Chiral Hydroxamic Acids as Ligands for the Vanadium Catalyzed Asymmetric Epoxidation of Allylic Alcohols

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Intensive research has been performed in the field of the asymmetric oxidation of functionalized and unfunctionalized olefins[1] and especially the protocol developed by Sharpless[2] has proven to be an extraordinary useful tool for the preparation of enantiomerically enriched compounds. In contrast to the titanium catalysts used in the Sharpless epoxidation reaction, relative few examples of chiral vanadium catalysts[3] have been reported so far, although $VO(acac)_2$ is often the catalyst of choice in the epoxidation of allylic alcohols with hydroperoxides.[4] Chiral hydroxamic acids are most conveniently prepared by acylation of a hydroxylamine, of which one or both building blocks carry the chiral information. In contrast to other studies[5] we report on new hydroxamic acids that bear the chiral center in α-position to the nitrogen atom.

The preparation of the optically active hydroxylamine **2** started from (*R*)-α-phenethylamine (**3**), which was converted with anisaldehyde to its Schiff base **4** and epoxidized with MCPBA to the oxaziridine **5**. The C-O bond cleavage of **5** with hydroxylamine hydrochloride, followed by neutralization with sodium hydrogen carbonate afforded the nicely crystallizing compound **2** in 41% overall yield. Conveniently, the whole reaction sequence could be performed without isolation of the intermediates. The transformation of **2** to the hydroxamic acids **1a-d** was carried out by reaction with the corresponding acid chloride in the presence of K_2CO_3 as base (Scheme 1).

To test the catalytic activity of the ligands **1a-1d**, the epoxidation of 3-methyl-2-buten-1-ol was preliminarily tested under vanadyl acetoacetonate/**1b** with the ratio of 1 : 1 and 1 : 3 using 2 eq. *t*-butyl hydroperoxide. The better enantiomeric excess was obtained in case of metal/ligand=1 : 3 ratio (with 1 mol% $VO(acac)_2$, the e.e values were given as 3% and 10.4% for metal/ligand=1 : 1 and 1 : 3 ratio, respectively.). As shown in Figure 1 (a complexation mode proposed by Sharpless[4d]), an excess of hydroxamic acid is necessary to avoid the racemic pathway that decreases the enantiomeric excess (*via* complex A).

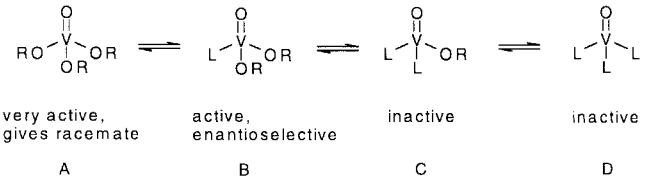
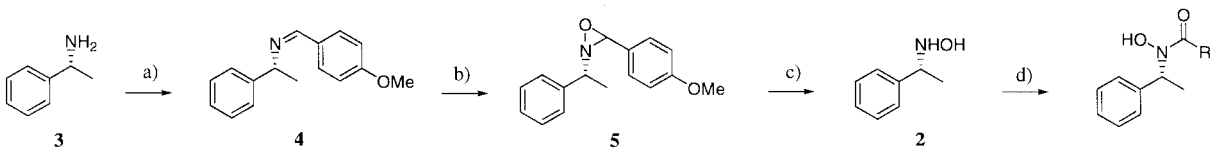


Figure 1. Vanadium alkoxide complex. L=ligand **1a-1d**.

The hydroxamic acids (**1a-d**) were tested on their asymmetric induction in the vanadium (5 mol% $VO(acac)_2$) epoxidation of allylic alcohols (Table 1).

In all cases, *t*-BuOOH proved to be the superior oxygen source over cumene hydroperoxide (entries 3-10, 17-19, 20, 22, 24, 25). 2,3-Disubstituted allylic alcohols showed uniformly poor selectivities (entries 11, 12, 16) whereas 2,3-trisubstituted allylic alcohols exhibited enantioselectivities up to 95% (entries 4, 15, 17, 19). Surprisingly, the different steric and electronic properties seem to be of little influence on the enantioselectivity: Every hydroxamic acid turned out to be the most effective one in at least one case and the sterically least demanding **1a** was often the ligand of choice. Furthermore, in some cases a change in the acid moiety (entries 1, 2, 11, 12, 19, 20) or the temperature (entries 19, 21-23)

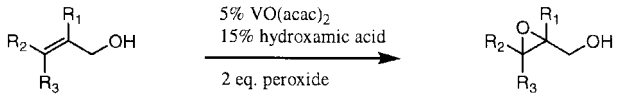


hydroxamic acid	yield from **2** (%)
1a (R = Me)	51
1b (R = Ph)	75
1c (R = t-Bu)	56
1d (R = 1-Adamantyl)	34

Reagents and conditions: a) anisaldehyde, Na_2SO_4, MeOH, r.t. b) MCPBA, CH_2Cl_2, -10° to r.t. c) i) NH_2OH•HCl, MeOH, r.t. ii) $NaHCO_3$, H_2O, r.t. d) a: AcCl, b: BzCl, c: pivaloyl chloride, d: 1-adamantoyl chloride, K_2CO_3, Na_2SO_4, CH_2Cl_2, r.t.

Scheme 1. Preparation of the hydroxamic acids **1a-d**.

Table 1. Catalytic Enantioselective Epoxidation of Allylic Alcohols



entry	R1	R2	R3	lig.	ROOH	cond. (°C, time)	yield (%)	e.e (%)	cfg
1	Ph	Ph	H	**1c**	CHP	0, 4d	83	10	S, S
2	Ph	Ph	H	**1d**	CHP	0, 4d	88	38	S, S
3	Ph	Ph	H	**1a**	TBHP	-20, 5d	83	67	S, S
4	Ph	Ph	H	**1b**	TBHP	-20, 5d	77	95	S, S
5	Ph	Ph	H	**1c**	TBHP	-20, 5d	84	56	S, S
6	Ph	Ph	H	**1d**	TBHP	-20, 5d	97	89	S, S
7	Ph	Ph	H	**1a**	CHP	-20, 5d	23	20	S, S
8	Ph	Ph	H	**1b**	CHP	-20, 5d	47	58	S, S
9	Ph	Ph	H	**1c**	CHP	-20, 5d	62	45	S, S
10	Ph	Ph	H	**1d**	CHP	-20, 5d	20	63	S, S
11	H	Ph	H	**1a**	TBHP	-20, 7d	nd	9[ref.7]	S, S
12	H	Ph	H	**1c**	TBHP	-20, 7d	nd	12[ref.7]	S,S
13	H	Me	Me	**1a**	TBHP	-20, 1d	57	6	S
14	-C_4H_8-		H	**1a**	TBHP	0, 2d	83	39	R, R
15	-C_4H_8-		H	**1a**	TBHP	-20, 2d	19	58	R, R
16	H	Prenyl	H	**1a**	TBHP	0, 4d	100	11	S, S
17	-C_3H_6-		H	**1d**	TBHP	-20, 1d	88	22	S, S
18	-C_3H_6-		H	**1d**	CHP	-20, 1d	87	2	R, R
19	Me	Ph	H	**1a**	TBHP	0, 6d	29	49	R, R
20	Me	Ph	H	**1b**	TBHP	0, 6d	74	15	S, S
21	Me	Ph	H	**1a**	TBHP	25, 6d	56	11	R, R
22	Me	Ph	H	**1a**	TBHP	-20, 7d	74	39	S, S
23	Me	Ph	H	**1a**	TBHP	-40, 7d	8	31	S, S
24	Me	Ph	H	**1a**	CHP	0, 6d	69	5	S, S
25	Me	Ph	H	**1a**	CHP	-20, 7d	71	1	S, S

All reactions were carried out in toluene. CHP=cumene hydroperoxide. TBHP=*t*-butyl hydroperoxide. cfg=absolute configuration. Nd=not determined. Yields were determined by GC analysis. The absolute configurations and ee values were determined by chiral GC (cyclodextrin B).[2(c),2(d),2(e),3(a),4(a)] Entries 1-10 were analyzed as their TMS-ethers.

reversed the chirality of the epoxide formed.

In conclusion, new hydroxamic acid ligands for the vanadium catalyzed asymmetric epoxidation of allylic alcohols have been developed. Further studies of the scope are in progress.

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6. Physical properties of the ligands **1a-1d**.
   (a) **1a** (oily liquid): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, J = 6.8 Hz, 3H), 2.06 (s, 3H), 5.73 (br s, 1H), 7.28-7.36 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 19.30, 21.05, 58.51, 126.29, 126.69, 127.64, 127.94, 128.80, 140.40, 172.34; MS (positive ion FAB) m/z 180 (M+1); $[\alpha]_D^{18}$ +52.5° (c=1, EtOH).
   (b) **1b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, J = 6.8 Hz, 3H), 5.30 (br s, 1H), 7.31-7.55 (m, 10H), 8.96 (br s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.77, 59.72, 127.21, 128.16, 128.28, 128.84, 129.04, 129.09, 130.12, 130.59, 131.42, 133.35, 133.94, 140.16, 171.60; MS (positive ion FAB) m/z 242 (M+1); mp 105 °C; $[\alpha]_D^{20}$ +65.8° (c=0.69, EtOH).
   (c) **1c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.61 (d, J = 6.5 Hz, 3H), 5.71 (br s, 1H), 7.26-7.39 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.67, 27.71, 39.19, 56.01, 126.29, 126.69, 127.64, 127.97, 128.96, 140.33, 178.33; MS (positive ion FAB) m/z 222 (M + 1); mp 90 °C; $[\alpha]_D^{21}$ +79.9° (c=1.09, EtOH).
   (d) **1d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (d, J = 6.4 Hz, 3H), 1.64-2.07 (m, 15H), 4.17 (quartet, J = 6.7, 1H), 7.30-7.44 (m, 5H), 8.36 (br s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) 19.79, 28.32, 28.70, 36.72, 36.84, 38.91, 39.33, 40.72, 126.52, 127.53, 128.20, 128.87, 129.06, 141.52, 177.83; MS (positive ion FAB) m/z 300 (M+1); mp 155 °C; $[\alpha]_D^{22}$ +69.7° (c=1, EtOH).
7. In case of using the ligand **1b** and **1d**, lower enantiomeric excesses were given.