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Synthesis of sterically controlled chiral β-amino alcohols and their application to the catalytic asymmetric sulfoxidation of sulfides

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Abstract—Sterically hindered and enantiomerically pure β-amino alcohols **8a** and **8b** were prepared from the enantiomerically pure aziridine-2-carboxylic acid menthol ester **13**. Vanadium complexes of the chiral Schiff-base ligands prepared from the β-amino alcohols catalyze an efficient enantioselective sulfoxidation of alkyl aryl sulfides, while enantioselectivities as high as 96% ee can be observed in the sulfoxidation of benzyl aryl sulfides.

1. Introduction

Enantiomerically pure sulfoxides are of great value as auxiliaries or intermediates in asymmetric synthesis.[1] Recently, we have been interested in the asymmetric sulfoxidation of sulfides to develop a methodology for the synthesis of drugs containing a chiral sulfoxide moiety, such as chiral lansoprazol or omeprazol. There are a number of catalytic systems that enable us to perform the asymmetric oxidation of sulfides to sulfoxides, involving various transition metal complexes.[2–4] In particular, the asymmetric sulfoxidation catalyzed by the chiral vanadium complex derived from tricoordinated ligands, such as **1**,[3a] **2**[3b] and **3**,[3c] has received great attention recently because of the facile syntheses of the ligands from chiral amino alcohols and salicylaldehyde derivatives in one step. We have reported that ligand **4a**[3d] also catalyzes the enantioselective sulfoxidation of sulfides efficiently.

In a continuing study with ligand **4**, it was thought that a bulky amino alcohol, which may give a steric effect larger than *tert*-butyl on R_1 is necessary to improve the enantioselectivity compared to the reaction with **4a**. Since a sterically hindered chiral amino alcohol is not readily available, we decided to develop a synthetic method for an enantiomerically pure amino alcohol, such as **8**, whose structural variation at the substituent R_1 may provide useful information on the enantioselectivity of the asymmetric sulfoxidation. Thus, we herein report the efficient synthesis of bulky amino alcohols, **8a** and **8b** and their applications to the enantioselective sulfoxidation of sulfides via chiral Schiff-base **5**. We also report the asymmetric sulfoxidation using chiral indanol, **9**.

2. Results and discussion

To prepare amino alcohol **8**, oxazoline derivative **11** was synthesized and reacted with Grignard reagents according to the literature procedure (Scheme 1).[5a] However, we found that the oxazoline **11** was partially racemized in the reaction with Grignard reagents. Thus, we devised a new synthetic method for the amino alcohols according to Scheme 2.

Our method used a readily available chiral aziridine **13**,[6] which has been applied in the synthesis of various chiral intermediates, as a starting material.

Aziridine (*R*,*S*)-**13** was reacted with alkyl Grignard reagent, RMgBr (R = ethyl, isobutyl), to give an aziridine-2-alcohol derivative that was then treated with methyl iodide and potassium hydride to produce **14**. The

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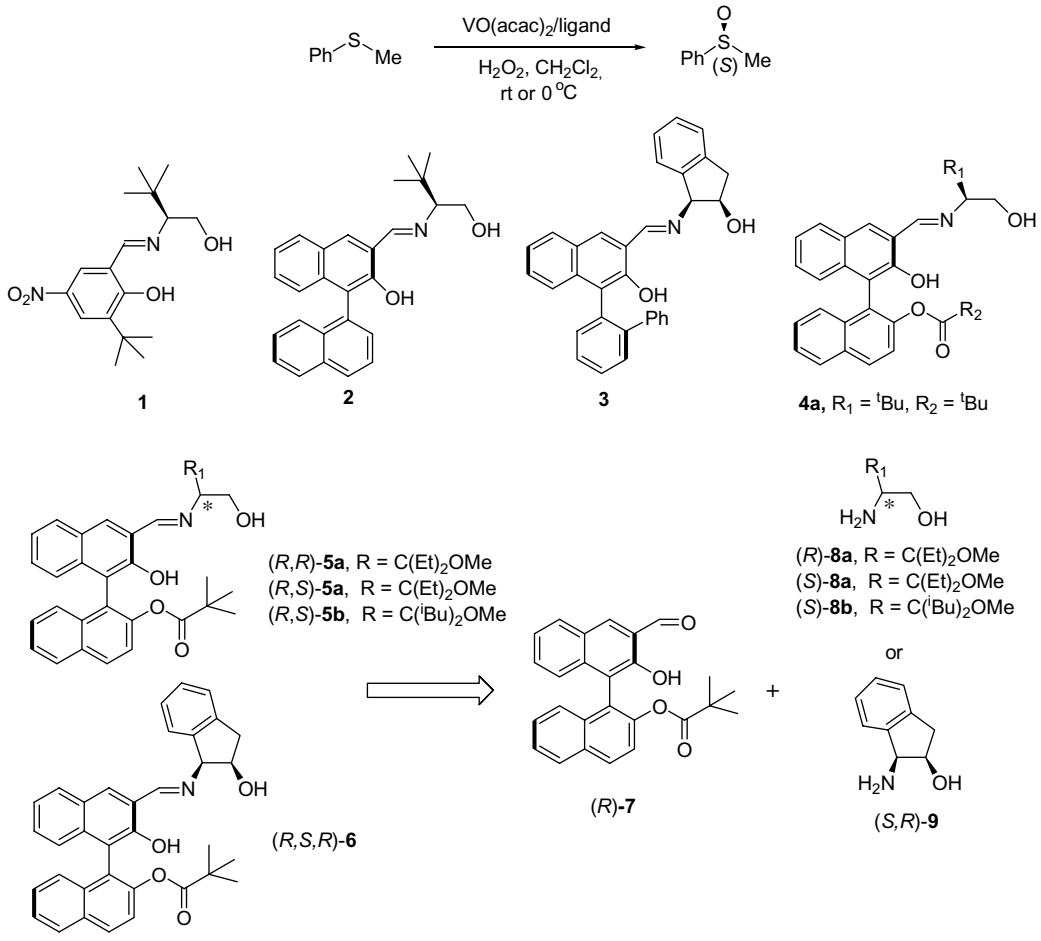
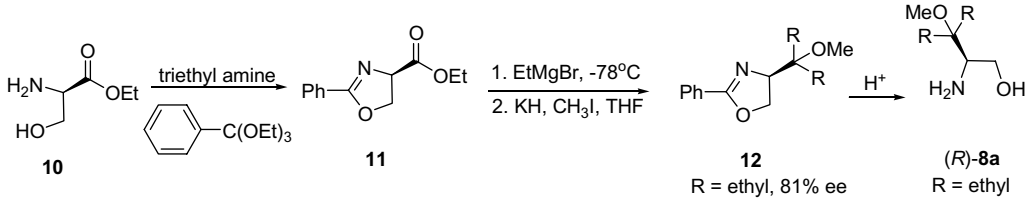
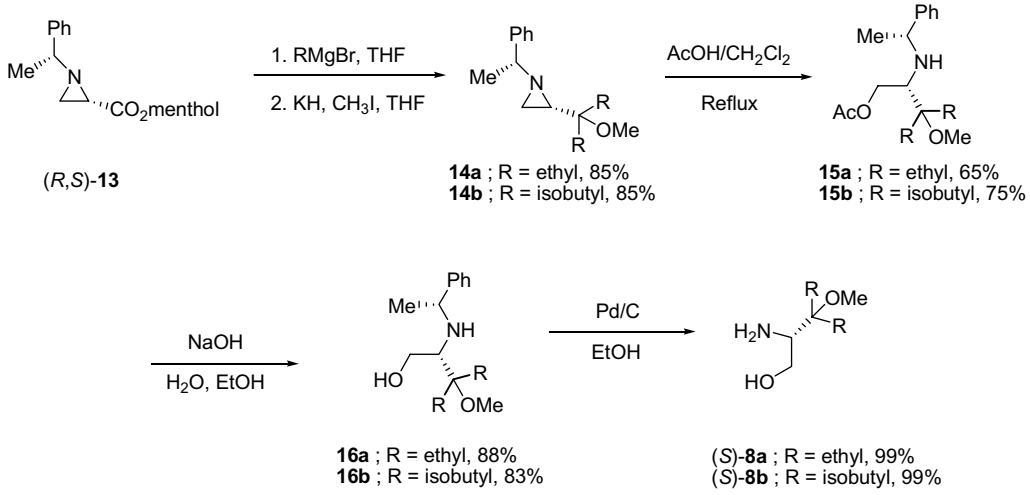


ring opening of **14** by acetic acid gave **15**, indicating that the acetate nucleophile attacks the aziridine ring at the less sterically hindered C(3) position to form **15**.[6a] Deacetylation of **15** by NaOH in refluxing ethanol–water and debenzylation catalyzed by palladium carbon in ethanol gave amino alcohols (*S*)-**8a** and (*S*)-**8b**.[7] Amino alcohol (*R*)-**8a**[7] was also prepared from (*R*,*R*)-**13** according to Scheme 2. Enantiomeric excesses of amino alcohols **8a** and **8b** were determined by chiral HPLC analysis of the oxazolines **12** prepared from the amino alcohols and triethyl orthobenzoate, and found to be more than 99% ee.

After the successful synthesis of enantiomerically pure amino alcohols, **8**, we tried to use these compounds in the vanadium-catalyzed asymmetric sulfoxidation of sulfides. At first, the Schiff-base, (*R*,*R*)-**5a**[8] prepared from (*R*)-**7**[5b] and (*R*)-**8a** was applied to the asymmetric sulfoxidation of thioanisole at 0 °C.[9] The reaction produced (*S*)-methyl phenyl sulfoxide in 83% yield with an enantioselectivity of 84% ee (Table 1, entry 2), which is similar to the result obtained with (*R*,*S*)-**4a** (Table 1, entry 1) reported previously.[3d] The enantioselectivity obtained with (*R*,*S*)-**5a**, whose amino alcohol subunit was an (*S*)-configuration was also 85% ee with (*R*)-methyl phenyl sulfoxide as the major product. Unfortunately, more sterically hindered (*R*,*S*)-**5b** gave an inferior enantioselectivity (entry 4), indicating that a proper steric effect at R_1 of **5** is necessary to gain a high enantioselectivity. Ligand (*R*,*S*,*R*)-**6** showed a good enantioselectivity of 82% ee (entry 5). However, (*S*,*S*,*R*)-**6** whose binaphthyl subunit is in an (*S*)-configuration different from (*R*,*S*,*R*)-**6** also gave the same (*S*)-isomer of methyl phenyl sulfoxide as the major enantiomer, although with an inferior enantioselectivity (entry 6). The formation of the (*S*)-isomer of methyl phenyl

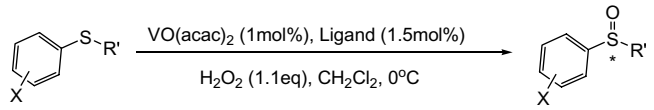


Scheme 1.



Scheme 2.

Table 1. Asymmetric sulfoxidation of aryl sulfides with Schiff-bases **5** and **6**



Entry	Sulfide	Schiff base	Yield (%)[a]	ee (%)[b]	Config[c]
1	C_6H_5–S–CH_3	(*R*,*S*)-**4a**	90	86	*S*
2		(*R*,*R*)-**5a**	83	84	*S*
3		(*R*,*S*)-**5a**	84	85	*R*
4		(*R*,*S*)-**5b**	82	65	*R*
5		(*R*,*S*,*R*)-**6**	81	82	*S*
6		(*S*,*S*,*R*)-**6**	88	67	*S*
7	*p*-MeO–C_6H_5–S–CH_3	(*R*,*R*)-**5a**	80	79	*S*
8		(*R*,*S*)-**5a**	80	81	*R*
9	*p*-Me–C_6H_5–S–CH_3	(*R*,*R*)-**5a**	81	83	*S*
10		(*R*,*S*)-**5a**	80	83	*R*
11	*p*-Br–C_6H_5–S–CH_3	(*R*,*R*)-**5a**	80	59[d]	*S*
12		(*R*,*S*)-**5a**	72	66[d]	*R*
13	*p*-NO_2–C_6H_5–S–CH_3	(*R*,*R*)-**5a**	74	31[e]	*S*
14		(*R*,*S*)-**5a**	80	55[e]	*R*
15	*o*-Br–C_6H_5–S–CH_3	(*R*,*R*)-**5a**	84	34	*S*
16		(*R*,*S*)-**5a**	82	40	*R*
17	Phenyl vinyl sulfide	(*R*,*R*)-**5a**	58	79	*S*
18		(*R*,*S*)-**5a**	56	58	*R*
19	Benzyl phenyl sulfide	(*R*,*R*)-**5a**	89	96[f]	*S*
20		(*R*,*S*)-**5a**	84	96[f]	*R*

[a] Isolated yield.
[b] Determined by HPLC with a Dicel Chiralcel OD column.
[c] Absolute configuration of the major product was determined by comparison of its sign of specific rotation with the literature data.
[d] Determined by ^{1}H NMR ($CDCl_3$, 400 MHz) analysis using (*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl as a shift reagent.
[e] Determined by ^{1}H NMR ($CDCl_3$, 400 MHz) analysis using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthyl)ethanol as a shift reagent.
[f] Determined by HPLC with a Dicel Chiralcel OJ column.

sulfoxide from both (*R*,*S*,*R*)-**6** and (*S*,*S*,*R*)-**6** suggests that the configuration of the sulfoxide is decided by the configuration of R_1 instead of the configuration of the binaphthyl subunit.

Oxidations of aryl sulfides with various substituents were also examined with ligand **5a** (entries 7–16). Interestingly, the enantioselectivities obtained in the oxidation of thioanisole derivatives containing electron donating groups (entries 7–10) were similar to the oxidation of thioanisole (entries 2 and 3). However, thioanisoles, which had electron withdrawing substituents gave their sulfoxide with poor enantioselectivities (entries 11–14). Additionally, (*R*,*S*)-**5a** showed better enantioselectivity compared to (*R*,*R*)-**5a** in the sulfoxidation of thioanisoles with electron withdrawing substituents. Sulfones that were expected from oxidation of the corresponding sulfoxides were formed only to a minor extent (less than 3%).

We also examined the oxidation of benzyl phenyl sulfides with ligand **5a** (entries 19 and 20). The reaction proceeded with an excellent enantioselectivity producing chiral benzyl phenyl sulfoxide in 96% ee (entries 19 and 20). These results being a little inferior compared to the result obtained with **4a** (99% ee),[3d] however, still demonstrate the potential of our catalytic system.

3. Conclusion

In summary, we developed a new synthetic method for sterically hindered chiral amino alcohol **8**. The Schiff-base ligand **5** derived from **8** showed a good enantioselectivity reaching 96% ee in the oxidation of sulfides.

Acknowledgement

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7. Selected data **8a**: (*S*)-form, $[\alpha]_D = -16.8$ (*c* 0.5, $CHCl_3$); (*R*)-form, $[\alpha]_D = +17.8$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.69 (dd, 1H, $J_1 = 10.4$ Hz, $J_2 = 4.0$ Hz), 3.48 (dd, 1H, $J_1 = 10.4$ Hz, $J_2 = 8.4$ Hz), 3.21 (s, 3H), 2.94 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.0$ Hz) 2.45 (br s, 3H), 1.63–1.57 (m, 4H), 0.93–0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 79.57, 62.89, 57.04, 49.48, 25.26, 25.13, 8.39, 8.24; HRMS (HFAB), *m*/*z* calcd for $C_8H_{20}NO_2$ 162.1494, found 162.1489.
Amino alcohol (*S*)-**8b**: $[\alpha]_D = -10.0$ (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.71 (dd, 1H, $J_1 = 10.7$ Hz, $J_2 = 3.7$ Hz), 3.45 (dd, 1H, $J_1 = 9.6$ Hz, $J_2 = 8.7$ Hz), 3.19 (s, 3H), 3.03 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 3.7$ Hz), 3.21 (br s, 3H), 1.90–1.78 (m, 2H), 1.52–1.37 (m, 4H), 0.99–0.94 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 80.64, 62.83, 58.16, 49.52, 41.78, 41.50, 224.94, 24.71, 24.51, 24.39, 23.87, 23.49; HRMS (HFAB), *m*/*z* calcd for $C_{12}H_{27}NO_2$ 218.2120, found 218.2117.
8. Selected data (*R*,*R*)-**5a**: mp 92 °C; $[\alpha]_D = -36.0$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.62 (s, 1H), 8.01–7.94 (m, 3H), 7.85–7.83 (m, 1H), 7.48–7.38 (m, 3H), 7.33–7.26 (m, 3H), 7.12–7.09 (m, 1H), 4.15–4.07 (m, 1H), 3.72 (t, 1H, $J = 9.6$ Hz), 3.54 (dd, 1H, $J_1 = 9.3$ Hz, $J_2 = 2.4$ Hz), 3.25 (s, 3H), 2.26 (s, 1H), 1.74–1.47 (m, 4H), 0.91–0.81 (m, 6H), 0.76 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1, 166.4, 154.4, 146.9, 135.1, 133.8, 133.3, 131.7, 129.0, 128.4, 128.1, 127.1, 126.3, 126.1, 125.3, 125.0, 124.2, 123.4, 122.0, 120.3, 115.6, 80.0, 76.1, 63.1, 50.0, 38.6, 26.5, 26.0, 25.4, 8.55, 7.47. Anal. Calcd for $C_{34}H_{39}NO_5 \cdot H_2O$: C, 72.96; H, 7.38; N, 2.50. Found: C, 73.04; H, 7.01; N, 2.45.
Schiff-base (*R*,*S*)-**5a**: mp 98 °C; $[\alpha]_D = +12.2$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1H), 8.01–7.93 (m, 3H), 7.86–7.84 (m, 1H), 7.47–7.43 (m, 2H), 7.35–7.26 (m, 4H), 7.09–7.07 (m, 1H), 4.09 (d, 1H, $J = 8.4$ Hz), 3.74 (t, 1H, $J = 8.0$ Hz), 3.52 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.4$ Hz), 3.26 (s, 3H), 2.13 (s, 1H), 1.73–1.49 (m, 4H), 0.94–0.83 (m, 6H), 0.78 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0, 166.4, 154.4, 147.1, 135.2, 133.9, 133.3, 131.7, 129.1, 128.4, 127.0, 126.5, 125.9, 125.3, 125.1, 124.2, 123.4, 122.0, 120.3, 115.7, 79.8, 76.5, 62.9, 50.0, 38.6, 26.5, 26.0, 25.4, 14.2, 8.5, 7.5. Anal. Calcd for $C_{34}H_{39}NO_5 \cdot H_2O$: C, 72.96; H, 7.38; N, 2.50. Found: C, 73.12; H, 7.09; N, 2.49.
Schiff-base (*R*,*S*,*R*)-**6**: mp 126 °C; $[\alpha]_D = +53.2$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 12.54 (s, 1H), 8.83 (s, 1H), 8.02–7.84 (m, 4H), 7.43–7.15 (m, 11H), 4.83 (d, 1H, $J = 6.0$ Hz), 4.68 (d, 1H, $J = 6.0$ Hz), 3.21 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 6.0$ Hz), 3.04 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 6.0$ Hz), 0.75 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.39, 166.44, 154.21, 147.05, 140.71, 140.30, 135.30, 134.12, 133.32, 131.74, 129.17, 128.77, 128.61, 128.52, 128.20, 127.23, 127.03, 126.55, 125.87, 125.45, 125.40, 125.12, 125.04, 124.19, 123.62, 122.02, 120.42, 115.97, 75.68, 75.26, 39.47, 38.59, 26.41. Anal. Calcd for $C_{35}H_{31}NO_4 \cdot H_2O$: C, 76.76; H, 6.07; N, 2.56. Found: C, 76.94; H, 6.09; N, 2.33.
Schiff-base (*S*,*S*,*R*)-**6**: mp 201 °C; $[\alpha]_D = -25.6$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 12.54 (s, 1H), 8.85 (s, 1H), 8.03–7.85 (m, 4H), 7.47–7.11 (m, 11H), 4.86 (d, 1H, $J = 6.0$ Hz), 4.70 (d, 1H, $J = 6.0$ Hz), 3.22 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 6.0$ Hz), 3.03 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 6.0$ Hz), 0.72 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.28, 166.59, 154.28, 147.06, 140.73, 140.35, 135.35, 134.16, 133.38, 131.76, 129.19, 128.75, 128.64, 128.56, 128.24, 127.65, 127.23, 126.53, 125.99, 125.51, 125.44, 125.22, 124.79, 124.05, 123.63, 122.08, 120.42, 115.95,

75.81, 75.29, 39.58, 38.57, 26.40. Anal. Calcd for $C_{35}H_{31}NO_4$: C, 79.37; H, 5.90; N, 2.64. Found: C, 79.23; H 5.97; N, 2.64.

9. The general procedure used for the sulfoxidation reactions is as follows: Vanadyl acetylacetonate (5.3 mg, 0.02 mmol) and a ligand (0.03 mmol) were dissolved in CH_2Cl_2 (3 mL) and then stirred for 10 min at room temperature. A sulfide (1.0 mmol) and 30% H_2O_2 were added after 10 min stirring at 0 °C. The mixture was stirred for 24 h at 0 °C and quenched with satd Na_2SO_3 solution. The resulting solution was extracted with CH_2Cl_2. The organic layer was briefly dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography.