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Asymmetric epoxidation of styrenes catalyzed by molybdenum complexes with amino alcohol ligands

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ABSTRACT

Two common amino alcohols, prolinol and isolucinol, and their derivatives have been screened to coordinate with $MoO_2(acac)_2$ to form in situ catalysts for asymmetric epoxidation of styrenes with the highest enantioselectivity of 84% for 4-fluoro-styrene under the optimized reaction conditions.

The demand for enantiopure chiral compounds rises continuously, facilitated among other reasons, by the increasing number of government regulations and health concerns as well as the need for efficiency in industry.[1a] Asymmetric catalysis is a particularly elegant and efficient method to achieve the introduction of chiral groups into larger organic compounds.[1] One of important factors for the design and development of chiral catalysts is the need for the use of simple and easily available chiral starting materials, so as to be able to assemble the final catalyst in large scale and at the cheapest cost possible.[2] Taking this into account, it is easy to understand that natural (and sometime unnatural) amino acids are, most likely, one of the most useful chiral sources for this purpose, and many different kinds of chiral ligands and catalysts have been prepared from them.[3] For example, C_2-symmetric bisoxazoline ligands derived from amino acids have become one of the leading classes of chiral ligands in asymmetric C–C bond formation reactions.[4] Moreover, some amino acids or their derivatives such as amino alcohols have been recently successfully applied as chiral organocatalysts in asymmetric catalysis.[5] However, the applications of amino alcohols as ligands in catalysis have less been reported.[6]

On the other hand, molybdenum is reported to be less toxic than manganese and highly available to biological systems.[7] The coordination chemistry of Mo(VI) has aroused considerable interests in view of its biochemical significance, and many Mo(VI) complexes have been studied as models of molybdoenzymes.[8,12] A large number of important chemical reactions were catalyzed by molybdenum(VI) complexes with various types of chiral ligands. Pyridyl alcohols and phosphinoylalcohols have been reported recently to induce enantioselective epoxidation of unfunctionalized olefins when coordinated to dioxo and peroxomolybdenum fragments with moderate 20–40% ees.[9]

Continuation of our studies in transition metal catalyzed asymmetric oxidation,[10] herein is reported the first example of in situ asymmetric epoxidation of styrenes by molybdenum complexes with amino alcohols and their derivatives as ligands.[11]

Among the ligands used in this work shown in Figure 1, chiral amino alcohols **1c** and **1d** were easily prepared by the reduction of the corresponding amino acids with sodium borohydride and iodine in THF.[12] Compounds **1f** and **1g** were synthesized in high yields by condensation of isoleucinol **1d** with corresponding salicylaldehydes followed by reduction by sodium borohydride. The other three ligands were commercially available. The structures

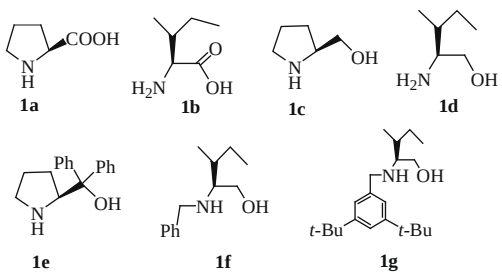

Figure 1. The amino alcohol ligands and their derivatives.

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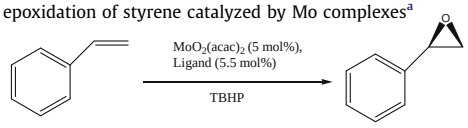
of the ligands were confirmed by IR, NMR and Mass spectra with satisfactory data.[12]

Initially, all of the ligands were screened in situ asymmetric epoxidation of styrene by using 5 mol % $MoO_2(acac)_2$ and 5.5 mol % ligands with *tert*-butyl hydroperoxide as oxidant, the reaction conditions were also optimized, and the results are listed in Table 1.

As shown in Table 1, direct application of natural amino acids **1a** and **1b** as ligands resulted in low ee values less than 10%, and only a small amount of epoxide was detected in the presence of aqueous *t*-butyl hydroperoxide (TBHP) in CH_2Cl_2 (Table 1, entries 1 and 2). Their reductive products amino alcohols **1c** and **1d**, which bear amino or hydroxy groups, led to the formation of the epoxide in much higher yields and ees around 50% and 20%, respectively, under similar reaction conditions (Table 1, entries 3 and 4). The other two amino alcohols such as glycinol and phenylalaninol have also been used to give 18% and 19% enantioselectivities, respectively.

Furthermore, it is notable that modification of prolinol to diphenyl-2-pyrrolidine methanol **1e** increased the enanotioselectivity to 46%. It indicated the major role of phenyl substitutes in controlling the asymmetric induction during catalysis. Meanwhile, changing the oxidant to cumene hydroperoxide (CHP) did not improve the result (Table 1, entry 6). However, using anhydrous TBHP (40% in toluene)[13] instead of aqueous oxidant benefited to the catalysis with 67% yield and 69% ee (Table 1, entry 7). The molar rate of molybdenum and ligand had also strong effects on the results. When the ratio increased from 1:1.1 to 1:2.2, the enantioselectivities declined from 69% to 25% (Table 1, entries 7 and 8). Meanwhile, the other two secondary amino alcohol derivative ligands **1f** and **1g** have also been examined with enantioselectivities 29% and 44%, respectively (Table 1, entries 9 and 10). Other solvents such as toluene, THF and CH_3CN were tested with lower yields and ees (Table 1, entries 11–13). Reaction temperature, on the other hand, exhibited effects on the results. Lower temperature than 25 °C decreased the catalytic activity and higher temperature declined the enantioselectivity (Table 1, entries 7, 14 and 15). Thus, the reaction temperature of 25 °C was selected for the further studies.

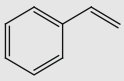
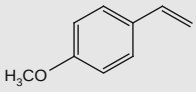
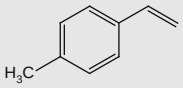
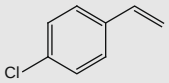
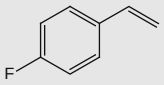
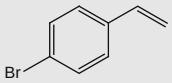
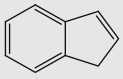
Table 1
Asymmetric epoxidation of styrene catalyzed by Mo complexes[a]



Entry	Oxidant	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	TBHP(aq)	**1a**	CH_2Cl_2	23	9
2	TBHP(aq)	**1b**	CH_2Cl_2	26	2
3	TBHP(aq)	**1c**	CH_2Cl_2	52	23
4	TBHP(aq)	**1d**	CH_2Cl_2	48	17
5	TBHP(aq)	**1e**	CH_2Cl_2	57	46
6	CHP	**1e**	CH_2Cl_2	68	50
7	TBHP(toluene)	**1e**	CH_2Cl_2	67	69
8[d]	TBHP(toluene)	**1e**	CH_2Cl_2	69	25
9	TBHP(toluene)	**1f**	CH_2Cl_2	51	29
10	TBHP(toluene)	**1g**	CH_2Cl_2	56	44
11	TBHP(toluene)	**1e**	Toluene	62	66
12	TBHP(toluene)	**1e**	CH_3CN	65	62
13	TBHP(toluene)	**1e**	THF	43	51
14[e]	TBHP(toluene)	**1e**	CH_2Cl_2	25	71
15[f]	TBHP(toluene)	**1e**	CH_2Cl_2	66	47

[a] Reactions were performed with $MoO_2(acac)_2$:ligand:styrene:hydroperoxide molar ratio of 0.05:0.055:1:1.5 except other descriptions.
[b] Based on styrene used.
[c] Determined by GC with chiral column. The major enantiomer was *R*-styrene oxide.
[d] $MoO_2(acac)_2$:ligand = 1:2.2.
[e] The reaction temperature is 0 °C.
[f] The reaction temperature is 40 °C.

Table 2
Asymmetric epoxidation of other olefins[a]

Entry	Substrate	Yield[b] (%)	ee[c] (%)
1		67	69
2		70	72
3		73	70
4		75	81
5		78	84
6		72	73
8		76	68[d]

[a] Reactions were run at rt with $MoO_2(acac)_2$:ligand:styrene:TBHP molar ratio of 0.05:0.055:1:1.5 in CH_2Cl_2.
[b] Based on olefins used.
[c] Determined by GC or HPLC with chiral column. All the styrene epoxides were in *R* configuration compared with those in literature.
[d] The configuration was 1*R*, 2*S*.

The other substrates were then examined by using **1e** as ligand under the optimized reaction conditions and the results are summarized in Table 2.

In general, the catalytic reactions proceeded smoothly at room temperature with moderate to good results. As shown in Table 2, styrenes with electron-withdrawing substituents were epoxidized with better results than those with electron-donating groups. For example, when the substrate changed from 4-methylstyrene to 4-chloro-styrene, ee value increased from 70% to 81% (Table 2, entries 3 and 4). And the best result of enantioselectivity of 84% was obtained in the catalytic epoxidation of 4-fluoro-styrene (Table 2, entry 5), which is much higher than the reported 20–40% ees by using pyridyl alcohols as ligands.[9] Indene had also been examined under similar conditions with moderate result of 68% ee (Table 2, entry 8).

In summary, two chiral amino alcohols and their derivatives were found to promote the enantioselective epoxidation of styrenes in moderate to good enantiomeric excess up to 84%. Further studies dealing with the application of this type of ligands in asymmetric reactions are in progress.

Acknowledgements

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11. *General procedure for asymmetric epoxidation of styrene*: $[MoO_2(acac)_2]$ (16.3 mg, 0.05 mmol) was added to a solution of ligand (0.055 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred for 1 h at room temperature. Olefin (1.0 mmol) and alkyl hydroperoxide (1.5 mmol) were then added. The mixture was kept stirring for 12 h at 25 °C. Saturated Na_2SO_3 solution (10 mL) was then added and the mixture was stirred for 30 min at rt. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4. The chemical yield and enantioselectivity were determined by GC or HPLC.
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