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Catalytic enantioselective oxidation of sulfides and disulfides by a chiral complex of bis-hydroxamic acid and molybdenum

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This work is dedicated to Jack Halpern on the occasion of his 80th birthday and his wonderful contributions to organic chemistry

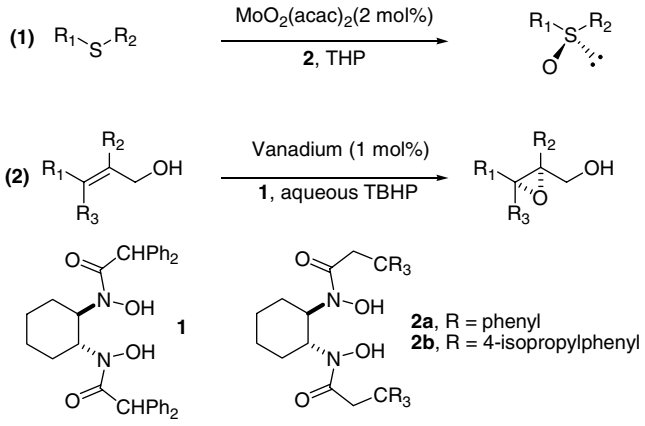
Abstract—A chiral bis-hydroxamic acid (BHA)-molybdenum complex was used for the catalytic asymmetric oxidation of sulfides and disulfides utilizing one equivalent of alkyl peroxide with yields up to 83% and ee up to 86%. An extension of our methodology combines the asymmetric oxidation with kinetic resolution providing excellent enantioselectivity (ee 92–99%).

1. Introduction

Metal catalyzed asymmetric oxidation of sulfides, a powerful strategy for the rapid preparation of enantiopure sulfoxides, has garnered extensive attention from the synthetic community. Of particular value are those compounds which contain chiral sulfoxides, a structural class widely utilized in both the pharmaceutical industry and academia.[1] Although a number of methods for achieving high enantioselectivity during sulfide oxidation have emerged in the recent years, most notably the tri-coordinated vanadium catalyst system,[2,11] manganese,[3] iron-catalyzed oxidation,[4] and titanium-based reagents;[5] low enantioselectivity and restrictive structural requirements are still serious obstacles for this transformation.[1]

Specifically, the most extensively studied titanium reagents (1) often require an inert atmosphere and sufficient quantity of molecular sieves; (2) need an exact amount of water (or alcohol) to generate the active catalyst, and (3) demand high catalyst loading for conversion.[1,5] As an alternative, an indirect multi-step route to access these molecules has also been developed employing nucleophillic substitution of a chiral sulfinyl derivative with an organometallic reagent. This method, however, is limited by the availability of the appropriate intermediates.[6]

To this end, direct asymmetric oxidation of pro-chiral sulfides is the most convenient and straightforward method. However, to date, the application of molybdenum as a catalyst for the asymmetric oxidation of sulfide remains under-explored.[7] Herein, we report the first successful catalytic asymmetric oxidation of sulfides and disulfides utilizing a catalytic amount of a chiral molybdenum complex in the presence of an achiral oxidant under mild conditions (Scheme 1, Eq. 1).



Scheme 1.

2. Results and discussion

Our continuous research in the area of asymmetric oxidation revealed that the vanadium complex of the

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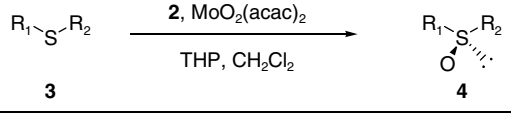
hydroxamic acid efficiently oxidizes allylic and homoallylic alcohols.[8] More recently, we also reported a vanadium-bis-hydroxamic acid catalyst system, which induces excellent enantioselectivities during oxidation of both cis-substituted and trans-substituted allylic alcohols (Scheme 1, Eq. 2).[9a] The preparation of these bis-hydroxamic acids has been described earlier.[9b]

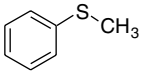
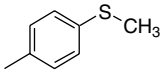
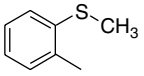
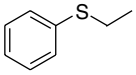
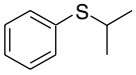
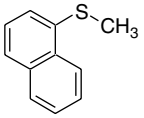
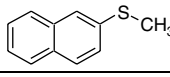
To evaluate the general applicability of BHA as a ligand for asymmetric synthesis, the oxidation of various sulfides was explored. Thus, methyl phenyl sulfide **3a** was treated with the vanadium-**1** complex (and vanadium-**2a** complex) at 0 °C for 17 h affording the desired sulfoxide **4a** in a modest yield (17% and 20%, respectively) with moderate enantioselectivity (ee 30% and 47%, respectively). Despite the inefficiency of the oxidation, we were encouraged by the selectivity and decided to survey other metal complexes for the oxidation. Reasoning that a dioxo-molybdenum complex of the bis-hydroxamic acid would be a stronger oxidizing agent,[7a] we opted to study the oxidation of **3a** under these new conditions.[10] As expected, the modified catalyst produced methyl phenyl sulfide **4a** in a significantly improved yield (77%) after 17 h (Table 1, entry 1). Interestingly, the molybdenum complex of **2a** also provided higher enantioselectivity (ee 54%). At this stage, an array of ligands, reaction conditions and oxidants were surveyed. We found that 2 mol % molybdenum catalyst in the presence of trityl hydroperoxide (THP) is optimal for the high enantioselectivity (entry 3). Cumene hydroperoxide (CHP) also provided good enantioselectivity (entry 2) under similar reaction conditions. The highest enantioselectivity was obtained when the bulkier BHA **2b** was utilized. To determine the general scope of the sulfide oxidation, a number of substrates with differing substitution patterns were tested under the optimized conditions; the results of which are summarized in Table 1. It is important to note that, isopropyl phenyl sulfide **3e**, which usually provides relatively low enantioselectivity,[1a,2d] also provided good selectivity (entry 8) and the (*R*)-configuration due to the steric hindrance of the isopropyl group. The oxidation of dialkyl sulfides such as cyclohexyl methyl sulfide, however, exhibited low selectivity, ee 20%. Efforts are being focused to optimize the catalyst system for dialkyl sulfides.

High enantioselectivity during sulfide oxidation is often due to kinetic resolution of the newly formed sulfoxides

Table 1. Asymmetric oxidation of sulfides **3**[a]

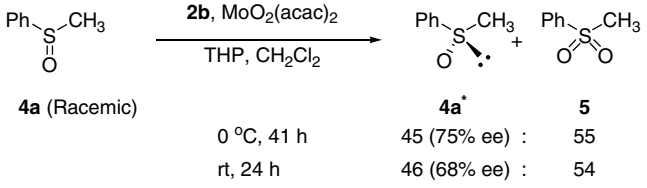


3 **4**

Entry	Sulfide		Ligand	Time (h)	Yield[b] (%)	ee (%),[c] config[d]
1		**3a**	**2a**[e]	17	77	54 (*S*)
2			**2a**[f]	26	89	65 (*S*)
3			**2a**	20	83	68 (*S*)
4			**2b**	16	81	79 (*S*)
5		**3b**	**2b**	20	75	81 (*S*)
6		**3c**	**2b**	19	76	75 (*S*)
7		**3d**	**2b**	18	81	82 (*S*)
8		**3e**	**2b**	24	66	62 (*R*)
9		**3f**	**2b**	17	82	86 (*S*)
10		**3g**	**2b**	19	83	72 (*S*)

[a] All reactions were carried out in CH_2Cl_2 in the presence of 1.0 equiv of THP and 2 mol % of molybdenum catalyst at 0 °C, unless otherwise indicated.
[b] Isolated yield after chromatographic purification.
[c] Ee values were determined by chiral HPLC.
[d] Configurations determined by comparison of specific rotation to literature.
[e] 1.0 equiv TBHP.
[f] 1.0 equiv CHP.

by generating a significant amount of sulfones.[2–6,11] However, by employing the molybdenum-**2b** catalyst in the presence of 1.0 equiv of THP, it did not produce any sulfone. A key question was raised by this result as to whether our catalyst was capable of performing selective oxidation of one of the enantiomer of a racemic mixture of sulfoxides. Thus, we decided to explore oxidations of sulfoxides (Scheme 2). We found that the oxidation of phenyl methyl sulfoxide **4a** was slow, but molybdenum-**2b** complex selectively oxidized one of the enantiomers. We were pleased to find that the (*R*)-isomer of **4a**, which the minor isomer produced during oxidation of **3a**, was oxidized in a faster rate.



Scheme 2.

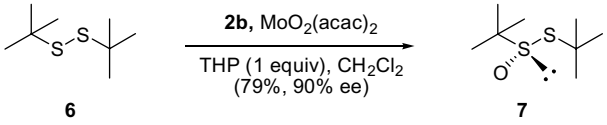
In the next stage, the scope of the asymmetric oxidation followed by kinetic resolution was examined. The results of this study are listed in Table 2. Both oxidants CHP and THP provided excellent selectivity during the process (ee 92–99%). The key feature of our catalyst is that after the initial oxidation of sulfides to sulfoxides the extent of kinetic resolution can be controlled by choosing the oxidant and also its amount. This absolute control of the asymmetric oxidation and kinetic resolution makes our process more attractive than other available methods.

Table 2. Asymmetric oxidation with kinetic resolution[a]

Entry	Sulfide	Oxidant	Sulfoxide: Sulfone	Yield[b] (%)	ee (%),[c] config
1	**3a**	THP[d]	81:19	68	92 (*S*)
		CHP[e]	49:51	43	96 (*S*)
2	**3b**	THP	74:26	55	94 (*S*)
		CHP[e]	46:54	37	95 (*S*)
3	**3d**	THP	72:28	51	96 (*S*)
		CHP[f]	32:68	31	97 (*S*)
4	**3g**	THP	76:24	50	93 (*S*)
		CHP[e]	50:50	47	99 (*S*)

[a] All reactions were carried out in CH_2Cl_2 in the presence of 1.5 equiv of THP and 2 mol % of molybdenum-**2b** catalyst at −40 °C, 19 h then 0 °C, 24 h unless otherwise indicated.
[b] Isolated yield of sulfoxide after chromatographic purification.
[c] Ee values were determined by chiral HPLC.
[d] −40 °C, 44 h then 0 °C, 47 h.
[e] 1.55 equiv CHP.
[f] 1.75 equiv CHP.

Finally, to study whether the substrate scope could be extended beyond sulfides; 2-*tert*-butyldisulfanyl-2-methylpropane, **6**, was subjected to the same reaction conditions (Scheme 3).[12] Gratifyingly, simple aqueous work up followed by chromatographic separation provided a high yield of **7** with excellent selectivity (ee 90%). It is important to note here that pre-distillation of the disulfide is not necessary to achieve high enantioselectivity.[12]



Scheme 3.

3. Conclusion

In conclusion, this work represents the first successful application of the molybdenum catalyzed asymmetric oxidation of sulfides and disulfides. These mild oxidizing conditions provides moderate to good enantioselectivity for the isolated sulfoxides. A kinetic resolution was further developed to enrich the enantioselectivity of sulfoxides.

Acknowledgements

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9. (a) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389; (b) *General procedure for preparation of bis-hydroxamic acids:* To a stirred solution of **6** (1 mmol) and DIEA (1.04 mL, 6 mmol) in CH_2Cl_2 (20 mL) was added acid chloride (3 mmol, dissolved in 5 mL CH_2Cl_2) under nitrogen. After 24–72 h, the reaction mixture was treated with 3 M HCl (or 1 M HCl/MeOH). After stirring for 30 min the reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel 60 extra pure to provide the bis-hydroxamic acid. Compound **2b**: Yield 64%, solid; $R_f = 0.62$ (EtOAc/hexanes, 1:3); FTIR (film) υ_{max} 3126, 2958, 2870, 1616, 1507, 1457, 1418, 1240, 1173, 1057, 1019, 910, 828, 734, 584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 2 H), 7.14 (d, $J = 7.5$ Hz, 12H), 6.97 (d, $J = 7.5$ Hz, 12H), 4.07 (br d, $J = 14.5$ Hz, 2H), 3.80–3.78 (br m, 2H), 3.59 (br d, $J = 14.5$ Hz, 2H), 2.85–2.79 (m, 6H), 1.54–1.50 (m, 2H), 1.29–1.15 (m, 40H), 0.95–0.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 146.3, 144.9, 129.6, 125.7, 55.8, 55.0, 42.2, 33.7, 27.4, 24.5, 24.3, 24.1.
10. *Typical procedure for oxidation of sulfide:* To a solution of BHA (0.03 mmol) in dichloromethane (3 mL) was added $MoO_2(acac)_2$ (5 mg, 0.015 mmol), and the mixture stirred for 1 h at room temperature. The resulting solution was cooled to 0 °C, and then sulfide (0.75 mmol), and THP (207 mg, 0.75 mmol) were added and stirring continued in air at the same temperature for several hours. The oxidation process was monitored by TLC. Saturated aqueous Na_2SO_3 was added, and the mixture was stirred for 30 min at 0 °C. The mixture was then allowed to warm to room temperature, 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 the sulfoxide.
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