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Catalytic Enantioselective Allylic Oxidation of Olefins with Copper Complexes of Chiral Nonracemic Bis(oxazolinyl)pyridine Type Ligands

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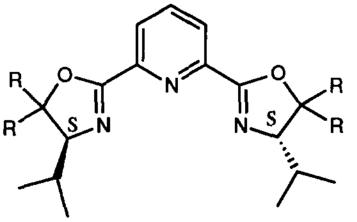
Abstract: Olefins, on treatment with *tert*-butyl perbenzoate in the presence of a catalytic amount of chiral copper bis(oxazolinyl)pyridine complexes, gave optically active allylic benzoates. A variety of cyclic olefins were tried in the reaction and a maximum of 81% ee was obtained during this asymmetric oxidation reaction. Copyright © 1996 Elsevier Science Ltd

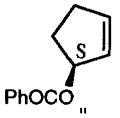
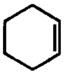
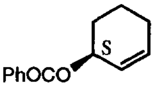
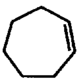
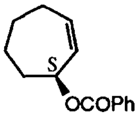
Enantiopure alcohols are very important structural units for synthesis of biologically active compounds. The direct route to these units could be *via* enantioselective reduction of corresponding ketones.[1] However, this approach has not been very successful due to lack of enough steric biasness in the appendages of ketones. Another nonenzymatic way to prepare allylic alcohols is *via* enantioselective deprotonation of epoxides using chiral nonracemic lithium amide bases. In our laboratory, we have made good progress in this area.[2] The drawback with the method is that it is not catalytic and more than stoichiometric amount of ligands is needed. The other possible approach could be based on the well known Kharasch reaction in which allylic oxidation of olefin took place with *t*-butyl perbenzoate in the presence of a catalytic amount of copper salt.[3] Allylic esters, thus obtained, could be converted into allylic alcohols by hydrolysis or reduction method. Early attempts to develope asymmetric version of the reaction using copper camphorate complexes and copper salt with aminoacids gave very poor enantioselectivity.[4] Recently, Muzart reported a maximum of 54% ee during the oxidation of cyclopentene with *t*-butyl perbenzoate or a mixture of *t*-butyl hydroperoxide and benzoic acid in the presence of copper salt of (*S*)- and (*R*)-proline.[5] Use of propionic acid in conjunction with t-butyl hydroperoxide did not have much effect on the enantioselectivity.[6] As a part of our programme in the area of asymmetric synthesis, we, recently, reported bis (oxazolinyl)pyridine type ligands for asymmetric cyclopropanation reactions.[7] In this paper we report further application of the same type of the chiral ligands in enantioselective allylic oxidation of olefins.[8]

The ligand **1** was synthesized following the procedure of Nishiyama.[9] The ligand **2** was prepared following our own procedure.[7] Allylic oxidation of a variety of olefins was carried out with these ligands under different conditions and results are summarized in the table. It is gratifying that high enantioselectivity (81% ee) was obtained in the case of cyclohexene. The procedure for this case is described as follows: A solution of the ligand **2** (0.06 mmol) and $Cu(OTf)_2$ (0.05 mmol) in 4 mL CH_3CN was stirred at rt for 1 h. Phenylhydrazine (0.06 mmol) was added and the colour of the solution changed from blue green to red (an indication for reduction of Cu(II) into Cu(I) species). After 10 min of stirring, a few grains of 4Å molecular sieves and



1, R = H
2, R = Ph

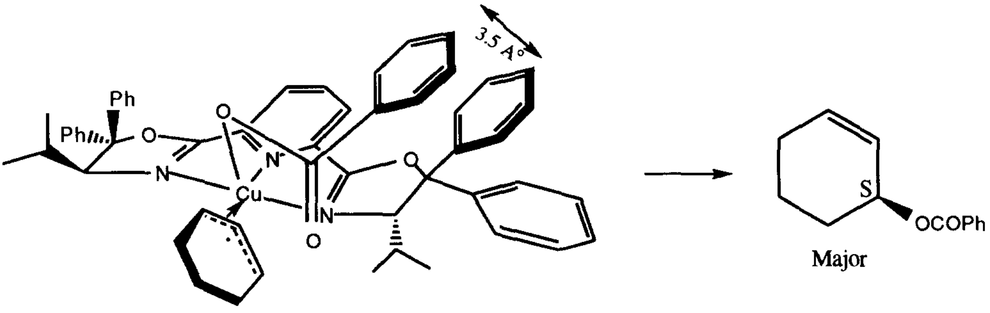
Table: Asymmetric Catalytic Allylic Oxidation of Olefins with Ligands **1** & **2** in CH_3CN solvent at rt.

Entry	Olefin	Product	Ligand	Reagents[a]	Time (days)	Yield (%)	$[\alpha]_D$ (c 2-4, $CHCl_3$)	% ee[b]
1.			**1**	Cu(OTf), $PhCO_3{}^tBu$	6	48	-86.4°	45
2.	"	"	**1**	Cu(OTf), $PhCO_3{}^tBu$, 4A° mol. sieves	20	59	-107.5°	56
3.	"	"	**2**	Cu(OTf), $PhCO_3{}^tBu$	4	38	-80.8°	42
4.	"	"	**2**	Cu(OTf), $PhCO_3{}^tBu$, 4A° mol. sieves	4	70	-112.0°	59
5.	"	"	**2**	CuCN, $PhCO_2H$, ${}^tBuOOH$	5	64	-88.6°	46
6.	"	"	**2**	$Cu(OTf)_2$, $PhCO_3{}^tBu$	2	28	-26.0°	14
7.			**1**	$Cu(OTf)_2$, $PhCO_3{}^tBu$	10	35	-24.5°	13
8.	"	"	**1**	$Cu(OTf)_2$, $PhCO_3{}^tBu$, 4A° mol. sieves	20	63	-84.0°	45
9.	"	"	**2**	Cu(OTf), $PhCO_3{}^tBu$	10	43	-127.9°	70
10.	"	"	**2**	Cu(OTf), $PhCO_3{}^tBu$, 4A° mol. sieves	15	58	-147.8°	81
11.	"	"	**2**	CuCN, $PhCO_2H$, ${}^tBuOOH$	5	48	-77.5°	42
12.	"	"	**2**	$Cu(OTf)_2$, $PhCO_3{}^tBu$	5	48	-95.5°	52
13.			**2**	CuCN, $PhCO_2H$, ${}^tBuOOH$	5	39	-11.5°	25

[a] Cu(I)OTf was prepared *in situ* from Cu (II) triflate and phenylhydrazine. [b] %ee was determined by 400 and 600 MHz ^1H NMR spectrum in the presence of chiral shift reagent $Eu(hfc)_3$ and by $[\alpha]_D$ comparison with the known values.

cyclohexene (10 mmol) were added. *tert*-Butyl perbenzoate (1 mmol) was added dropwise (colour changed from red to green). The reaction mixture was left at rt for 15 days. Usual work up and purification gave allylic benzoate in 58% yield and 81% ee (Entry 10). It was observed that if molecular sieves were not used, the enantioselectivity dropped to 70% (Entry 9). Variation of Cu salt had a major effect on the enantioselectivity in the reaction. Cu(I) triflate, which was prepared *in situ* by a reduction method[10] with phenylhydrazine, proved to be the best. CuCN and Copper (II) triflate both lowered down the enantioselectivity (Entries 11 and 12). It was further to note that the ligand **2** gave better enantioselectivity than the ligand **1** (Compare entries 8 & 10). The reaction was extended to other cyclic olefins. Cyclopentene showed the similar kind of behaviour during the oxidation reaction. In this case also, molecular sieves proved to be benificial in enhancing the enantioselectivity. Thus, a maximum of 59% ee was obtained with Cu(OTf) complex of the ligand **2** and *tert*-butyl perbenzoate in the presence of 4Å molecular sieves (Entry 4). Surprisingly, cycloheptene and cyclooctene, under the above conditions, gave messy products. However, when the reaction of cycloheptene was tried with benzoic acid and *tert*-butyl hydroperoxide in the presence of CuCN complex of ligand **2**, the desired product was obtained, at best, in 39% yield, but the asymmetric induction was poor (Entry 13).

There is enough evidence in the literature that the reaction proceeds *via* a radical intermediate. The Cu (I) cleaves the perester into benzoate anion and t-butoxy radical.[11] The t-butoxy radical abstracts an allylic hydrogen atom to give t-butanol and an allylic radical.[12] It is proposed in the literature that the next step is rapid addition of Cu(II) to the allylic radical to generate Cu(III) benzoate which rearranges to the product *via* a six-membered intermediate.[13] In view of our findings that $Cu(OTf)_2$ catalyses the reaction equally well, it is unlikely that the above intermediate is formed, at least in case of $Cu(OTf)_2$ as the Cu(II) has to go to Cu(IV) which is not a stable species. We assume that there is a coordination between the incipient double bond of the allylic radical and copper species. After the benzoate oxygen attacks the allylic carbon of olefin, the Cu species is reduced to the original oxidation state which enters the catalytic cycle of the reaction. A transition state model (Figure 1) is proposed to account for the stereoinduction in the reaction.



Favourable T.S. Assembly

Figure 1

In this favourable transition state assembly, copper benzoate attains an orientation in such a way that there is a π-stacking[14] of the two aromatic rings. Since the distance between both the rings is approximate 3.5 Å, there will be some attractive interaction which will stablize the drawn conformation. In that case, allylic radical will approach the Cu species from the less hindered side as shown in the Figure 1. The benzoate oxygen attacks the allylic carbon which is electrophilic in nature due to coordination of incipient double bond with Cu species. This follows the reduction of Cu species into its original oxidation state. Thus, the catalytic cycle of the allylic oxidation of alkenes continues.

In conclusion, we have shown that copper complexes of the chiral bis(oxazolinyl)pyridine type ligands are good catalysts for allylic oxidation of olefins. In case of cyclohexene, we have achieved 81% ee, which is highest to date, for this kind of reaction. While the optical induction for other olefins is not very high, a beginning has been made. Further work is in progress to expand the scope of this reaction.

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