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Synthesis of Chiral 2,3-Disubstituted 1,4-Diazabicyclo[2.2.2]octane. New Ligand for the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins

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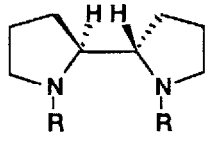
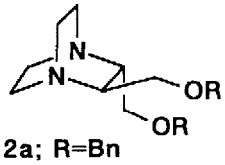
Key Words: DABCO; OsO_4; $K_3Fe(CN)_6$; Catalytic Asymmetric Dihydroxylation; Olefin

Abstract: *Chiral 2,3-disubstituted 1,4-diazabicyclo[2.2.2]octane (DABCO) derivatives have been synthesized and utilized as a chiral ligand for the osmium-catalyzed asymmetric dihydroxylation of olefins. Optically active diols in up to 41%ee are obtained in good yields.*

Recently, we have reported the enantioselective dihydroxylation of olefins with chiral 1,1'-dineohexyl-2,2'-bipyrrolidine (1) and osmium tetroxide (OsO_4) complex.[1,2] This system achieved very high enantioselectivity, but is limited only to the stoichiometric reactions at low temperature, because the catalytic cycle was interrupted by the formation of too stable diamine (1)-osmate ester complex,[1b,3a] and because the mixture of 1 and OsO_4 deteriorated at room temperature resulting in low yields of the diol products. The only example of successful catalytic asymmetric dihydroxylation has been discovered by Sharpless et al. utilizing cinchona alkaloids as the chiral ligands, while quinuclidine itself inhibits the catalytic process.[3] On the other hand, Yamamoto et al. have disclosed that 1,4-diazabicyclo[2.2.2]octane (DABCO) as well as quinuclidine can accelerate the osmium tetroxide catalyzed dihydroxylation when potassium hexacyanoferrate(III) [$K_3Fe(CN)_6$] is used as a cooxidant.[4,5] DABCO forms a stable complex with OsO_4[6] like quinuclidine[7] and its basicity in water (pKa_1 = 8.82, pKa_2 = 2.97) appeares to be weaker than that of quinuclidine (pKa = 11.0).[8] These features suggested that substituted chiral DABCO derivatives, if available,[9] may serve as effective ligands for asymmetic catalysis with better turnover. Synthesis of some C_2-symmetrical 2,3-disubstituted DABCO's (2) and preliminary studies of the catalytic dihydroxylation of olefins using 2 as the chiral ligand are disclosed herein.

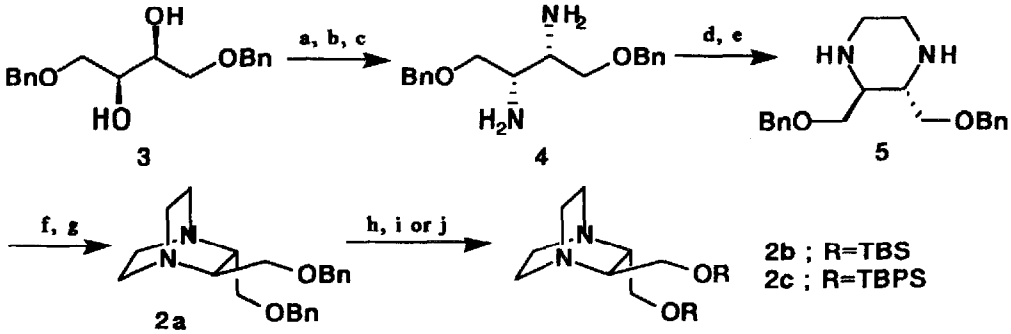


1; R=neohexyl



2a; R=Bn
2b; R=TBS
2c; R=TBPS

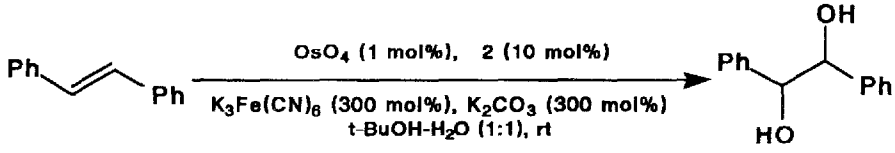
Optically pure (*S, S*)-2,3-disubstituted DABCO's (2a-c)[10] were synthesized from readily available (*S, S*)-threitol 1,4-dibenzyl ether 3[11] through piperazine derivative 5 by the conventional procedures shown in Scheme 1.[12]



Scheme 1. a) MsCl (2.4 mol. eq), triethylamine (3.0 mol. eq), CH_2Cl_2, 0°C, 1 h, 98%; b) NaN_3 (3.0 mol. eq), DMF, 100°C, 1 d, 89%; c) $LiAlH_4$ (2.0 mol. eq), THF, reflux, 12 h, 66%; d) $(CO_2Et)_2$ (1.1 mol. eq), toluene, reflux, 5 h, 83%; e) $LiAlH_4$ (3.0 mol. eq), THF, reflux, 12 h, 70%; f) 1,2-dibromoethane-EtOH (1:2), K_2CO_3 (10 mol. eq), reflux, 12 h; g) Zn (20 mol. eq), AcOH, reflux, 12 h, 39-63% (2steps); h) H_2, 10% Pd/C, 0.5M $HClO_4$, MeOH, rt, 5 d; i) TBSCl (3.0 mol. eq), triethylamine (10 mol. eq), DMAP (0.1 mol. eq), acetonitrile, rt, 3 d, 74% (2 steps); j) TBPSCl (3.0 mol. eq), triethylamine (10 mol. eq), DMAP (0.1 mol. eq), acetonitrile, rt, 4 d, 76% (2 steps).

We first examined the osmium tetroxide-catalyzed dihydroxylation of trans-stilbene by using **2a-2c** as the chiral ligands. Results are summarized in Table 1. The reactions using $K_3Fe(CN)_6$ as co-oxidant proceeded in good yields and gave a better enantiomeric excess than that using N-methylmorpholine-N-oxide (NMO) in accordance with the results using cinchona alkaloids.[3b-f] When the alcohol was protected with sterically more demanding t-butyldimethylsilyl (TBS, **2b**) or t-butyldiphenylsilyl (TBPS, **2c**) groups, the sense of stereoselectivity has been changed from **2a**, and **2c** gave higher selectivity.

Table 1. Asymmetric dihydroxylation of trans-stilbene using **2a-2c**.



ligand	yield (%)	$[\alpha]_D$	ee (%)[a]	configuration
2a	83	+21.5° (c 1.00, EtOH)	24	*RR*
2a	89	+6.0° (c 1.01, EtOH)	7[b]	*RR*
2b	87	-17.2° (c 1.03, EtOH)	19	*SS*
2c	91	-37.5° (c 1.01, EtOH)	41	*SS*

a) Determined by comparison of $[\alpha]_D$. b) NMO (120 mol%) in acetone-H_2O at 0°C.

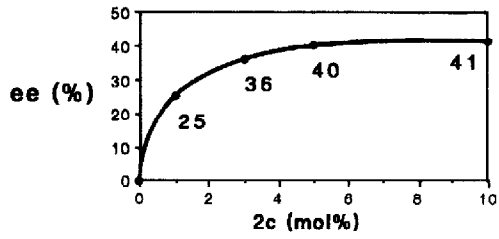
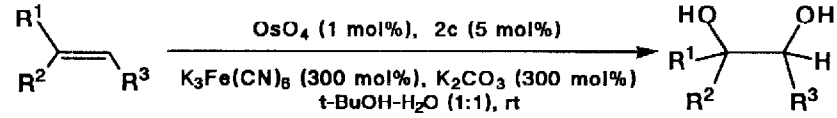
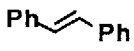
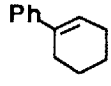
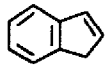


Figure 1. Plot of **2c** mol% versus %ee for the catalytic dihydroxylation of trans-stilbene at 22°C.

As indicated in Fig. 1, the amount of **2c** can be reduced to 5 mol% without decreasing enantiomeric excess [conditions: trans-stilbene, 0.061 M in t-BuOH-H_2O (1:1); OsO_4, 1 mol%; $K_3Fe(CN)_6$, 300 mol%; K_2CO_3, 300 mol%; 22°C]. This might be an advantage of the DABCO ligands.[3b] Then, the oxidations of various olefins were tested by using 5 mol% of **2c** under the above conditions (Table 2). While these enantioselectivities are still far from satisfactory, substituted chiral DABCO derivatives appear to be promising ligands for the catalytic asymmetric dihydroxylation. Further syntheses and search of optimal DABCO derivatives are currently under investigation in our laboratory.

Table 2. Catalytic asymmetric dihydroxylation of olefins using **2c**.



olefin	yield (%)	$[\alpha]_D$	ee (%)[a]	configuration
	85	-36.3° (c 1.00, EtOH)	40[13a]	*SS*
	95	+5.84° (c 1.01, EtOH)	19[13b]	*SS*
	80	+13.6° (c 1.01, $CDCl_3$)	21[13c]	*S*
	83	-9.25° (c 1.02, H_2O)	41[13d]	*SS*
	92	-4.48° (c 1.02, EtOH)	27[13e]	*S*
	95	-3.46° (c 1.01, C_6H_6)	18[13f]	*SS*
	66	-5.92°(c 1.00, $CHCl_3$)	12[13g]	*1S2R*

a) Determined by comparison of $[\alpha]_D$.[13]

A typical catalytic dihydroxylation procedure is as follows: To 15.5 mL of a stirred 0.65 mM solution of OsO_4 (0.01 mmol, 0.01 eq) in t-butyl alcohol-water (1:1) were added 1 mL of a 0.05 M solution of **2c** (0.05 mmol, 0.05 eq) in t-butyl alcohol, olefin (1mmol), K_2CO_3 (3 mmol, 3.0 eq), and $K_3Fe(CN)_6$ (3 mmol, 3.0 eq). After the reaction mixture was stirred for 8-24 h at room temperature (20-22°C), solid $Na_2SO_3 \cdot 7H_2O$ (1.0 g) was added and stirred further for 3 h. The mixture was then concentrated in vacuo. The residue was extracted with ether (100 mL) and washed with satd. NH_4Cl (3 mL) and satd. NaCl (3 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexane-ethyl acetate).

References and Notes

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5. By using this reoxidant, Sharpless has improved his original catalytic system (OsO_4-NMO-cinchona alkaloid), see ref 3b-3f.
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10. Physical data: **2a** , colorless oil , $[\alpha]_D^{27}$ -41.9° (c 1.01, EtOH); ^1H NMR (200MHz, $CDCl_3$): δ 2.50-2.69 (4H, m), 2.69 (6H, m), 3.46 (2H, dd, J=10.0, 4.8 Hz), 3.56 (2H, dd, J=10.0, 7.3 Hz), 4.55 (4H, s), 7.31 (10H, m); ^{13}C NMR (50MHz, $CDCl_3$): δ 41.49, 49.78, 58.50, 70.65, 73.52, 127.80, 127.86, 128.58; IR (film): ν 3090, 3066, 3032, 2936, 2874, 1497, 1456, 1367, 1319, 1209,1093, 1029cm^{-1}; MS (EI, 25eV, 120°C) m/z (%) : 352 (M^+, 5), 245 (100); **2b** , colorless oil, $[\alpha]_D^{25}$ -46.6° (c 1.00, $CHCl_3$); **2c** , colorless amorphous, $[\alpha]_D^{26}$ -7.31° (c 1.04, $CHCl_3$).
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12 Zinc reduction is necessary to recover **2a** after the treatment of **5** with 1,2-dibromoethane because of the formation of quarternary ammonium salts.
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