Stereoselective Reactions. XIX.[1] Asymmetric Dihydroxylation of Olefins by Employing Osmium Tetroxide–Chiral Amine Complexes

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Enantioselective dihydroxylation of *E*-stilbene afforded (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol in 70% ee by employing a stoichiometric amount of osmium tetroxide-chiral amine 5, prepared from *N*-methylephedrine and 2-bromopyridine.

Keywords asymmetric synthesis; dihydroxylation; chiral ligand; diol; amino acid; pyridine; osmium tetroxide

Enantioselective vicinal dihydroxylation of carbon–carbon double bonds has been a challenge in recent asymmetric synthesis. Highly efficient processes have been developed recently by employing stoichiometric or substoichiometric amounts of osmium tetroxide–chiral amine complexes.[2-5] As part of our program aimed at development of enantioselective reactions by employing chiral ligands,[5,6] we have also engaged in the design and application of chiral amines to the highly selective asymmetric dihydroxylation of olefins.[5] We describe herein another approach to this objective.

Although pyridine is known to coordinate osmium tetroxide and to promote dihydroxylation of olefins,[7] simple pyridine derivatives have been reported to effect dihydroxylation of olefins to afford the corresponding diols in quite poor enantioselectivity.[3a] We designed chiral amines, **1**, **2**, **4**, and **5**, having a pyridine moiety as an additional coordination site, which were expected to afford optically active diols in reactions of olefins with osmium tetroxide–amine complexes.

Synthesis of Chiral Amines Amines **1**—**5** used in the present study were prepared starting from easily available optically pure compounds, L-phenylalanine, L-proline, and ephedrine. Reaction of *N*,*N*-dimethyl-L-phenylalaninol (**6**),[8] *N*-methyl-L-prolinol (**7**),[8] and *N*-methylephedrine (**8**)[9] with 2-bromopyridine provided the corresponding pyridine derivatives **1**, **4**, and **5**, respectively. A chloride **9**, derived from phenylalaninol (**6**), was treated with sodium salts of 8-hydroxyquinoline and *o*-methoxyphenol to afford the corresponding **2** and **3**, respectively.

Asymmetric Dihydroxylation of Styrene Enantioselectivity was studied in the reaction of styrene in toluene at room temperature with osmium tetroxide in the presence of chiral amines, followed by reduction of the corresponding osmate esters with lithium aluminum hydride, producing phenylethane-1,2-diol.[10] The results are summarized in Table I. The amines **1**—**4**, prepared from L-phenylalanine and L-proline, showed only poor enantioselectivities, irrespective of pyridine, quinoline and methoxybenzene moieties. However, the amine **5**, prepared from *N*-methylephedrine (**8**), exhibited a better enantioselectivity of 15%. *N*-Methylephedrine (**8**) showed only marginal selectivity, indicating the effect of the pyridine moiety of **5**.

Asymmetric Dihydroxylation of Olefins in the Presence of 5 Some olefins were oxidized by employing a stoichiometric amount of osmium tetroxide–amine **5** at −78 °C in

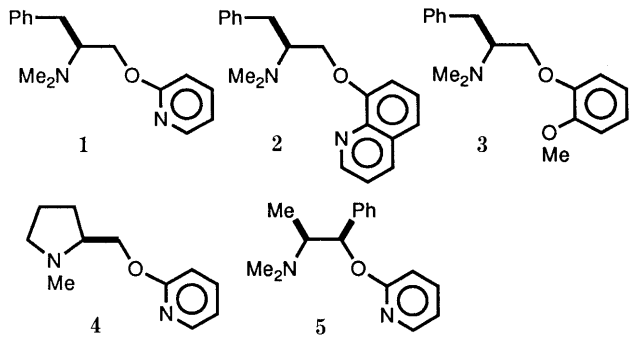
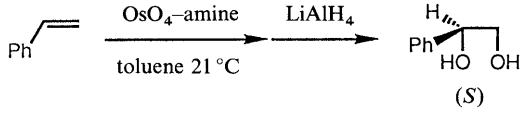


Fig. 1

TABLE I. Asymmetric Dihydroxylation of Styrene



Amine	%ee	*R*/*S*	Yield (%)
1	6	*S*	81
2	3	*S*	88
3	4	*S*	74
4	4	*R*	71
5	15	*S*	83
8	<1		75

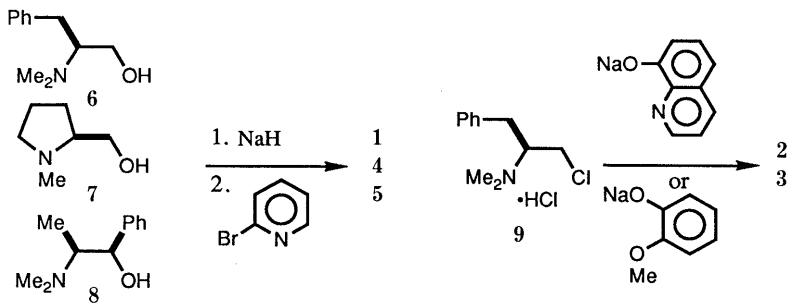
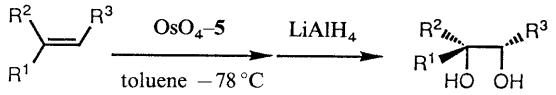


Fig. 2

TABLE II. Asymmetric Dihydroxylation with **5**



Olefin	%ee	*R*/*S*	Yield (%)
E-Stilbene	70[a]	1*S*,2*S*	82[11]
Styrene	34	*S*	83[10]
Indene	30	1*S*,2*R*	94[12]
Allylbenzene	30	*S*	78[13]
α-Methylstyrene	30[a]	*S*	74[14]
3,3-Dimethylpropene	25[a]	*S*	27[15]
E-β-Methylstyrene	8	1*S*,2*S*	91[5a]

a) Enantiomeric excess was diterminded by NMR analysis in the presence of $Eu(hfc)_3$.

toluene. It is important to note that dihydroxylation proceeded at the low temperature of −78 °C, indicating acceleration by the chiral amine **5**. Enantioselectivity and absolute configuration were determined by optical rotation of the produced diols.[5a,10-15] The results are summarized in Table II. In some diols, ee were determined by nuclear magnetic resonance (NMR) analysis in the presence of a chiral shift reagent $Eu(hfc)_3$. After dihydroxylation, the amine **5** was recovered without any loss of optical purity in high yield. *E*-Stilbene was oxidized to afford the diol in 70% ee.[11] Other olefins were oxidized to afford the corresponding diols in around 30% ee. However *E*-β-methylstyrene was converted to the diol in only 8% ee.

Conclusion

Enantioselective dihydroxylation of olefins with amines having a pyridine moiety as an additional coordination site to osmium was studied and the amine (**5**) derived from ephedrine showed good enantioselectivity in the oxidation of *E*-stilbene. Mechanistic aspects of the asymmetric induction exhibited by **5** should be clarified in further studies.[5b,7] Further efforts toward development of much more effective ligands are in progress in our laboratories.[16]

Experimental[17]

(+)-2-((2*S*)-2-Dimethylamino-3-phenylpropyloxy)pyridine (1) A solution of *N*,*N*-dimethylphenylalaninol (**6**)[8] (21.4 g, 0.12 mol) in dimethylsulfoxide (DMSO) (70 ml) was added at room temperature to a suspension of sodium hydride (0.156 mol, washed with dry hexane three times) in DMSO (250 ml). The mixture was stirred at room temperature for 2 h and at 60 °C for 0.5 h, then 2-bromopyridine (14.9 ml, 0.156 mol) was added at room temperature and the whole was stirred at room temperature for 18 h and diluted with water (100 ml). The mixture was extracted with ether (300 ml × 3) and the combined extracts were washed successively with water (300 ml × 3) and brine (300 ml), and dried over K_2CO_3. Concentration and distillation (bp 158—162 °C (3 mmHg)) provided **1** (27.1 g, 89%) as a pale yellow oil which was solidified on standing. mp 36—37 °C. $[\alpha]_D^{20}$ +92.1° (*c*=1.69, $CHCl_3$). IR (film): 1595 cm^{-1}. NMR ($CDCl_3$) δ: 2.43 (6H, s), 2.5—3.4 (3H, m), 4.3—4.4 (2H, m), 6.72 (1H, br d, *J*=7 Hz), 6.79 (1H, dd, *J*=5, 7 Hz), 7.13 (5H, s), 7.46 (1H, ddd, *J*=2, 7, 7 Hz), 8.06 (1H, dd, *J*=2, 5 Hz). MS *m*/*z*: 256 (M^+). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.82; H, 7.98, N; 10.72.

(+)-(*S*)-1-Chloro-2-dimethylamino-3-phenylpropane Hydrochloride (9) A solution of thionyl chloride (84 mmol) in 1,4-dioxane (40 ml) was added under ice bath cooling to a solution of **6**[8] (7.7 g, 42 mmol) in dioxane (80 ml). The mixture was stirred under reflux for 1.5 h. After cooling, the solid was collected by filtration and washed with ether (20 ml). Recrystallization from ethanol (60 ml) afforded **9** (6.19 g, 63%) as colorless plates of mp 160.5—162 °C. $[\alpha]_D^{24}$ +35.4° (*c*=2.20, EtOH). IR (KBr): 1590 cm^{-1}. NMR (CD_3OD) δ: 3.04 (6H, s), 3.1—4.2 (6H, m), 7.35 (5H, s). *Anal.* Calcd for $C_{11}H_{16}ClN \cdot HCl$: C, 56.42; H, 7.32; N, 5.98. Found: C, 56.27; H, 7.30; N, 5.89.

(+)-8-((2*S*)-2-Dimethylamino-3-phenylpropyloxy)quinoline (2) A solution of 8-hydroxyquinoline (930 mg, 6.4 mmol) in dimethylformamide (DMF) (2 ml) was added at room temperature to a suspension of NaH (6.5 mmol, washed with dry hexane three times) in DMF (2 ml). A solution of **9** (2.1 mmol) in DMF (2 ml) was added and the mixture was stirred at room temperature for 25 h then diluted with water (30 ml), and extracted with AcOEt (50 ml × 3). The combined extracts were washed successively with 10% aq. NaOH, water, and brine, and dried over K_2CO_3. Concentration and silica gel column chromatography ($CHCl_3$–EtOH 5:1) afforded **2** (240 mg, 35%) as a pale yellow oil. $[\alpha]_D^{20}$ +46.2° (*c*=0.952, $CHCl_3$). IR (film): 1590 cm^{-1}. NMR ($CDCl_3$) δ: 2.54 (6H, s), 2.8—3.1 (2H, m), 3.3 (1H, m), 4.18 (1H, dd, *J*=4, 9 Hz), 4.38 (1H, dd, *J*=6, 9 Hz), 6.80 (1H, dd, *J*=6, 8 Hz), 7.2—7.5 (3H, m), 7.23 (5H, s), 8.08, (1H, dd, *J*=2, 8 Hz), 8.91 (1H, dd, *J*=2, 4 Hz). MS *m*/*z*: 306 (M^+).

(+)-(*S*)-1-Benzyl-2-(2-methoxyphenoxy)-*N*,*N*-dimethylethylamine (3) *o*-Methoxyphenol (44.6 ml, 0.4 mol) was added to a suspension of NaH (0.4 mol, washed with dry hexane three times) in DMF (60 ml) under ice bath cooling. The mixture was stirred at room temperature for 40 min, then a solution of **9** (23.4 g, 0.1 mol) in DMF (600 ml) was added. The mixture was stirred at room temperature for 17 h, then concentrated to *ca.* 100 ml, diluted with water (300 ml), and extracted with ether (300 ml × 3). The combined extracts were washed successively with 10% aq. NaOH, water, and brine, and dried over K_2CO_3. Concentration afforded a yellow oil, which was treated with hydrogen chloride in MeOH to afford a solid after concentration. The solid was collected by filtration and recrystallized from a mixture of AcOEt (60 ml) and EtOH (0.5 ml) to afford the hydrochloride of **3** (21.8 g, 77%) as colorless needles of mp 143—144 °C. $[\alpha]_D^{20}$ +50.3° (*c*=1.14, EtOH). IR (KBr): 1590 cm^{-1}. NMR (CD_3OD) δ: 2.96—3.12 (1H, m), 3.36 (6H, s), 3.1—3.4 (3H, m), 3.81 (3H, s), 3.8—4.2 (2H, m), 6.7—7.0 (4H, m), 7.26 (5H, s). *Anal.* Calcd for $C_{18}H_{23}NO_2 \cdot HCl$: C, 67.16; H, 7.52; N, 4.35. Found: C, 67.19; H, 7.45; N, 4.26.

The free amine **3** was obtained by treating the hydrochloride with 10% aq. NaOH followed by extraction with ether. $[\alpha]_D^{20}$ +66.6° (*c*=2.46, $CHCl_3$). IR (film): 1588 cm^{-1}. NMR ($CDCl_3$) δ: 2.47 (6H, s), 2.6—3.4 (3H, m), 3.78 (3H, s), 3.9—4.1 (2H, m), 6.9 (4H, m), 7.24 (5H, s). MS *m*/*z*: 285 (M^+).

(−)-2-((*S*)-*N*-Methylpyrrolidin-2-ylmethoxy)pyridine (4) A solution of (*S*)-*N*-methylprolinol (**7**)[8] (2.87 g, 25.0 mmol) in DMSO (10 ml) was added at room temperature to a suspension of NaH (30.0 mmol, washed with dry hexane three times) in DMSO (70 ml). The mixture was stirred at room temperature for 40 min and at 60 °C for 20 min, 2-bromopyridine (4.74 g, 30 mmol) was added. The mixture was stirred at room temperature for 95 h, then diluted with water (50 ml), and extracted with ether (200 ml × 3). The combined extracts were washed successively with water (60 ml × 3) and brine, and dried over K_2CO_3. Concentration and distillation (bp 98 °C (2 mmHg)) afforded **4** (3.27 g, 68%) as a colorless oil. $[\alpha]_D^{20}$ −64.9° (*c*=1.17, $CHCl_3$). IR (film): 1580 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—3.3 (7H, m), 2.43 (3H, s), 4.2—4.3 (2H, m), 6.6—8.2 (4H, m). MS *m*/*z*: 192 (M^+).

(+)-2-((1*R*,2*S*)-2-Dimethylamino-1-phenylpropyloxy)pyridine (5) A solution of *N*-methylephedrine (**7**)[9] (5.19 g, 29 mmol) in DMSO (15 ml) was added at room temperature to a suspension of NaH (35 mmol, washed with dry hexane three times) in DMSO (25 ml). The mixture was stirred at room temperature for 40 min and at 60 °C for 20 min, then 2-bromopyridine (5.53 g, 35.0 mmol) was added. The mixture was stirred at room temperature for 52 h, then diluted with water (50 ml), and extracted with ether (200 ml × 3). The combined extracts were washed successively with water (60 ml × 3) and brine, and dried over K_2CO_3. Concentration and distillation (bp 133—135 °C (0.5 mmHg)) afforded **5** (5.73 g, 77%) as a colorless oil. $[\alpha]_D^{20}$ +5.6° (*c*=3.56, $CHCl_3$). IR (film): 1595 cm^{-1}. NMR ($CDCl_3$) δ: 1.15 (3H, d, *J*=7 Hz), 2.33 (6H, s), 2.94 (1H, qd, *J*=4, 7 Hz), 6.35 (1H, d, *J*=4 Hz), 6.72 (1H, br d, *J*=6 Hz), 6.75 (1H, dd, *J*=5, 7 Hz), 7.26 (5H, s), 7.51 (1H, ddd, *J*=2, 6, 7 Hz), 8.03 (1H, dd, *J*=2, 5 Hz). MS *m*/*z*: 256 (M^+). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.72; H, 7.90; N, 10.75. Found: C, 74.92; H, 7.87; N, 10.92.

General Procedure for Dihydroxylation of Olefins Exemplified by the reaction of *E*-stilbene at −78 °C (Table II). A solution of **5** (177 mg, 0.69 mmol) in toluene (1 ml) was added at room temperature to a yellow solution of osmium tetroxide (160 mg, 0.63 mmol) in toluene (2 ml). The mixture was stirred at −78 °C for 10 min, then a solution of *E*-stilbene (102 mg, 0.57 mmol) in toluene (1 ml) was added over a period of 5 min. The mixture was stirred at −78 °C for 10 h and diluted with ether (20 ml). Lithium aluminum hydride (150 mg, 4 mmol) was added and the

whole was allowed to warm to room temperature over 3 h and stirred at room temperature for an additional 5 h. Water (0.15 ml), 15% aq. NaOH (0.15 ml), and water (0.45 ml) were successively added, and the mixture was then filtered. Concentration and silica gel column chromatography (benzene/ether = 3/2) provided (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol (100 mg, 82%) of 70% ee. $[\alpha]_D^{21}$ −66.4° (*c* = 0.925, EtOH) (+91.0° for (1*R*,2*R*)-diol).[11] The chiral amine **5** was recovered in 80% yield.

References and Notes

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16) We are grateful to the Japan Foundation for Optically Active Compounds for financial support.
17) Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-181 digital polarimeter. IR spectra were taken with an infrared spectrometer model DS-402 G and a JASCO IRA-I grating infrared spectrometer. NMR spectra were taken with a JEOL FX-100 spectrometer at 100 MHz, or with a Hitachi R-24 spectrometer at 60 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. MS were taken with a JEOL JMS DX-300 mass spectrometer.