Asymmetric Catalysis

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Enantioselective Oxidation of Olefins Catalyzed by a Chiral Bishydroxamic Acid Complex of Molybdenum**

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Since the first report of Sharpless's titanium tartrate catalyst,[1] a number of useful methods for asymmetric oxidation

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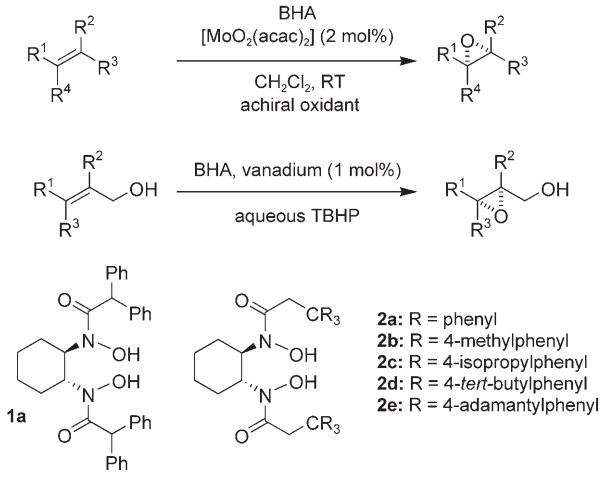
have been developed. Among these, the most practical method utilizes manganese–*N*,*N*'-bis(salicylidene)ethylenediamine dianion (Mn–salen) mediated epoxidation of alkenes (Jacobsen–Katsuki epoxidation). However, the application of the manganese–salen catalyst is limited by the requirement of a low reaction temperature and the lack of selectivity observed during the epoxidation of *Z* olefins.[2] More recently, a metal-free oxidation of alkenes has also been reported, mediated by a fructose-derived, chiral dioxirane.[3] Although this method complements the selectivity for *trans*-alkene oxidation, it often requires high catalyst loading to obtain good yield.

Our continuing efforts to develop a simple method for asymmetric oxidation revealed that a chiral vanadium–hydroxamic acid complex with an achiral oxidant induced high enantioselectivity in the epoxidation of allylic alcohols.[4] The recently discovered bishydroxamic acid (BHA; **2**) was utilized as a ligand for the vanadium-catalyzed asymmetric epoxidation of *cis*-allylic alcohols and for the molybdenum-catalyzed asymmetric oxidation of sulfides and disulfides (Scheme 1).[5] In these previous studies, it was found that the



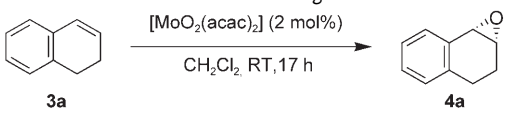
Scheme 1. acac = acetylacetone.

epoxidation of geraniol with the molybdenum complex of **2a** in the presence of *tert*-butyl hydroperoxide (TBHP) provided a 1:1 mixture of 2,3-epoxygeraniol and 6,7-epoxygeraniol.[5a,6] These results suggested that a Mo^{VI} complex of BHA in the presence of an organic hydroperoxide is a stronger oxidizing agent than the V^{V} complex, and that the former does not require substrate metal coordination during the catalytic cycle.[7] This prompted us to explore the enantioselective oxidation of olefins with the Mo–BHA catalyst.

The use of molybdenum-peroxo complexes for the industrial-scale epoxidation of alkenes has been extensively explored over the last 40 years, beginning with homogeneous Mo^{VI} catalysts in the Halcon and Arco processes.[8] Early reports of asymmetric epoxidation with a chiral molybdenum complex include the use of a stoichiometric molybdenum–(*S*)-lactic acid piperidineamide system by Schurig, Kagan and co-workers.[9] Consequently, considerable effort has been directed towards the development of enantioselective epoxidation protocols in which chiral molybdenum catalysts are used.[10,11] However, weak coordination of ligands with the molybdenum has resulted in very little success having been achieved. To this end, the Mo–BHA system has several advantages: 1) molybdenum is less toxic than manganese,[12] 2) in the ease of preparation of the Mo–BHA complex relative to other catalysts, (3) the ambient reaction temperature and the high stability of our catalyst system in air, and 4) the simple aqueous work-up needed to remove any metal residues as BHA acts as a metal scavenger.[13] Herein, we report a successful Mo–BHA catalyzed asymmetric oxidation of mono-, di-, and trisubstituted olefins under mild conditions to give epoxides in high yields and excellent selectivity.

In early experiments of the epoxidation of olefin **3a**, we found that ligand **2a** provided a higher selectivity than ligand **1a** in the presence of aqueous TBHP (Table 1, entries 1 and

Table 1: Effect of the achiral oxidant and ligand.[a]



3a **4a**

Entry	Oxidant	Ligand	Yield [%][b]	*ee* [%][c]
1	TBHP(aq)	**1a**	20	28
2	TBHP(aq)	**2a**	15	42
3	CHP	**2a**	72	66
4	THP	**2a**	27	96
5	CHP	**2c**	92	80
6	CHP	**2d**	82	87

[a] All reactions were carried out in CH_2Cl_2 in the presence of 1.5 equiv of oxidant and 2 mol% of molybdenum catalyst at RT in air unless otherwise indicated. [b] Yield of isolated product after chromatographic purification. [c] Determined by chiral HPLC or GC.

2). Changing the oxidant to cumene hydroperoxide (CHP) or tritylhydroperoxide (THP) did improve the selectivity, but reactivity was lower when bulkier THP was utilized. Furthermore, oxidation of **3a** with bulkier ligands (**2b**–**2d**) or a bulkier oxidant provided good to excellent selectivity (entries 4–6). It is noteworthy that oxidation of **3a** with vanadium complex of **2a** under similar reaction conditions was very slow, and only a small amount of epoxide (< 5%) was detected.

We examined the scope of the reaction under optimized conditions. In all cases, epoxidation with the Mo–BHA catalyst in the presence of a cooxidant proceeded smoothly in air at room temperature. More notably, the size of ligands and the number of alkene substituents play a crucial role in determining the rate of the oxidation. As illustrated in Table 2, all the *cis*-substituted olefins gave excellent selectivity during oxidation (entries 1–4). It is noteworthy that the epoxidation of **3c** generated only *cis* product; no *trans* product was detected (entry 3). Trisubstituted and terminal alkenes also provided good selectivity (entries 6–8, 10 and 11). Another important aspect of this Mo–BHA catalyst is that it selectively oxidizes the most electron-rich alkene in the presence of multiple double bonds (entries 12 and 13).

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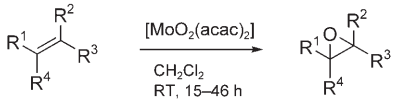
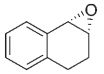
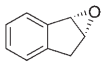
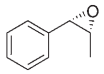
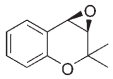
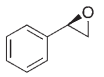
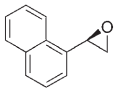
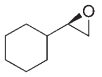
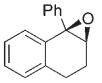
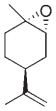
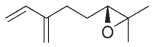
Table 2: Oxidation of olefins with different substitution patterns.[a]



3a–n **4a–n**

Entry	Epoxide	Ligand	Oxidant	*t* [h]	Yield [%][b]	*ee* [%][c] (Config)[d]
1		**2c**	THP	18	98	95 (*S*,*R*)
2		**2b**	THP	20	94	92 (*S*,*R*)
3		**2c**	THP	20	60	90 (*S*,*R*)
4		**2d**	TBHP	20	92	96 (*R*,*R*)
5		**2d**	CHP	22	77	64 (*R*,*S*)
6		**2d**	CHP	40	95	85 (*R*)
7		**2d**	CHP	36	84	82 (*R*)
8		**2d**	CHP	40	95	85 (*R*)
9		**2d**	CHP	40	92	50 (*R*)
10		**2d**	TBHP	36	44	62 (*R*,*S*)
11		**2d**	CHP	36	92	85 (*S*,*S*)
12		**2d**	CHP	46	94	66% *de* *trans*/*cis*
13		**2e**	CHP	42	82	76 (*R*)

[a] All reactions were carried out in CH_2Cl_2 in the presence of 1.5 equiv of oxidant and 2 mol% of molybdenum catalyst at RT unless otherwise indicated. [b] Yield of isolated product after chromatographic purification. [c] Determined by chiral HPLC or GC. [d] Configurations determined by comparison of the specific rotation to literature values.

Encouraged by the selectivity observed during the oxidation of myrcene (**3m**), squalene (**3n**), an important biogenetic precursor of steroids and polycyclic terpenoids, was subjected to similar reaction conditions (Scheme 2).[14] To our delight, the use of the Mo complex of **2e** in the presence of one equivalent of CHP selectively provided 2,3-epoxysqualene with good enantioselectivity (76% *ee*). It is noteworthy that the synthesis of **4n** often requires multiple steps.

We believe that the mechanism follows the concerted metal alkylperoxide mechanism supported by Sharpless.[15] The Mo–BHA complex combines with the achiral oxidant to oxidize the olefin in a concerted fashion by transfer of oxygen from the metal peroxide to the olefin. We are currently trying to elucidate the mechanism.

In conclusion, we have developed a catalytic asymmetric oxidation of mono-, di-, and trisubstituted olefins using chiral molybdenum catalysts in air at room temperature to obtain good to excellent selectivity. This method advances the use and application of molybdenum-catalyzed asymmetric oxidation of olefins.

Experimental Section

Representative experimental procedure: $[MoO_2(acac)_2]$ (6.5 mg, 0.02 mmol) was added to a solution of BHA (0.022 mmol) in CH_2Cl_2 (1 mL), and the mixture stirred for 1 h at RT. Olefin **3a** (1.0 mmol) and alkyl hydroperoxide (1.5 mmol) were added to the resulting solution and stirring continued at the same temperature for 18 h. The oxidation was monitored by TLC. Saturated aqueous Na_2SO_3 was then added and the mixture stirred for 30 min at RT. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel to provide epoxide **4a**. Determination of the *ee* values of the epoxides is provided in the Supporting Information.

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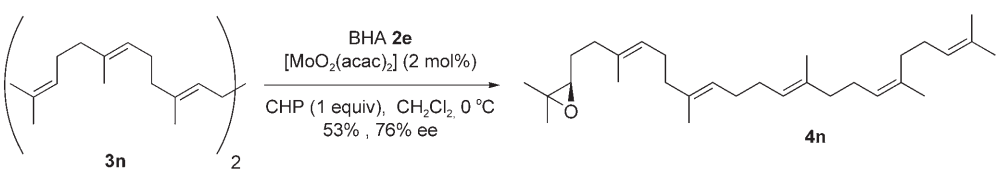

Scheme 2. Regio- and enantioselective oxidation of squalene.

Keywords: alkenes · asymmetric catalysis · enantioselectivity · epoxidation · molybdenum

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