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Highly Enantioselective Copper−Bisoxazoline-Catalyzed Allylic Oxidation of Cyclic Olefins with *tert*-Butyl *p*-nitroperbenzoate

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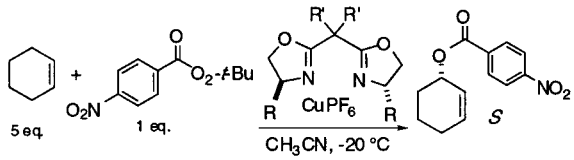
While a range of ligands have been explored, copper-catalyzed allylic oxidation with peresters[1] has been hampered by poor reactivity and selectivity. We now report a highly selective process using a panel of eight malonyl-derived bisoxazolines together with *tert*-butyl *p*-nitroperbenzoate to provide enantiomerically enriched ester products with cyclic olefins. Asymmetric versions[2] have been explored using camphorate esters and catalytic amino acid copper complexes at lower temperatures with varying results.[3] Enantioselectivities improved to 80% ee using di-*tert*-butyl and phenyl-bisoxazolines with *tert*-butyl perbenzoate.[4]

A number of bisoxazoline and trioxazoline ligands have been explored since that time that give, in the case of cyclopentene, high selectivity.[5] Pyridyl and bipyridyl bisoxazoline ligands with added phenylhydrazine in acetone show improved reactivity but again with only modest 80% ee selectivity at best.[6] Biaryl and aminoindanol ligands have also been explored with limited success.[7] We now report the results from a panel of eight malonyl-derived bisoxazoline complexes as catalysts reacted with *p*-nitroperbenzoate[8] with cyclic olefins. Unique ligand−substrate combinations are identified to now give excellent selectivities for the first time, 94−99% ee, for ester products. These selectivities now compliment catalytic epoxidation and dihydroxylation methods that occur with high selectivity.[9] Allylic oxidation offers the unique advantage of maintaining the alkene functionality in the allylic ester product. This utility is seen in the conversion of cyclohexenyl benzoate to the key intermediate in the synthesis of leukotriene B_4.[10]

Eight malonyl gem-dimethyl and gem-diethyl bisoxazolines[11] were used for this study together with *tert*-butyl *p*-nitroperbenzoate, mp 75 °C, made from anhydrous *tert*-butyl hydrogen peroxide and *p*-nitrobenzoyl chloride.[12] The reactions were performed by forming the copper(I) hexafluorophosphate[13]−bisoxazoline complex (15 mol %) in degassed acetonitrile (0.2 M) at room temperature and adding 5 equiv of olefin followed by perester (1 equiv) at −20 °C (Table 1). The reactions were monitored by TLC for consumption of perester and stopped at the given time. The yields are for isolated materials based on the perester, and the selectivities were determined by chiral HPLC with comparison to racemic compound. Yields were moderate for the purified ester products; however, the ligands could be recovered in 85% yield based on the amount used and recycled. In all cases the *S*,*S* ligands generated (*S*)-ester product.[14] The cyclohexenyl ester was obtained with very high 96% ee selectivity using the diphenyl gem-dimethyl bisoxazoline (entry 3). The gem-diethyl ligands showed lower reactivity and selectivity. Interestingly, in the case of entry 3, when the reaction was monitored every 48 h, a gradual increase in both yield and selectivity was noted.[15] The possibility of product resolution was explored in this case by treating racemic ester product with the ligand−copper(I) complex, perester, and *tert*-butyl alcohol in CH_3CN. After 11 days at −20 °C, the ester remained racemic. In contrast, 58% ee enriched ester product exposed to the reaction conditions for 17 days gave product in 85% yield enriched to 84% ee.

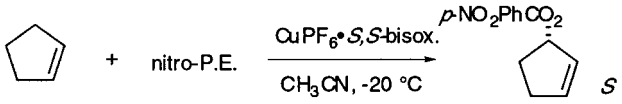
Table 1. Asymmetric Allylic Oxidation of Cyclohexene



entry	R	R′	time (d)[a]	% yield[b]	ee[c]
1	*t*-Bu	Me	7	61	84
2	−	Me	21	43	80[d]
3	Ph	Me	17	44	96
4	Bn	Me	6	30	71
5	*i*-Pr	Me	6	40	82
5	*t*-Bu	Et	16	25	16
6	Ph	Et	13	50	75
7	Bn	Et	12	50	53
8	*i*-Pr	Et	5	26	78

[a] Time in days, using a sealed vial placed in the freezer with stirring. [b] Yields are for isolated, chromatographed materials based on the perester. [c] Enantiomeric excesses were determined by chiral normal phase HPLC. [d] Unsubstituted perester. *tert*-Butyl perbenzoate used.

Table 2. Oxidation of Cyclopentene



entry	R	R′	time (d)[a]	% yield[b]	ee[c]
1	*t*-Bu	Me	10	52	79
2	Ph	Me	10	49	82
3	Bn	Me	10	25	75
4	*i*-Pr	Me	10	42	51
5	*t*-Bu	Et	10	31	38
6	Ph	Et	8	41	99
7	Bn	Et	8	28	80
8	*i*-Pr	Et	8	36	83

[a] Time in days, using a sealed vial placed in the freezer with stirring. [b] Yields are for isolated, chromatographed materials based on the perester. [c] Enantiomeric excesses were determined by chiral normal phase HPLC.

The oxidation of cyclopentene using gem-dimethyl ligands showed moderate to good selectivity, 51−82% ee (Table 2). In contrast, the use of the gem-diethyl set identified a highly selective catalyst, the diphenyl complex that gave product with remarkable 99% ee selectivity. In this case, both the di-Bn and di-*i*-Pr ligands were moderately selective (entries 7, 8), while the more sterically congested di-*tert*-butyl ligand gave poor selectivity (entry 5, 38% ee).

The panel of eight ligands was also applied to the asymmetric oxidation of the less reactive substrates cycloheptene and 1,5-

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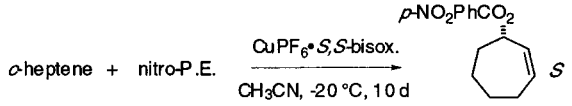
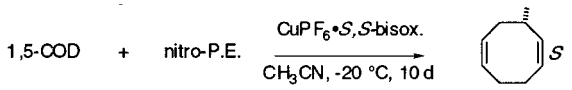
Table 3. Oxidation of Cycloheptene



entry	R	R′	% yield[a]	ee[b]
1	*t*-Bu	Me	3	95
2	ph	Me	23	56
3	*i*-Pr	Me	14	99
4	Ph	Et	12	86

[a] Yields are for isolated, chromatographed materials based on the perester. [b] Enantiomeric excesses were determined by chiral normal phase HPLC.

Table 4. Asymmetric Oxidation of COD



entry	R	R′	% yield[a]	ee[b]
1	*t*-Bu	Me	13	94
2	Ph	Me	46	74
3	*i*-Pr	Me	25	36
4	Ph	Et	34	59
5	*i*-Pr	Et	27	78

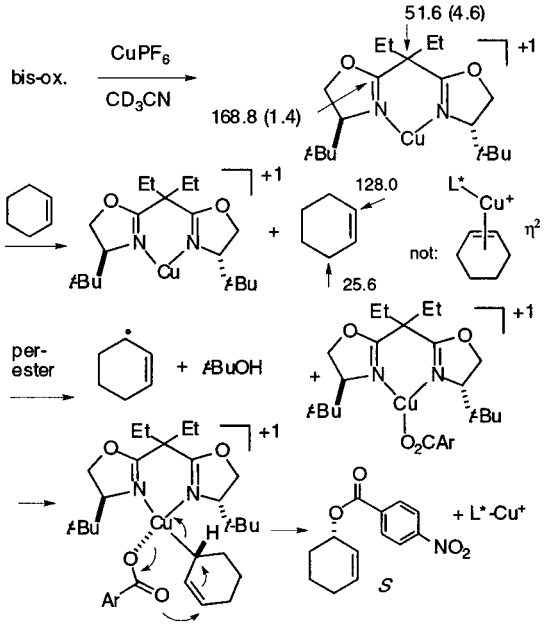
[a] Yields are for isolated, chromatographed materials based on the perester. [b] Enantiomeric excesses were determined by chiral normal phase HPLC.

cyclooctadiene. The results shown again indicate that very high selectivity can be obtained via a unique ligand combination. The gem-dimethyl di-*i*-Pr ligand (entry 3, Table 3) proved best at 99% ee for cycloheptene. In this case the reactivity was very poor at 14% yield, indicating only a single turnover of the catalyst. In general cycloheptene has shown lower reactivity and selectivity compared to cyclopentene and cyclohexene.[6,7] The di-*tert*-butyl ligand, while highly selective at 95% ee, again showed low reactivity. The gem-diethyl set was also low, yet the diphenyl ligand in this case showed good selectivity at 86% ee (entry 4). Cyclooctadiene was oxidized in high 94% ee selectivity using the gem-dimethyl di-*tert*-butyl copper catalyst (entry 1, Table 4). Higher yields were found with other ligands in this case, but the selectivities were lower.

The origin of the selectivity of the process was explored using 10-mm, low-temperature ^{13}C NMR (75 MHz, −35 °C) in CD_3CN at 1:1 stoichiometry. Shifts for the complex are shown, indicating the expected downfield shifts in parentheses relative to free ligand (Scheme 1). The gem-diethyl di-*tert*-butyl ligand was selected due to its low selectivity. Two or more orientations of the alkene were anticipated with the copper complex in this case. When cyclohexene (1 equiv) was added, only signals for the free, uncomplexed alkene were observed indicating the absence of an η^2 copper−olefin intermediate. Indeed when $CuPF_6$ is complexed alone with cyclohexene, shifts for the alkene and allylic carbons are seen indicating an η^2 interaction.[16] Yet upon addition of bisoxazoline, only free olefin was observed. The copper chelate is clearly favored, while a ligand−copper−cycloalkene complex is not. The selectivity then is most likely a consequence of the allylic radical approach to the copper(II) benzoate complex. Attack of the less hindered quadrant of the C_2-copper complex gives the copper(III) intermediate proposed by Beckwith and Zavistsas,[17] which rearranges to give *S*-ester product and copper(I) complex.

A panel of bisoxazoline ligands with *tert*-butyl *p*-nitroperbenzoate identified unique ligand−substrate combinations that now give very high enantioselectivities for asymmetric allylic oxidation. Efforts are now underway to improve the reactivity of the process and further explore the factors that contribute to the selectivity and catalyst activity.

Scheme 1



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Supporting Information Available: Experimental procedures, characterization, and HPLC data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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