Highly Enantioselective Dihydroxylation of Trans-Disubstituted and Monosubstituted Olefins

Tohru Oishi and Masahiro Hirama*

Department of Chemistry, Tohoku University, Sendai 980, Japan

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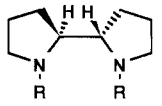
Summary: Extremely high levels of asymmetric induction have been achieved in osmium tetraoxide oxidation of trans-disubstituted and monosubstituted olefins by using chiral *N,N'*-dineohexyl-2,2'-bipyrrolidine ligand.

Sir: Although the recent development of stoichiometric[1,2] and catalytic[3] asymmetric dihydroxylations of olefins with OsO_4–chiral amine ligand complexes are remarkable, enantioselection of greater than 95% ee has been restricted to olefins conjugated with phenyl groups.[1d,3b] Thus, a superior chiral ligand giving virtually complete enantioselection is still desirable. In this short paper we disclose a ligand exhibiting the highest enantioselectivity yet reported in asymmetric OsO_4 oxidations,[1-3b] whose use is limited to the stoichiometric process.

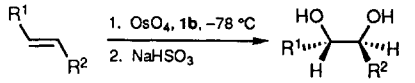
After considerable effort to discover a chiral ligand superior to the recently reported *N,N'*-dipentyl-2,2'-bipyrrolidine (**1a**),[2] we have found that *N,N'*-dineohexyl derivative (**1b**)[4] gives excellent enantioselectivities in the



1a, R=pentyl
1b, R=neohexyl

OsO_4 oxidation of various olefins at −78 °C as shown in Table I. The enantiomeric excess of the resultant diol was determined by HPLC analysis of the corresponding mono- or bisbenzoate on a DAICEL CHIRALCEL OD or a CHIRALPAK OT column.[5] It is remarkable that the present system shows an exceptionally high selectivity even for nonaromatic trans-disubstituted (entries 6–10) and monosubstituted olefins (entry 11). Another interesting feature is that the enantioselectivity is significantly affected by solvent as noticed previously in other derivatives of **1**:[2] olefins conjugated with a phenyl group give better results in toluene (entries 1–5 and 12) and nonaromatic olefins do so in nonaromatic solvents such as CH_2Cl_2 (entries 6–11). Although the mechanisms of these effects are not yet clear, it seems that in toluene coordination to osmium plays an important role in the ee-determining step.[6,7]

Table I. Oxidation of Trans-Disubstituted and Monosubstituted Olefins with OsO_4 in the Presence of (*S,S*)-(−)-1b

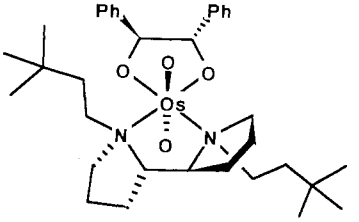


entry	olefin[a]	solvent	% ee	% yield[f]	configuration[g]
1	(*E*)-stilbene	toluene	100[b]	96	*SS*
2	(*E*)-stilbene	acetone	80[b]	93	*SS*
3	(*E*)-stilbene	CH_2Cl_2	56[b]	87	*SS*
4	ethyl (*E*)-3-phenylacrylate	toluene	99[b]	97	
5	(*E*)-1-phenylpropene	toluene	92[c]	95	*SS*
6	dimethyl fumarate	CH_2Cl_2	98[d]	79	*RR*
7	ethyl (*E*)-crotonate	CH_2Cl_2	98[e]	90	
8	(*E*)-2-heptene	CH_2Cl_2	98[e]	93	
9	(*E*)-3-hexene	CH_2Cl_2	96[c]	82	*SS*
10	(*E*)-3-heptene	CH_2Cl_2	93[b]	90	
11	1-heptene	CH_2Cl_2	91[b]	90	*S*
12	styrene	toluene	88[b]	90	*S*

[a] In each reaction, to a cooled (−78 °C) solution of **1b** (0.36 mmol) in a dry solvent (7 mL) was added a solution of OsO_4 (0.33 mmol) in the same solvent (2 mL). After the mixture was stirred at −78 °C for 1 h, a solution of olefin (0.3 mmol) in the solvent (1 mL) was added and stirred overnight at −78 °C. Then powdered $NaHSO_3$ (1 g) was added to the mixture, and the solvent was removed in vacuo at room temperature with stirring. After the residue was taken up in THF (7 mL) and water (0.5 mL), the mixture was refluxed for 2 h and filtered (We thank Prof. Kiyoshi Tomioka, Tokyo University, for this reductive procedure).[2] The solid was extracted with AcOEt, and the combined filtrates were washed with 2 M HCl, saturated NH_4Cl, saturated $NaHCO_3$, and saturated NaCl and dried over anhydrous $MgSO_4$. The diols were purified by silica gel column chromatography. [b] Enantiomeric excess was determined by HPLC of the corresponding bisbenzoate on CHIRALPAK OT column. [c] Monobenzoate on CHIRALPAK OT. [d] Bisbenzoate on CHIRALCEL OD. [e] Monobenzoate on CHIRALCEL OD. [f] Isolated yield after chromatography. [g] Determined by comparison of optical rotations with literature values.[1-3]

Compared to the excellent levels of asymmetric induction reported above, enantioselectivities for cis-disubstituted and trisubstituted olefins are not satisfactorily high, for instance, 67% ee for indene, 43% ee for 1,2-dihydronaphthalene, and 58% ee for 1-methylcyclohexene, though the selectivities for the cis olefins are still superior to those achieved with other chiral ligands.[1-3a,b]

In connection with our mechanistic study of the transmission of chirality to substrates, the structure of the osmium(VI) glycolate ester–diamine complex **2** prepared



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(4) (*S,S*)-**1b** ($[\alpha]^{24}_D$ −137° (*c* 1.0, $CHCl_3$)) was prepared from optically pure (*S,S*)-2,2'-bipyrrolidine in a standard manner.[2]

(5) Determination of ee by using the corresponding MTPA esters is often erratic due to the kinetic resolution during MTPA ester formations.

(6) Charge-transfer interactions and formations of weak complexes between OsO_4 and aromatic compounds are well known (see ref 7). It might be necessary that this coordination is taken into account in the mechanistic discussions on the asymmetric osmium tetraoxide oxidations.[1a,3]

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from OsO_4, **1b**, and stilbene in toluene was determined by X-ray crystallographic analysis (Figure 1).[8,9] The stable octahedral complex **2** is free of toluene, and the diamine **1b** is chelating to osmium as clearly indicated by their N···Os distances (2.16 and 2.22 Å), which are very close to those reported for the pyridine[10] and the quinuclidine[11] osmate complexes. Each osmate phenyl group is facing a bulky neohexyl substituent of **1b**. This is very similar to the stereostructure of the corresponding osmate ester–diamine complex reported by Tomioka and Koga et al.[1d] The study of the structure of the complex of **1b** and OsO_4 is currently underway. The detailed mechanisms for the asymmetric osmylation will be discussed in due course.

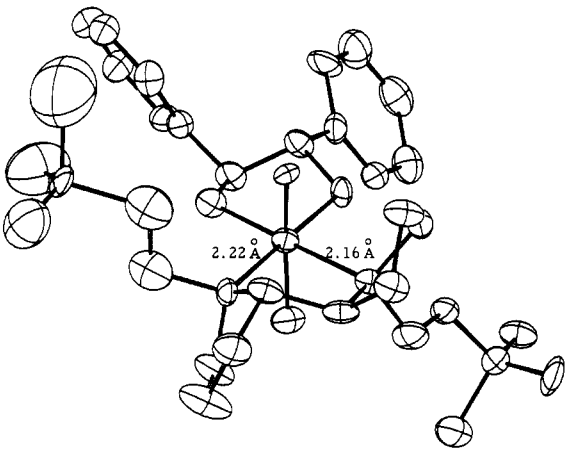

Figure 1. ORTEP drawing of **2**.

(8) After the 1:1:1 mixture was stirred at −78 °C for 12 h, the volatiles were removed in vacuo and the resultant dark brown slurry was purified on silica, recrystallized from hexane–CH_2Cl_2 to give **2** as brown needles: mp 180 °C dec. Crystal data: orthorhombic crystals, $P2_12_12_1$, with a = 25.92 Å, b = 12.16 Å, c = 10.57 Å, $\alpha = \beta = \gamma = 90.0°$, $Z = 4$, V = 3328 Å^3, D_{calcd} = 1.49 g cm^{-3}, final R value = 0.066 for 2879 reflections (Rigaku AFC5-R, Mo-Kα).

(9) Oxidative hydrolysis of the isolated **2** with *N*-methylmorpholine *N*-oxide in aqueous acetone turned out to be too slow in accordance with Sharpless' findings for chelating ligands.[3a]

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Chiral Recognition in Clefts and Cyclophane Cavities Shaped by the 1,1′-Binaphthyl Major Groove

Peter P. Castro, Taxiarchis M. Georgiadis, and François Diederich*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024-1569

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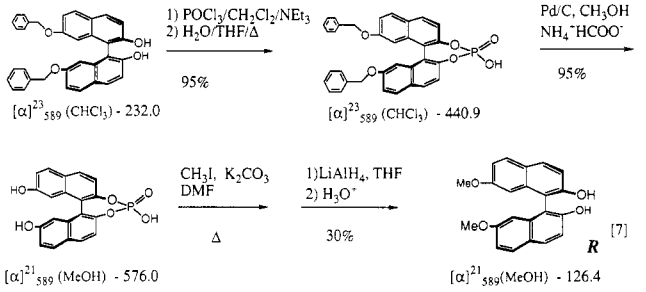
Summary: The optical resolution of 7,7′-bis(benzyloxy)-2,2′-dihydroxy-1,1′-binaphthyl through clathrate formation with quinine is described. Optically active cyclophanes incorporating this spacer bind enantioselectively naproxen derivatives. Hydrogen bonding and π–π interactions lead to a high degree of chiral recognition in the binding of cinchona alkaloids at the major groove of 1,1′-binaphthyls.

Sir: Chiral recognition of neutral organic substrates in designed molecular complexes has attracted increasing interest in recent years.[1] Successful developments in this research area promise to provide new approaches to enantiomer separation in chromatographic, crystallographic, or transport experiments as well as new chiral environments and reagents for asymmetric synthesis and catalysis.[2] In our exploration of optically active cyclophanes for the resolution of naproxen derivatives, e.g. **1a–f**, we recently prepared racemic cyclophane **3**.[3] We showed that the major groove of the 1,1′-binaphthyl unit is ideal for shaping cyclophane binding sites for aromatic guests like naproxen. In this paper, we report on the optical resolution of the binaphthyl spacer **4a** and on the preparation and chiral recognition properties of the optically active cyclophane **3** and chiral molecular clefts readily assembled from resolved **4a**.

Scheme I



Recently, quinine has been described as a useful chiral solvating agent for the determination of the enantiomeric composition of binaphthyl derivatives by ^{1}H NMR spectroscopy.[4] We found that quinine can also be used as a chiral resolving agent for these compounds, and the large-scale (0.1 mol) optical resolution of **4a** was readily

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