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Asymmetric Dihydroxylation of Chiral Olefins. High Control of Diastereofacial Selection

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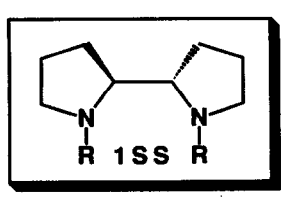
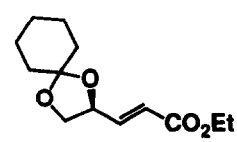
Abstract: *Highly diastereoselective dihydroxylation of 4,5-dihydroxy-2-pentenoate with osmium tetroxide using chiral N,N'-dialkyl-2,2'-bipyrrolidine ligands (1) is described. Either syn or anti selection was achieved for acetate (2d) and methyl ether (2e) by employing the enantiomeric ligands.*

Dihydroxylation of olefins with osmium tetroxide is the most reliable and versatile method for the preparation of cis-vicinal diols. It has been utilized for the synthesis of polyhydroxy natural products.[1] Kishi et al. reported an empirical rule on the stereochemistry of the dihydroxylation of chiral olefins bearing alkoxy-substituents at the allylic position using achiral OsO_4 reagent.[2] Related substrate-controlled oxidations have been also reported by several other groups.[3] Although these methods are very useful, the stereoselection was always controlled in the anti-sense to the allylic substituents. Very recently, Cozzi et al. attempted to overcome this problem for ethyl (*R*)-4,5-*O*,*O*-cyclohexylidenedioxy-2(*E*)-pentenoate (**2E**), a useful chiral synthon, by a reagent-controlled[4] OsO_4 oxidation with Sharpless' chiral ligands without much success.[5] Encouraged by our results of highly enantioselective dihydroxylation of trans-disubstituted and terminal olefins using chiral N,N'-dialkyl-2,2'-bipyrrolidine derivatives,[6] we have applied our stereoselective method to the asymmetric dihydroxylation of this chiral α,β-unsaturated ester system.

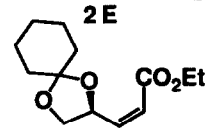
The reaction of **2E** using an achiral reagent under the catalytic conditions[7] (0°C-rt) gave a 2.3:1 ratio in favor of anti-attack. The anti selectivity increased to 12:1 when TMEDA was used as a diamine ligand at -78°C (Table 1). By using **1aRR** as a chiral ligand, the anti-selectivity was improved up to >50:1. However, combination using **1aSS** afforded only a low syn-selectivity (1.8:1). Smaller and larger ligands, **1bSS** and **1cSS**, respectively, didn't affect it (entries 5 and 6). We then examined the effect of the alkoxy substituents on the stereoselectivity (entries 7-21). When the protecting groups of the 4,5-diols became stereochemically less demanding, the syn selectivity by using **1aSS** seemed to be improved (entries 9, 12 and 15). Very high syn-selectivity was eventually achieved for the acetate (**2d**) as well as the methyl ether (**2e**) (entries 18 and 21).



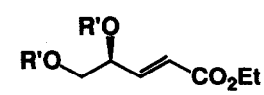
1a; R=neohexyl
1b; R=pentyl
1c; R=2-(1-adamantylethyl)



2E



2Z



2a; R'=TBS
2b; R'=MPM
2c; R'=MOM
2d; R'=Ac
2e; R'=Me

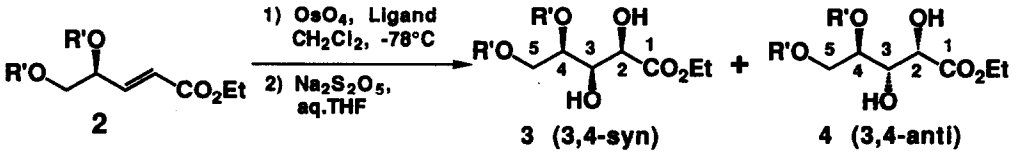


Table 1. Dihydroxylation of chiral α,β-unsaturated esters with a stoichiometric amount of OsO_4-diamine complex.

entry	olefin	ligand	yield(%)	3 : 4[d]
1	**2E**	—[a]	91	1 : 2.3[e]
2		TMEDA[b]	87	1 : 12[e]
3		**1aRR**	96	1 : > 50[e]
4		**1aSS**	95	1.8 : 1[e]
5		**1bSS**	71	1 : 1.1[e]
6		**1cSS**	85	1.1 : 1[e]
7	**2a**	—[a]	98	1 : 6.0[e]
8	**(R'=TBS)**	**1aRR**	97	1 : 9.2[e]
9		**1aSS**	96	2.8 : 1[e]
10	**2b**	—[a]	75	1 : 5.0[f]
11	**(R'=MPM)**	**1aRR**	94	1 : > 20[f]
12		**1aSS**	91	3.3 : 1[f]
13	**2c**	—[a]	73	1 : 3.0[f]
14	**(R'=MOM)**	**1aRR**	84	1 : 14[f]
15		**1aSS**	91	4.7 : 1[f]
16	**2d**	—[a]	79[c]	1 : 4.1[g]
17	**(R'=Ac)**	**1aRR**	97[c]	**1 : 23**[g]
18		**1aSS**	93[c]	**17 : 1**[g]
19	**2e**	—[a]	64	1 : 7.4[h]
20	**(R'=Me)**	**1aRR**	73	**1 : > 50**[h]
21		**1aSS**	72	**15 : 1**[h]
22	**2Z**	—[a]	96	1 : 1.1[e]
23		**1aRR**	98	1 : 1.8[e]
24		**1aSS**	94	1 : 1.1[e]

a) Achiral catalytic conditions [7]: OsO_4 (1-2mol%), NMO (1.2eq), acetone-H_2O, 0°C-rt. b) N,N,N',N'-tetramethylethylenediamine. c) Yield of corresponding tetraacetate. d) See ref 9. e) Determined by HPLC analysis. f) By NMR analysis of the corresponding diacetate. g) By HPLC analysis of the corresponding tetraacetate. h) By HPLC analysis of the corresponding diacetate.

For these last two substrates (**2d** and **2e**), the anti attack of OsO_4-**1aRR** complex was found to be also very high (entries 17 and 20). Thus, the reagent controlled asymmetric dihydroxylation to yield either 2,3-syn-3,4-syn or 2,3-syn-3,4-anti isomer has now been accomplished. To obtain 2,3-anti isomers of **3** and **4**, 2(Z)-pentenoate (**2Z**) was then subjected to the asymmetric dihydroxylation using **1aRR** or **1aSS**. However, **2Z** gave only poor selectivity for either case due to the inherent low selectivity for cis-olefins (entries 23 and 24).[6b]

While the mechanism of osmylation is not clear to date,[10] the diastereoselectivity can be explained by using Kishi's model[2] (Figure 1). The model said that the anti-attack of OsO_4 to the most stable conformer A is preferred under the conditions using achiral reagents due to the steric and electronic effects. Since the OsO_4-**1aRR** complex favored the bottom face attack to the achiral crotonate (Figure 2)[6], the synergistic effect should result in an enhanced anti-selectivities for the reaction of **2** and OsO_4-**1aRR** (matched pair, Figure 1). On the other hand, the top face attack of OsO_4-**1aSS** complex would be hindered by steric repulsion with the sterically demanding allylic substituent (OR').

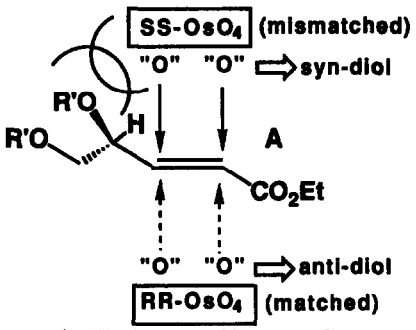


Figure 1. The Model of Reagent Controlled Diastereoselective Dihydroxylation.

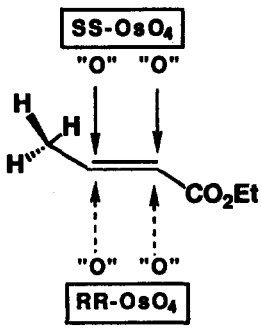


Figure 2. The Enantioface Selection Rule of the Dihydroxylation of Crotonate.

A typical stoichiometric dihydroxylation procedure is as follows: To a stirred solution of **1aRR** (68 mg, 0.22 mmol, 1.2eq) in CH_2Cl_2 (7 mL) was added a solution of OsO_4 (51 mg, 0.20 mmol, 1.1 eq) in CH_2Cl_2 (2 mL) at -78°C. After stirred for 10 min, a solution of olefin **2e** (34 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 1 h at -78°C, and solid $Na_2S_2O_5$ (1.0 g) was added and stirred further for 10 min at -78°C. After the removal of the CH_2Cl_2 in vacuo, THF (7 mL) and water (0.5 mL) were added, and the mixture was refluxed for 3 h. The insoluble materials were removed by filtration through Celite Hyflo Super-Cel® and the filtrate was extracted with ethyl acetate (100 ml), and then washed with 2N HCl (3 mL), satd. NH_4Cl (3 mL), satd. $NaHCO_3$ (3 mL), and satd. NaCl (3 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated, and purified by silica gel column chromatography (hexane-ethyl acetate) afforded the diol (30 mg, 73%).

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8. Olefins **2a-2e** were prepared from **2E** : (i) 1N HCl, THF. (ii) **2a**: TBSCl, imidazole, DMF. **2b**: MPMOC(=NH)CCl_3, H^+, CH_2Cl_2. **2c**: MOMCl, iPr_2NEt, CH_2Cl_2. **2d**: Ac_2O, pyridine, DMAP. **2e**: MeI, Ag_2O, CH_3CN.
9. Stereochemistry of **4E** was unambigously determined by conversion into the known *D*-(+)-arabitol pentaacetate **5**. Products **4E** and **4a-4d** gave an identical butyrolactone triacetate (**6**) which shows characteristic coupling constants, $J_{2,3}$=$J_{3,4}$=7.0Hz. Then we have found a useful emprical rule for a coupling constant difference between the diastereomeric diacetates (**7E**, **7a-7e**) and (**8E**, **8a-8e**): [$J_{2,3}$ (**7**)] > [$J_{2,3}$ (**8**)] ; [$J_{3,4}$ (**7**)] < [$J_{3,4}$ (**8**)] as shown in Table 2.

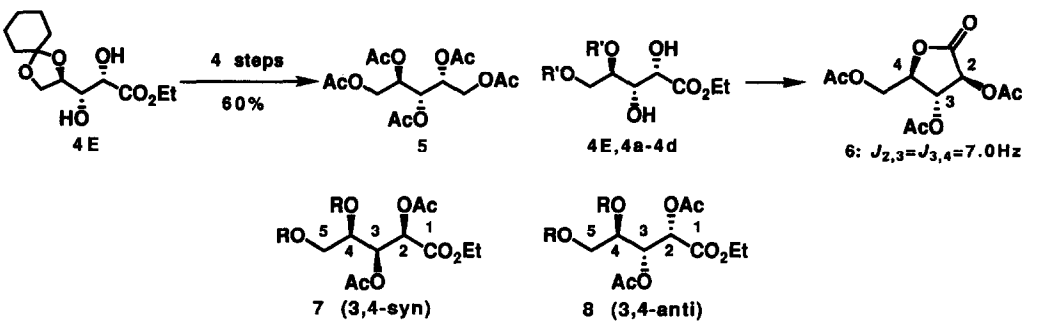

Table 2. ^1H NMR Data of **7** and **8** (200MHz, $CDCl_3$).

	syn (**7**)				anti (**8**)			
	δ (ppm)		*J* (Hz)		δ (ppm)		*J* (Hz)	
	H_2	H_3	$J_{2,3}$	$J_{3,4}$	H_2	H_3	$J_{2,3}$	$J_{3,4}$
E	5.27	5.45	2.9	6.7	5.27	5.41	2.2	7.8
a	5.34	5.45	2.2	7.1	5.25	5.44	1.8	8.3
b	5.19	5.48	3.3	6.4	5.37	5.52	1.8	9.3
c	5.32	5.64	3.0	7.0	5.34	5.57	1.9	9.1
d	5.24	5.61	3.6	6.2	5.29	5.67	2.1	9.2
e	5.26	5.51	3.5	5.7	5.41	5.50	2.1	8.7

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