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Remarkable Reversal of the Non-linear Effect in the Catalytic Enantioselective Allylic Oxidation of Cyclohexene Using Copper Proline Complexes and t-Butyl Hydroperoxide

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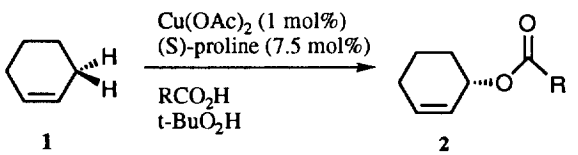
Abstract: Several examples of efficient catalytic conversions of cyclohexene to optically active 2-cyclohexenyl propionate are reported using *t*-butyl hydroperoxide as oxidant. With the bis (S)-prolinato copper(II) complex enantioselectivities up to 63% with good conversions were obtained. A negative non-linear ligand effect was observed. Addition of catalytic amounts of anthraquinone resulted in a higher enantioselectivity as well as a reversal of the non-linear effect.

Stereoselective functionalisation of unactivated olefins is a very active and challenging area of research. Now that the asymmetric epoxidation of alkenes[1] and allylic alcohols[2] and dihydroxylation of olefins[3] are well established, we are pursuing the catalytic asymmetric oxidation of olefins with enantiomerically pure copper complexes to yield allylic acyloxylated olefins. Only few examples of this reaction were known[4] and the reported enantioselectivities were typically below 30%. However, recently several groups have published significant improvements in enantioselectivities; for example Pfaltz[5b] and Andrus[5c] were able to benzyloxylate cyclopentene in good yields with enantioselectivities of 84% and 81% respectively using oxazoline ligands. Severe drawbacks in these systems are extremely low reactivity and the use of the expensive oxidant *t*-butyl peroxybenzoate. Previously we have shown the preparation of 2-cyclohexenyl propionate **2** from cyclohexene **1** and propionic acid using peroxyesters and Cu(I) species generated from Cu(II)/copper bronze and (S)-proline, with enantioselectivities up to 61%.[5a] In this paper we wish to report: (i) a highly efficient allylic acyloxylation with t-butyl hydroperoxide as oxidant using bis(prolinato) Cu(II) as catalyst (Scheme 1); (ii) a remarkable increase in enantioselectivity in the presence of anthraquinone; (iii) an unexpected reversal in non-linear effect in this catalytic asymmetric oxidation and (iv) a dependency of the enantioselectivity on conversion.



Scheme 1. Allylic oxidation of cyclohexene

In a typical procedure, 2 mL acetonitrile, 3 mL cyclohexene and 1 mL propionic acid are added to 18 mg Cu(II)acetate monohydrate (0.09 mmol) and 70 mg (S)-proline (0.60 mmol) under a nitrogen atmosphere, yielding a blue homogeneous solution. After stirring the mixture at 50 °C for 15 min. 1.0 mL *t*-butyl hydroperoxide (70% solution in water) is added. After 3 days at this temperature the internal standard is added and the mixture is poured into 50 mL 2N HCl and extracted with ether followed by standard purification. The

conversion (relative to the oxidant) and enantioselectivity are determined by GC, followed by careful distillation at 80 °C/10 mmHg which yields the optically active 2-cyclohexenyl propionate.

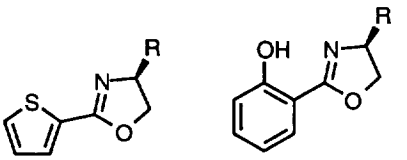
Previously some preliminary attempts to increase the enantioselectivity in the peroxyester system by modifying the proline framework were described. We have now executed extensive modification of the chiral aminoacid ligands, in particular modified prolines (see Table 1). From these results the absence of a relation between structural parameters and observed conversions and enantioselectivities is apparent. We can conclude that even minor changes in or at the ring framework have detrimental effects on conversion and e.e. (entries 1, 5-11). Much to our surprise the addition of anthraquinone gave a remarkable effect on the enantioselectivity: four equivalents with respect to copper result in an increase of the e.e. from 45 to 60%, but only when *t*-butyl hydroperoxide is used as oxidant (entry 2). With *t*-butyl peroxybenzoate no significant changes were observed (entry 3). The use of larger amounts of anthraquinone mainly resulted in a decrease in conversion. The exact role of anthraquinone is not clear at present; possibly it serves as cooxidant by activating the *t*-butyl hydroperoxide or as oxidant of low valent copper species. The latter role is played by anthraquinone in the autooxidation of saturated alkanes as reoxidant of Cu(I)[6] and by benzoquinone in the Pd(II)/MnO_2 system as reoxidant of Pd(0).[7] It should be noted that stoichiometric amounts of quinone are used in the Pd(II) system in contrast with the catalytic amounts used in this work.

Table 1. Influence of variation of amino acid ligands[a]

Entry	Ligand	Yield of **2** (%)	e.e. (%)[b]
1	(S)-proline	89	45
2	(S)-proline + 4 eq. anthraquinone[c]	80	60
3	(S)-proline + 4 eq. anthraquinone[d]	81	46
4	(S)-proline + 200 eq. anthraquinone	60	56
5	(R)-α-methylproline[8]	33	28
6	(R)-α-2-picolylproline[8]	nd[e]	<10
7	(R)-thiaproline	25	28
8	(R)-5,5-dimethyl-thiaproline	15	15
9	(R)-5,5-spirocyclohexyl-thiaproline	11	18
10	(S)-pyroglutamic acid	64	10
11	(R)-3,3-dimethyl-thiaproline	46	16

[a]All reactions resulted in the formation of (*S*)-2-cyclohexenyl propionate. TBHP was the oxidant unless otherwise stated. [b]determined by GC,(HP5890A with cappilary column coated with CP cyclodextrin B-2,3,6-M-19). [c]four equivalents of anthraquinone relative to Cu(II)acetate. [d]t-butyl peroxybenzoate is used as oxidant. [e]not determined.

In view of the good results with bis(oxazoline) ligands in peroxyester oxidations[5b,c] a number of neutral and anionic mono oxazoline bidentate ligands were also tested (Figure 1). Enantiomerically pure 2-oxazolyl thiophenes **3a-c** gave only 5-10% ee, although conversions were in the range of 50-90%. Modest results were obtained with 2-oxazolyl phenols **4a-c** which all gave reasonable conversions (typically 60%), with enantioselectivities in the order of 25%.

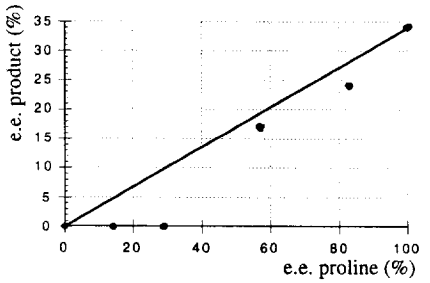


a) R = i-Pr
b) R = CH_2Ph
c) R = Ph

3a-c **4a-c**

Figure 1. Oxazolines derived from thiophene and phenol

The use of scalemic proline as ligand has been tested in order to obtain further information on the nature of the active catalyst. Using both Cu(II)acetate and Cu(I)oxide in the procedure described above without anthraquinone we unambiguously observed a small but distinct negative non-linear effect (Figure 2a).[9] This result demonstrates that more than one proline is involved in the stereodiscriminating step of the reaction, pointing to either a mononuclear copper complex binding to two proline ligands[10] or to dinuclear (or even oligonuclear) catalyst complexes. If two prolines are covalently attached to the metal centre as well as the carboxylate fragment that is to be transferred (*e.g.* propionate or benzoate) our observations support the existence of a Cu(III) intermediate as originally proposed by Beckwith.[11] Furthermore, it was clearly seen that the blue solution became increasingly turbid on lowering the enantiomeric purity of proline. The precipitate may be a non-chiral meso complex, e.g. (*R*)-prolinato-(*S*)-prolinato Cu(II). In view of the negative nonlinear effect, it appears that the remainder of this complex in solution is much more active than the optically active R,R and S,S catalysts present in solution. The addition of anthraquinone in these experiments resulted, much to our surprise, besides the selectivity enhancement also in a clear positive non-linear effect (Figure 2b). This reversal in non-linear effect on addition of a small amount of an achiral agent is as far as we know unprecedented and indicates either a change in mechanism or a structural change of the chiral catalyst.



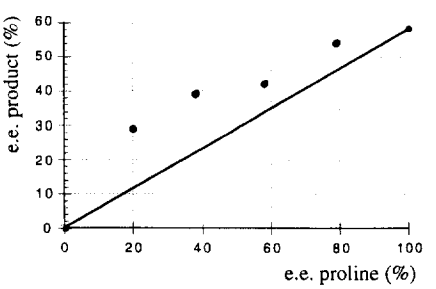


Figure 2a. Non-linear effect without anthraquinone

Figure 2b. Non-linear effect with anthraquinone

To gain further insight into the mechanism of the allylic oxidation the following experiments were performed (all using the standard procedure as described above, with 80 mg anthraquinone). i) A low concentration of oxidant was maintained by slow addition of *t*-butyl hydroperoxide over a period of two days under a constant flow of nitrogen, but no effect on the e.e. was found;[12] ii) by following the reaction against time, it was observed that the oxidation becomes slightly less efficient in terms of enantioselectivity during the course of the reaction; iii) the stability of 2-cyclohexenyl propionate under essentially the same reaction conditions was

examined by adding enantiomerically enriched material (e.e. of 59%) to the oxidation reaction of cyclopentene to 2-cyclopentenyl acetate. The e.e. of the recovered 2-cyclohexenyl propionate was 51%. No hydrolysis to 2-cyclohexenol nor transesterification to 2-cyclohexenyl acetate was observed. This indicates that some thermal racemisation occurs, probably *via* a Claisen-type rearrangement (Figure 3) and explains the observation described under ii; iv) bis(acetonitrile)$PdCl_2$ is a known catalyst for [3,3]-sigmatropic rearrangements[13] and could accelerate the racemisation whereas the palladium complex itself gave no reaction at all.[14] However, the presence of one equivalent of the palladium complex relative to copper in the reaction mixture did not result in the expected decrease in e.e. but in a slight increase to 63% (85% conversion).

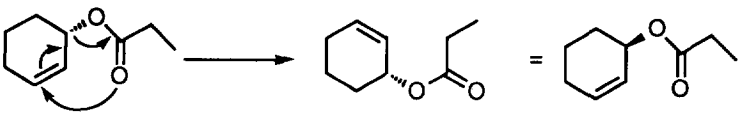


Figure 3. Possible racemisation pathway of 2-cyclohexenyl propionate

In conclusion we have shown that the presence of anthraquinone in the allylic oxidation of cyclohexene leads to a remarkable increase in enantioselectivity as well as a remarkable reversal in non-linear effect, although the exact role it plays remains elusive. Extensive ligand modification shows that further improvements in e.e. are not readily expected by modifications of the proline skeleton, but rather from a detailed mechanistic investigation. Studies along these lines are in progress.

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