Epoxidation

Asymmetric Epoxidation of Homoallylic Alcohols and Application in a Concise Total Synthesis of (−)-α-Bisabolol and (−)-8-*epi*-α-Bisabolol**

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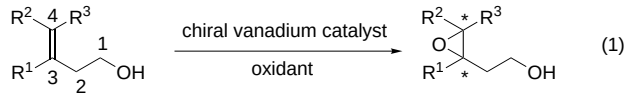
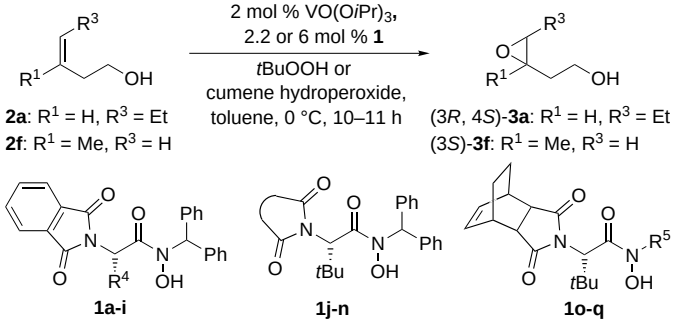
Catalytic asymmetric epoxidation is useful for the synthesis of chiral compounds in both academia and industry. A variety of carbon–carbon double bonds, for example those of allylic alcohols, α,β-unsaturated esters, and simple alkenes, can be catalytically epoxidized with several metal catalysts,[1] and catalytic asymmetric reactions have been developed.[2–4] Metal-catalyzed asymmetric epoxidation of homoallylic alcohols, however, is difficult with the catalysts reported previously.[5] It is well known that vanadium complexes effectively catalyze the epoxidation of allylic and homoallylic alcohols to the corresponding epoxy alcohols with good to high stereoselectivities.[6] In our research on the asymmetric epoxidation of allylic alcohols, we discovered that the chiral vanadium complex that was prepared from vanadium triisopropoxide oxide and an α-amino acid-based hydroxamic acid is an efficient catalyst for the epoxidation of disubstituted allylic alcohols with high enantioselectivities and in high yields (up to 96% *ee*, almost $>95\%$ yield).[7,8] Here we show that this catalytic system can also be used for the asymmetric epoxidation of homoallylic alcohols [Eq. (1)], and report the discriminating substitution pattern of the substrates. Concise total syntheses of (−)-α- and (−)-8-*epi*-α-bisabolol were achieved using this catalytic system.



(1)

homoallylic alcohol

Our investigation into the vanadium-catalyzed asymmetric epoxidation of homoallylic alcohols commenced with the screening of hydroxamic acid ligands. Analogous to the method reported previously by our group,[8a] we first adjusted the α-amino acid part to the vanadium-catalyzed epoxidation



Scheme 1. Reagents and conditions for the reactions collected in Table 1.

of *cis*-3-hexen-1-ol (Scheme 1 and Table 1, entries 1–11).[9] The reactivity was relatively high compared to reports for other metal catalysts[5] (only 2 mol% vanadium catalyst at 0°C for 10 to 11 h gave the epoxy alcohol in around 45% yield). The enantioselectivities were low, and only when a hydroxamic acid derived from *tert*-leucine (trimethylalanine) was used as the ligand (**1g**), moderate enantioselectivity was obtained (entry 7, 23% *ee*). Next, the reaction conditions were optimized for **1g** as the ligand, and enantioselectivity went up to 52% *ee* with a slight loss of reactivity (entry 9). After a variety of homoallylic alcohols had been examined

Table 1: Ligand optimization for the asymmetric epoxidation of homoallylic alcohols **2a**[a] and **2f**[b] (see Scheme 1).

Entry	Homoallylic alcohol **2**	Hydroxamic acid **1**	*ee* [%][c]	Yield [%]
1	**2a**	**1a**: R^4 = Me	6	43
2	**2a**	**1b**: R^4 = *i*Pr	6	49
3	**2a**	**1c**: R^4 = *i*Bu	2	34
4	**2a**	**1d**: R^4 = *s*Bu	1	37
5	**2a**	**1e**: $R^4 = (CH_2)_2SMe$	–	trace
6	**2a**	**1f**: $R^4 = (CH_2)_4N$(phthaloyl)	7	41
7	**2a**	**1g**: R^4 = *t*Bu	23	24
8	**2a**[d]	**1g**: R^4 = *t*Bu[e]	44	48
9	**2a**[d]	**1g**: R^4 = *t*Bu[f]	52	41
10	**2a**	**1h**: $R^4 = CH_2$(3-indolyl)	8	35
11	**2a**	**1i**: $R^4 = CH_2(p\text{-}OMeC_6H_4)$	1	37
12	**2f**	**1e**: $R^4 = (CH_2)_2SMe$	84	58
13	**2f**	**1j** (1,8-naphthalenedicarbonyl)	85	69
14	**2f**	**1k** (2,3-naphthalenedicarbonyl)	85	45
15	**2f**	**1l** (2,3-dimethylmaloyl)	85	31
16	**2f**	**1m** (2,3-diphenylmaloyl)	82	23
17	**2f**	**1n** (bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl)	85	68
18	**2f**	**1o**: R^5 = diphenylmethyl	87	44
19	**2f**	**1p**: R^5 = cyclohexyl	70	4
20	**2f**	**1q**: R^5 = 9-fluorenyl	42	36

[a] Reaction conditions: $VO(OiPr)_3$ (2 mol%), **1** (2.2 mol%), *t*BuOOH (1.5 equiv), toluene, 10–11 h. [b] Reaction conditions: $VO(OiPr)_3$ (2 mol%), **1** (6 mol%), cumene hydroperoxide (1.5 equiv), toluene, 10 h. [c] The *ee* values of **3a** and **3f** were determined by chiral GLC (column, γ-TA) analysis, their absolute structures by comparison of the optical rotation with published data. [d] Cumene hydroperoxide was used as an oxidant. [e] 3 mol% of **1g** was used. [f] 6 mol% of **1g** was used.

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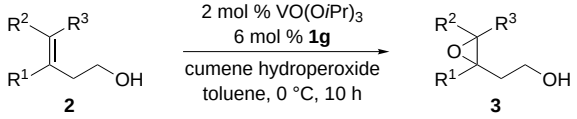
[**] Support of the Japan Science and Technology Corporation (JST) is gratefully acknowledged.

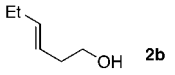
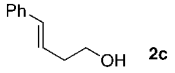
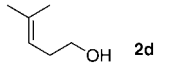
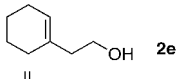
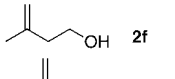
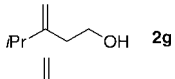
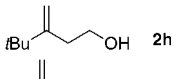
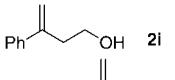
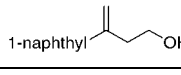
and after we had determined the discriminating selection in the reaction, the imido and the hydroxylamine part of the hydroxamic acid ligand were changed as previously reported,[8a] however, in all cases nearly the same selectivities were obtained (entries 12–20).[10] Based on these results, it is likely that the asymmetric epoxidation of homoallylic alcohols is not parallel to that of allylic alcohols using these chiral vanadium catalysts.

We now turned our attention to the structure of the homoallylic alcohol **2** because asymmetric epoxidation of such alcohols has been rarely investigated. The epoxidation of 4-disubstituted alcohols **2** using ligand **1g** was faster than that of 4-monosubstituted ones (entries 3 and 4 vs. entries 1 and 2 in Table 2).[11,12] On the other hand, 3-monosubstituted alcohols **2** were effectively epoxidized with good to high enantioselectivities (see Experimental Section and entries 5–9). For example, the simple homoallylic alcohol 3-methyl-3-buten-1-ol **2f** was epoxidized to give (*S*)-3,4-epoxy-3-methyl-1-butanol with 84% *ee*, and the 3,4-disubstituted alcohol **2e** was epoxidized with moderate enantioselectivity (74% *ee*). It is likely that the 3-position of homoallylic alcohols is strongly recognized by catalysts with a positive effect on the selectivity, and that substituents in the 4-position provide a slightly negative effect.

To demonstrate that our method is useful for synthetic purposes, the total synthesis of (−)-α-bisabolol, which is known as a fragrance, was executed (Scheme 2).[13] Hydroxymethylation of (*S*)-limonene gave *S* alcohol **5**,[14] which was epoxidized diastereoselectively using hydroxamic acid D-**1g** as ligand to give epoxy alcohol **6** in 84% yield with 90% *de*. This optically active alcohol was reduced by lithium aluminum hydride to diol **7**, which was tosylated at the primary hydroxy group, and coupled with isopropenyl magnesium bromide to give (−)-(4*S*,8*S*)-α-bisabolol **9** ($[\alpha]_D^{25} = -51.0$ ($c = 1.22$ in ethanol); total yield 21%).[15] With L-**1g**, *S* alcohol **5** was epoxidized to give epoxy alcohol (8*R*)-**6** (82% yield, 94% *de*), which was converted to (−)-(4*S*,8*R*)-*epi*-α-bisabolol in the same manner as described above.[16]

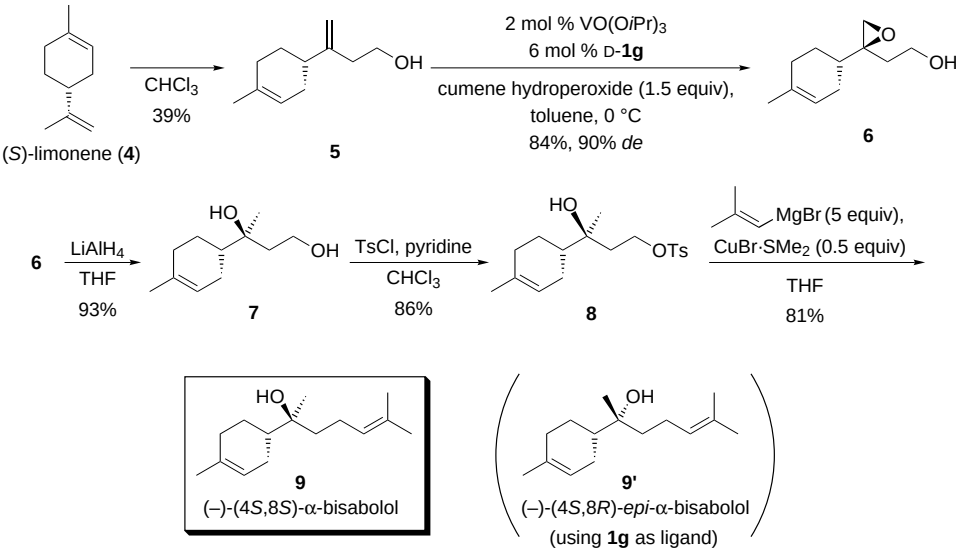
Table 2: Asymmetric epoxidation of homoallylic alcohols **2** using **1g** as ligand.



Entry	Homoallylic alcohol **2**	*ee* [%]	Yield [%]
1	 **2b**	40[a]	25
2	 **2c**	46[c]	24
3	 **2d**	36[a]	67
4	 **2e**	74[b]	61
5	 **2f**	84[a]	58
6	 **2g**	90[a]	77
7	 **2h**	90[b]	89
8	 **2i**	89[c]	70
9	 **2j**	91[d]	42

[a] Determined by chiral GLC (column, γ-TA). [b] Determined by chiral GLC (column, β-DM). [c] Determined by chiral HPLC (column, AD-H). [d] Determined by chiral HPLC (column, OD-H).

In summary, the asymmetric epoxidation of homoallylic alcohols using chiral vanadium catalysts was conducted under mild conditions, and a discriminating reactivity and selectivity for 3-monosubstituted homoallylic alcohols was determined (58–89% yield, 84–91% *ee*). To show its synthetic utility, the reaction was applied to the key step of the total synthesis of (−)-α- and (−)-8-*epi*-α-bisabolol.



Scheme 2. A concise and stereoselective total synthesis of (−)-(4*S*,8*S*)-α- and (−)-(4*S*,8*R*)-*epi*-α-bisabolol.

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Experimental Section

Representative experimental procedure: $VO(OiPr)_3$ (5 μL, 20 μmol) and hydroxamic acid (26.6 mg, 60 μmol) were dissolved in toluene (1 mL), stirred for 1 hour, and cooled to 0 °C. Cumene hydroperoxide (275 μL, 1.5 mmol) and 3-(1-naphthyl)-3-buten-1-ol (**2j**) (198 mg, 1.0 mmol) were added at 0 °C. The reaction mixture was stirred for 10 h, then trimethylphosphite (177 μL, 1.5 mmol) was added at that temperature. The mixture was allowed to reach room temperature, then it was extracted with ethyl acetate, dried over sodium sulfate, and evaporated. The crude product was purified by column chromatography on a silica gel (eluent ethyl acetate/hexane, 1:1) to give 3,4-epoxy-3-(1-naphthyl)-1-butanol in 42% yield with 91% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.13$ (d, $J = 8.0$ Hz, 1H; Ar-H), 7.90 (d, $J = 8.0$ Hz, 1H; Ar-H), 7.83 (d, $J = 8.0$ Hz, 1H; Ar-H), 7.50 (m, 4H; Ar-H), 3.71 (m, 2H; CH_2OH), 3.35 (d, $J = 6.0$ Hz, 1H; OCH_2), 3.00 (d, $J = 6.0$ Hz, 1H; OCH_2), 2.45 (m, 1H; CCH_2CH_2), 2.29 (m, 1H; CCH_2CH_2), 1.69 ppm (br, 1H; OH). HPLC analysis (column: OD-H, Daisel): retention times 44.9 (main peak) and 68.1 min (minor peak) using hexane/2-propanol (40:1) as the eluent at a flow rate of 1.0 mL min^{-1}. For the epoxy alcohols **3a–e**, a saturated aqueous solution of sodium sulfite instead of trimethylphosphite was used for quenching the reaction.

Received: September 24, 2002 [Z50233]

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[9] The absolute configuration of **3a** (3*R*,4*S*) was determined by comparison of the optical rotation with published data.[5b]

[10] The absolute configuration of **3f** (*S*) was determined by comparison of the optical rotation of the derivative *O*-methoxymethyl-3,4-epoxy-3-methyl-1-butanol with published data, see: D. Behnke, L. Henning, M. Findeisen, P. Welzel, D. Müller, M. Thormann, H.-J. Hofmann, *Tetrahedron* **2000**, *56*, 1081.

[11] (*Z*)-4-Phenyl-3-buten-1-ol (**2c**) was obtained from *trans*-styrylacetic acid (*trans*-4-phenyl-3-butenoic acid) and lithium aluminum hydride. 3-Phenyl-3-buten-1-ol (**2i**) was prepared by Heck reaction according to ref. [12]. The homoallylic alcohols **2e, g, h,** and **j** were prepared by ene reaction using $BF_3{\cdot}OEt_2$ or Me_2AlCl and formaldehyde according to ref. [14a].

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[15] **9**: $[\alpha]_D^{25} = -54.9$ ($c = 1.27$ in ethanol);[13d] ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 133.9$, 131.3, 124.6, 120.6, 74.1, 42.9, 40.1, 31.0, 26.9, 25.6, 23.3, 23.2, 23.0, 22.0, 17.6 ppm.

[16] **9′**: $[\alpha]_D^{25} = -61.4$ ($c = 1.70$ in ethanol), -69 ($c = 1.3$ in ethanol);[13d] ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 133.9$, 131.8, 124.7, 120.9, 74.4, 43.4, 39.4, 31.1, 26.2, 25.8, 24.1, 24.0, 23.5, 22.4, 17.8 ppm.

Catalytic Asymmetric Hydrogenation

Phospholane–Oxazoline Ligands for Ir-Catalyzed Asymmetric Hydrogenation**

*Wenjun Tang, Weimin Wang, and Xumu Zhang**

Although a lot of progress has been made in Rh- or Ru-catalyzed asymmetric hydrogenation, Ir-catalyzed asymmetric hydrogenation is relatively unexplored.[1] Pfaltz and co-workers first reported several Ir-phosphinooxazoline complexes as catalysts for asymmetric hydrogenation. With leading efforts by Pfaltz and co-workers,[2] and Burgess and

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[**] This work was supported by the National Institute of Health.

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