Enantioselective Allylic Oxidation of Olefins Using Chiral Quinolinyl-oxazoline Copper Complex Catalysts†

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Copper complexes of chiral quinolinyl-oxazoline have been studied as the catalysts for enantioselective allylic oxidation of cycloalkenes with *tert*-butyl perbenzoate. Using 5 mol% of these chiral catalysts, optical active allylic benzoates were obtained in moderate enantiomeric excesses. CuOTf prepared *in situ*, $CuClO_4$ and $CuPF_6$ were found to be good precatalysts in acetone.

Keywords Asymmteric catalysis, allylic oxidation, chiral oxazoline

Introduction

The development of methodology for enantioselective functionalizaton of C—H bonds is still a challenge in asymmetric synthesis, and is continuing to attract considerable attention. Asymmetric allylic oxidation of olefin using hydroperoxides or peresters and copper catalysts is one of this type of transformation and significant progress has been achieved in last few years. Kharasch and Sosnovsky first reported that C—H bond in allylic position of olefin could be oxidized with *tert*-butyl perbenzoate in the presence of catalytic amount of copper salt.[1] Kharasch-Sosnovsky reaction products, allylic esters, and their hydrolyzed products, allylic alcohols, have many potential synthetic applications.[2] Early attempts to develop asymmetric version of this reaction employed copper complexes of camphor or amino acids as catalysts and low enantioselectivities (< 30% *ee*) were obtained.[3] Recently, a number of chiral ligands were used to control enantioselectivities in copper-catalyzed allylic oxidation of olefins.[4] Among these ligands, bisoxazoline and trisoxazoline compounds with C_2 or C_3 symmetry have been well studied and impressive enantiomeric excesses were achieved in some cases.[4a,4e,4f] However, other chiral oxazoline ligands which are lacking of symmetry have not been investigated in this reaction. As part of our studies on the new nitrogen-containing chiral ligands, we have designed and synthesized nonsymmetric quinolinyl-oxazoline **1** as ligands in copper-catalyzed cyclo propanation reaction of styrene and diazoacetates.[5] We now report our investigation of ligands **1**, as well as Brunner's ligands **2**[6] and methylene-bridged pyridinyl-oxazoline ligands **3**[7] in copper-catalyzed allylic oxidation of cyclic olefins.

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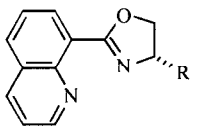

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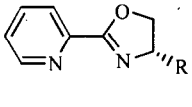

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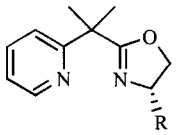

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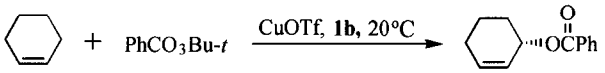
a R = Me
b R = Bn
c R = *i*-Pr
d R = Ph
e R = *t*-Bu

Results and discussion

Copper(I) complexes derived from ligands **1** were found to be efficient catalysts in the allylic oxidation of cyclic olefins. We first examined the reaction of cyclohexene and *tert*-butyl perbenzoate catalyzed with Cu(I) triflate prepared *in situ* by reduction of Cu(II) triflate using phenyl hydrazine. The reaction was taken placed smoothly in acetone or mixed solvent of acetone and chloroform at 20℃. After two weeks, 2-cyclohexenyl-1-benzoate, allylic oxidation product, was isolated in moderate yields and enantiomeric excesses (Table 1, Entry 4 and 5). The allylic oxidation of cyclohexene can also be carried out in acetonitrile and the mixed solvent of acetone and acetonitrile, but the rate of reaction was too slow (Table 1, Entry 3 and 6) and quite amount of unreacted oxidizing reagent, *tert*-butyl perbenzoate, was recovered after reaction.

Table 1 Effect of solvent in enantioselective allylic oxidation of cyclohexene with CuOTf [a] and ligand **1b** [b]

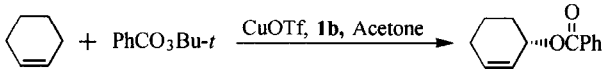


Entry	Solvent	Time (d)	Yield (%) [c]	*ee* (%) [d]
1	PhH	21	trace	
2	$CHCl_3$	21	trace	
3	MeCN	14	10	45
4	Acetone	14	51	41
5	Acetone + $CHCl_3$ (1:1)	14	53	41
6	Acetone + MeCN (1:1)	14	25	43

[a] Prepared *in situ* by reduction of $Cu(OTf)_2$ with $PhNHNH_2$. [b] 5 mol % Cu(I), 6 mol % **1b**. [c] Isolated yield. [d] Determined by HPLC on Chiralcel OD-H column.

Because allylic oxidation of cyclohexene was rather slow at 20℃, we investigated the effect of temperature for finding right condition to speed up the reaction. When the reaction temperature changed from −25℃ to 40℃, the rate of reaction increased constantly without affecting the enantioselectivity (Table 2, Entry 1—4). However, when the reaction was carried out at 50℃, allylic oxidation product was isolated in very poor enantiomeric excess (Table 2, Entry 5). This might because that *tert*-butyl perbenzoate decomposed at 50℃ to generate *tert*-butoxy radical, which can yield racemic product without chiral copper catalyst.

Table 2 Effect of temperature on catalytic enantioselective allylic oxidation of cyclohexene with CuOTf [a] and ligand **1b** [b]

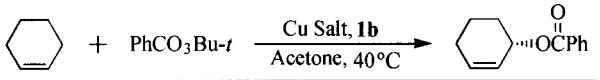


Entry	Temp. (℃)	Time (d)	Yield (%) [c]	*ee* (%) [d]
1	−25	21	27	42
2	0	21	41	40
3	20	14	51	41
4	40	0.5	60	41
5	50	0.5	53	5

[a] Prepared *in situ* by reduction of $Cu(OTf)_2$ with $PhNHNH_2$. [b] 5 mol % Cu(I), 6 mol % **1b**. [c] Isolated yield. [d] Determined by HPLC on Chiralcel OD-H column.

Different copper salts were compared in the catalytic enantioselective allylic oxidation of cyclohexene at 40℃. It was found that commercially available $(CuOTf)_2PhH$ gave much low chemical yield than fresh CuOTf which was generated *in situ* from reduction of $Cu(OTf)_2$ with phenyl hydrazine (Table 3, Entry 1 and Entry 2, 28% *vs*. 60%). $CuClO_4$ and $CuPF_6$[8] were also prepared and tested in this reaction, and comparable yields and enantioselectivities to fresh CuOTf were obtained (Table 3, Entry 3 and 4) although these two copper(I) salts need little longer time to finish reaction. It was beneficial to use $CuClO_4$ and $CuPF_6$ because, unlike CuOTf, they are stable in atmosphere and easy to handle. It was interesting that $Cu(OTf)_2$ itself also could be served as source of Cu in the catalytic enantioselective allylic oxidation of cyclohexene with slightly low *ee*.

Table 3 Effect of copper salt in the complex with ligand **1b** on catalytic enantioselective allylic oxidation of cyclohexene



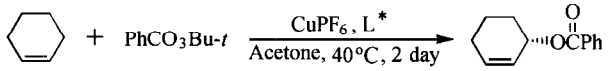
Entry	Cu Salt	Time (d)	Yield (%)[a]	*ee* (%)[b]
1	[CuOTf]	0.5	28	43
2	$Cu(OTf)_2/PhNHNH_2$	0.5	60	41
3	$CuClO_4$	2	56	42
4	$CuPF_6$	2	59	43
5	$Cu(OTf)_2$	0.5	57	34

[a] Isolated yield. [b] Determined by HPLC on Chiralcel OD-H column.

The mechanism of Kharasch reaction has been studied and there are some evidences in the literature to propose that reaction proceeded through a radical intermediate. In this radical mechanism, reaction was initiated by homolysis of the oxygen-oxygen bond of perester with copper(I) to generate a copper(II) benzoateand *tert*-butoxy radical.[9] The *tert*-butoxy radical abstracted prochiral hydrogen atom at allylic position of olefin to produce allylic radical.[10] This allylic radical reacted with Cu(II) benzoate through a Cu(III) intermediate to give allylic benzoate and regenerate Cu(I) catalyst.[11] However, the findings from us and others[4c,4h] that reaction also can be catalyzed by copper(II) complex suggested that different mechanisms might be involved in Kharasch reaction which needs to be further investigated.

The effect of ligand on the asymmetric allylic oxidation of cyclohexene by using $CuPF_6$ and *tert*-butyl perbenzoate was explored and the results were summarized in Table 4. In the series of ligands **1**, **1b**, **1c** and **1d** gave higher ee (Table 4, Entry 2, 3 and 4). Ligand **1c**, with a bulky *tert*-butyl group at C(4) of oxazoline ring, gave not only a low ee but also an opposite configuration of product (Table 4, Eentry 5). As acomparison, we further investigated ligands **2b** and **3b** in allylic oxidation of cyclohexene (Table 4, Entry 6 and Entry 7), and ligand **2b** was found to have lowest enantioselectivity. This sequence of selectivity, same as that in copper(I) catalyzed cyclopropanation of styrene with diazo esters,[5] shows that six-membered chelate ring, upon coordination, is again necessary for heteroaryl-oxazoline ligands to enhance chiral discrimination in the copper catalyzed allylic oxidation of cyclic olefins.

Table 4 Enantioselective allylic oxidation of cyclohexene catalyzed by copper(I) with different ligands[a]

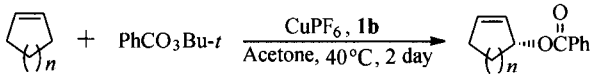


Entry	Ligand	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	**1a** (R = Me)	56	10	*S*
2	**1b** (R = Bn)	59	43	*S*
3	**1c** (R = *i*-Pr)	61	43	*S*
4	**1d** (R = Ph)	41	36	*S*
5	**1e** (R = *t*-Bu)	68	14	*R*
6	**2b** (R = Bn)	49	11	*S*
7	**3b** (R = Bn)	33	29	*S*

[a] 5 mol % of $CuPF_6$ and 6 mol% of ligand (L*) were used. [b] Isolated yield. [c] Determined by HPLC on Chiralcel OD-H column. [d] Assigned by optical rotation.[12]

Cycloheptene showed a similar reactivity and enantioselectivity to cyclohexene, whereas cyclopentene gave very poor enantioselectvity (Table 5, Entry 1). Surprisingly, cyclooctene, under the same conditions, produced only trace amount of allylic oxidation product.

Table 5 Enantioselective allylic oxidation of cyclic olefins catalyzed by $CuPF_6$ and ligand **1b**[a]



Entry	Olefin	Yield (%)[b]	*ee* (%)[c]
1	Cyclopentene	55	6
2	Cyclohexene	49	43
3	Cycloheptene	37	48
4	Cyclooctene	trace	

[a] 5 mol% $CuPF_6$, and 6 mol% **1b** were used. [b] Isolated yield. [c] Determined by HPLC on Chiralcel OD-H column.

In conclusion, we have studied enantioselective allylic oxidation of olefins with copper complexes of chiral quinolinyl-oxazoline ligands. Under optimized condition, cyclic olefins could be converted to allylic benzoates in moderate chemical yields and enantiomeric excesses. Cu(I) triflate prepared *in situ* from reduction of Cu(II) triflate by phenyl hydrozine, $CuClO_4$ and $CuPF_6$ were found to be superior copper source of chiral copper catalyst of quinolinyl-oxazolines in the allylic oxidation of cyclic olefins.

Experimental

General Acetone was refluxed with $KMnO_4$, dried with $CaSO_4$ and distilled. Benzene was distilled from sodium. Acetonitrile was distilled from calcium hydride. Chloroform was distilled from P_2O_5. *tert*-Butyl perbenzoate was synthesized using literature method.[13] $[CuOTf]_2PhH$ and $Cu(OTf)_2$ were purchased from Aldrich and used without further purification. $CuClO_4$ and $CuPF_6$ were prepared according to literature.[8] Allylic oxidation reactions were run under an atmosphere of dry argon using flame-dried glassware. ^1H NMR spectra were recorded at 500 MHz in $CDCl_3$.

Enantioselective allylic oxidation of cyclohexene with tert-butyl perbenzoate in the presence of **1b**, $Cu(OTf)_2$ *and* $PhNHNH_2$

General procedure To a solution of $Cu(OTf)_2$ (18.0 mg, 0.05 mmol) in acetone (2 mL), ligand **1b** (17.3 mg, 0.06 mmol) in acetone (2 mL) was added. After stirring 1 h, phenyl hydrazine (6 μL, 0.7 mmol) and cyclohexene (1 mL, 10 mmol) were added successively. Five minutes later, *tert*-butyl perbenzoate (0.19 mL, 1 mmol) was added, and the resulting mixture was stirred under argon at 20℃ for 14 days. 2 mL of water was then added, and the mixture was extracted by ethyl acetate (2 × 15 mL). Organic phases were combined and washed with water and dried with anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was chromatographed on silical gel (petroleum ether/ethyl acetate 98:2) to give 103 mg (51% yield) of 2-cyclohexenyl-1-benzoate as a colorless oil. ^1H NMR ($CDCl_3$) δ: 8.05(d, J = 7.5 Hz, 2H), 7.52(t, J = 7.5 Hz, 1H), 7.41(t, J = 7.5 Hz, 2H), 6.01—5.98(m, 1H), 5.84—5.82(m, 1H), 5.51—5.48(m, 1H), 2.21—1.78(m, 6H). Enantiomeric excess (41% *ee*) was determined by HPLC on a Chiralcel OD - H column [Hexane / 2 - propanol 1000: 0.5, 1.0 mL/min, t_R = 10.09 min (*S*), 10.55 min (*R*)].

2-Cyclopentenyl-1-benzoate A colorless oil. ^1H NMR ($CDCl_3$) δ: 8.04 (d, J = 7.4 Hz, 2H), 7.53(t, J = 7.4 Hz, 1H), 7.42(t, J = 7.4 Hz, 2H), 6.03—5.99 (m, 1H), 5.86—5.82(m, 1H), 5.52—5.50(m, 1H), 2.13—1.72(m, 4H). Enantiomeric excess was determined by HPLC on a Chiralcel OD-H column [Hexane/2-propanol 1000:0.5, 1.0 mL/min, t_R = 11.77 min (*S*), 12.31 min (*R*)].

2-Cycloheptenyl-1-benzoate A colorless oil. ^1H NMR ($CDCl_3$) δ: 8.06(d, J = 7.5 Hz, 2H), 7.55(t, J = 7.5 Hz, 1H), 7.43(t, J = 7.4 Hz, 2H), 5.90—5.64 (m, 3H), 2.25—1.50(m, 8H). Enantiomeric excess was determined by HPLC on a Chiralcel OD-H column [Hexane/2-propanol 1000: 0.5, 1.0 mL/min, t_R = 10.18 min (*S*), 10.87 min (*R*)].

Enantioselective allylic oxidation of cyclohexene with tert-butyl perbenzoate in the presence of **1b** *and* $CuPF_6$

General procedure To a solution of $CuPF_6$ (10.5 mg, 0.05 mmol) in acetone (2 mL), ligand **1b** (17.3 mg, 0.06 mmol) in acetone (2 mL) was added under argon. The resulting solution was stirred for 1 h at room temperature, then cyclohexene (1 mL, 10 mmol) was added. Five minutes latter, *tert*-butyl perbenzoate (0.19 mL, 1 mmol) was added dropwise, and the reaction mixture was stirred at 40℃ under argon for 2 days. After TLC showed that reaction was complete, 2 mL of water was added. Usual workup and chromatography produced 119 mg (59% yield) of 2-cyclohexenyl-1-benzoate with 43% *ee*.

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