (27.6 mg, 73%, 85% ee).

In conclusion, we were able to demonstrate that the newly introduced C_3-symmetric tris(oxazoline) ligand **4b** showed wider applicability in the asymmetric Kharash–Sosnovsky reaction of cycloalkenes and a racemic cyclopentene derivative, as compared with the previously reported auxiliaries. An attractive interaction between the allyl radicals and the aryl substituents in the oxazoline subunits was suggested to promote the reactions, though further improvement of the reaction rate is required for the oxidation of some substrates such as cyclooctene. However, these results should give a clue for further study in this area of chemistry, which is proceeding in our laboratory.

Acknowledgements

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