Asymmetric Dihydroxylation of Alkenes with Osmium Tetroxide: Chiral *N,N'*-Dialkyl-2,2'-bipyrrolidine Complex

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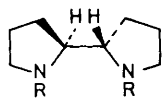
Asymmetric osmylation of alkenes by using *N,N'*-dialkyl-2,2'-bipyrrolidines as the chiral ligands shows a high asymmetric induction and a marked dependence of the enantioselectivity on both the *N*-alkyl group and the reaction solvent.

Osmium tetroxide is the most reliable reagent available for *cis*-hydroxylation of alkenes to give the corresponding *cis*-diols[1] and enantioselective reactions have been developed by utilizing rate acceleration with chiral tertiary amines.[2] Recent reports in this field[3,4] prompt us to disclose our results using new chiral amines, *N,N'*-dialkyl-2,2'-bipyrrolidines (**1**), with C_2 symmetry.

The optically pure ligands (**1**) were prepared from resolved 2,2'-bipyrrolidine (**2**)[5] *via* acylation followed by reduction with $LiAlH_4$. The oxidation of (*E*)-stilbene with a stoicheiometric amount of OsO_4 in toluene or CH_2Cl_2 at −78 °C in the presence of (*S*,*S*)-(−)-(**1**) affords the *threo*-hydrobenzoin, after reductive hydrolysis, with the enantiomeric excess (e.e.) shown in Table 1. The enantioselectivity proved to be highly dependent not only on the *N*-alkyl group, as expected, but also on the reaction solvent.† While the reactions in CH_2Cl_2 with the dimethyl, diethyl, and dipropyl derivatives (**1a**—**c**) yield the (*R*,*R*)-diol (**3**) with moderate selectivity, the dibutyl (**1d**) and dipentyl (**1e**) derivatives show an opposite face



(**1**) R = Alkyl

(**2**) R = H

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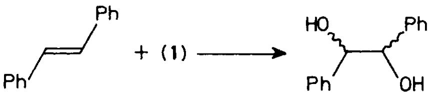
† The osmylation did not proceed smoothly in either ether or tetrahydrofuran.

Table 1. Asymmetric oxidation of (*E*)-stilbene with OsO_4 in the presence of (*S*,*S*)-(−)-(**1**).[a]

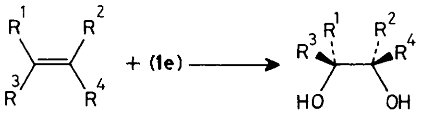


(3)

Diamine (*S*,*S*)-(−)-(**1**)[b]	Solvent	% Yield[c]	% E.e.[d]	Confgn. of diol.
R = Me (**1a**)	CH_2Cl_2	49	40	(*R*,*R*)
	Toluene	55	7	(*R*,*R*)
R = Et (**1b**)	CH_2Cl_2	63	43	(*R*,*R*)
	Toluene	71	28	(*S*,*S*)
R = Pr (**1c**)	CH_2Cl_2	54	52	(*R*,*R*)
	Toluene	65	54	(*S*,*S*)
R = Bu (**1d**)	CH_2Cl_2	43	26	(*S*,*S*)
	Toluene	67	85[e]	(*S*,*S*)
R = Pe[h] (**1e**)	CH_2Cl_2	68	28	(*S*,*S*)
	Toluene	67	89[e]	(*S*,*S*)
	Toluene[f]	80[g]	91[e]	(*S*,*S*)

[a] In each reaction, to a cooled (−78 °C) solution of (**1**) (0.36 mmol) in dry CH_2Cl_2 or toluene (7 ml) was added a solution of OsO_4 in the same solvent (2 ml). After the mixture had been stirred at −78 °C for 1 h, a solution of stilbene (0.3 mmol) in solvent (1 ml) was added, and the mixture stirred overnight at −78 °C, and concentrated *in vacuo* at room temperature. To the mixture were added dry tetrahydrofuran (THF) (10 ml) and excess of $LiAlH_4$ (3.3 mmol) and the mixture was stirred at room temperature for 24 h. Water (1.5 ml) was added and the mixture was filtered. The filtrate was diluted with ether, washed with 2 M HCl and aqueous saturated $NaHCO_3$, and dried over anhydrous $MgSO_4$. The product was purified by silica gel column chromatography. [b] $[\alpha]_D$ of amines in $CHCl_3$: (**1a**) −108.5°, (**1b**) −148.9°, (**1d**) −128.0°, (**1e**) −131.7°. [c] Isolated yield after reductive work-up with $LiAlH_4$, unless otherwise indicated. [d] Enantiomeric excess was determined by comparison of optical rotation with literature value {(*R*,*R*): $[\alpha]_D^{21}$ +91.0° (EtOH), G. Berti and F. Bottari, *J. Org. Chem.*, 1960, **25**, 1286} unless otherwise indicated. [e] Determined by h.p.l.c. analysis of dibenzoate by using CHIRALPAK OT column with hexane/Pr^iOH (1 : 1) as eluant. [f] Carried out at −93 °C. [g] After the osmylation mixture had been concentrated, THF (7 ml), water (0.5 ml), and $NaHSO_3$ (1 g) were added, and the mixture refluxed for 2 h, and filtered. The solid was extracted with AcOEt. The combined filtrates were treated as above. This reductive work-up always gives a better yield of diol than the use of $LiAlH_4$. We thank Prof. Kiyoshi Tomioka, Tokyo University, for this procedure. [h] Pe = pentyl.

Table 2. Oxidation of alkenes with OsO_4 in the presence of (**1e**).[a]



Alkene	Solvent	% Yield[b]	% E.e.	Confgn. of diol
(*E*)-Stilbene	CH_2Cl_2	68[c]	28[d]	(1*S*,2*S*)
	Toluene	67[c]	89[e]	(1*S*,2*S*)
	Toluene[f]	80	91[e]	(1*S*,2*S*
(*E*)-Hex-3-ene	CH_2Cl_2	86	92[g]	(1*S*,2*S*)
	Toluene	88	57[g]	(1*S*,2*S*)
Dimethyl fumarate	CH_2Cl_2	77	91[h]	(1*R*,2*R*)
	Toluene	75	63[h]	(1*R*,2*R*)
Styrene	CH_2Cl_2	76[c]	27[d]	(*S*)
	Toluene	49[c]	58[d]	(*S*)
Hept-1-ene	CH_2Cl_2	90	68[d]	(*S*)
	Toluene	95	40[d]	(*S*)
1-Methylcyclohexene	CH_2Cl_2	78	12[g]	(1*S*,2*R*)
	Toluene	77	31[g]	(1*S*,2*R*)
Indene	CH_2Cl_2	77	20[d]	(1*S*,2*R*)
	Toluene	85	35[d]	(1*S*,2*R*)

[a] Carried out at −78 °C unless otherwise indicated. [b] Osmium ester was reduced with $NaHSO_3$ in aqueous THF unless otherwise indicated. [c] Osmium ester was reduced with $LiAlH_4$ in THF. [d] Determined by comparison of $[\alpha]_D$ with literature values [(*E*)-stilbene: see Table 1; styrene: J. A. Dale and H. S. Mosher, *J. Org. Chem.*, 1970, **35**, 4002; hept-1-ene: P. A. Levene and A. Walti, *J. Biol. Chem.*, 1932, **98**, 735; indene: M. Imuta and H. Ziffer, *J. Org. Chem.*, 1978, **43**, 4540. [e] Determined by h.p.l.c. analysis of dibenzoate by using CHIRALPAK OT column and hexane/Pr^iOH (1 : 1) as eluant. [f] Carried out at −93 °C. [g] Determined by h.p.l.c. analysis of monobenzoate by using CHIRALPAK OT column and methanol as eluant. [h] Determined by h.p.l.c. analysis of dibenzoate by using CHIRALCEL OD column and hexane/Pr^iOH (10 : 1) as eluant.

selectivity. In toluene, the (*S*,*S*)-selectivity is dramatically improved as the length of the alkyl group increases; the dipentyl derivative (**1e**) affords the highest e.e. among those examined. It is further improved to 91% e.e. when the reaction is carried out at −93 °C. It is also noteworthy that the dipropyl derivative (**1c**) shows the opposite face selectivity between the two solvents.

Other alkenes were tested for oxidation with the OsO_4–chiral diamine [(*S*,*S*)-(−)-(**1e**)] complex (Table 2). (*E*)-Disubstituted alkenes are oxidized with unusually high stereoselectivity. Particularly, 92% e.e. in the oxidation of (*E*)-hex-3-ene is the highest selectivity that has been reported so far.[3,4] It is also interesting that toluene seems to be the solvent of choice for the oxidation of alkenes conjugated with a phenyl group [(*E*)-stilbene, styrene, and indene], while higher selectivity is obtained in CH_2Cl_2 for other alkenes except for the trisubstituted 1-methylcyclohexene.

Thus, (**1e**) is found to be a good ligand for asymmetric osmylation of (*E*)-disubstituted alkenes. Further improvements and mechanistic considerations of the solvent effect will be discussed in a full account. In addition, as the chiral amines (**1**) have the advantage of structural variation, there are numerous other potential applications of (**1**) for asymmetric synthesis. Work along these lines is in progress.

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5 The optically pure (*S*,*S*)-(+)-(**2**) was synthesized from the readily available 2,2′-(1′-pyrrolinyl)pyrrole (H. Rapoport and N. Castagnoli, Jr., *J. Am. Chem. Soc.*, 1962, **84**, 2178) in four steps: (a) H_2 (4 atom), 5% Rh/Al_2O_3, MeOH–AcOH (1 : 1); (b) PhCOCl, NEt_3, CH_2Cl_2; chromatographic separation (SiO_2) of (±)-isomer from *meso*-isomer (1.2 : 1); (c) conc. HCl, reflux; (d) optical resolution with D-(−)-tartaric acid in MeOH–H_2O (3 : 1).