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Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins Using Chiral Isoxazolidine Ligands

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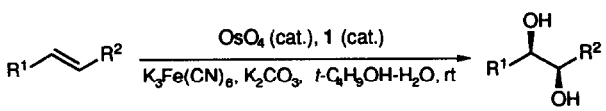
Abstract: *Chiral isoxazolidines, which are readily obtained by 1,3-dipolar cycloaddition of nitrones with olefins, are found to be effective chiral ligands for osmium-catalyzed asymmetric dihydroxylations of olefins.*

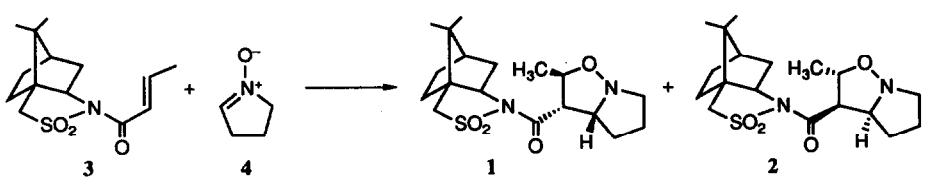
The enantioselective dihydroxylation of olefins promoted by osmium tetroxide has been studied extensively, and highly enantioselective oxidations have been achieved by using some chiral ligands. However, most of the oxidations require stoichiometric amounts of both osmium tetroxide and chiral ligands.[1] Sharpless has demonstrated that highly enantioselective catalytic oxidation proceeds by using naturally occurring amines and modified compounds such as cinchona alkaloids.[2] Therefore, systematic design of artificial ligands is of interest in view of synthetic and mechanistic aspects. Recently Hirama achieved catalytic dihydroxylation with good enantiomeric excess by using chiral DABCO ligands that have C_2 symmetry.[3]

We found that chiral isoxazolidines such as (2*R*,3*S*,4*R*)-*N*-[(2-methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*] isoxazolidin-3-yl)carbonyl]bornane-10,2-sultam (**1**) are highly effective chiral ligands for the osmium-catalyzed asymmetric dihydroxylation of olefins as depicted in eq 1.



(1)

Chiral isoxazolidine ligands can be prepared readily by 1,3-dipolar cycloaddition of nitrones with chiral olefins. Typically, cycloaddition of *N*-[(*E*)-2-butenoyl]bornane-10,2-sultam (**3**) with 1-pyrroline *N*-oxide (**4**)[4] gave a mixture of two diastereomers of isoxazolidines. Pure isoxazolidines **1** ($[\alpha]^{27}_D$ +15.2° (*c* 1.00, $CHCl_3$), mp 163.7–164.4 °C) and **2** ($[\alpha]^{27}_D$ –187° (*c* 1.01, $CHCl_3$), mp 206.9–207.6 °C) were obtained as a single diastereomer by simple recrystallization in 33% and 11% yields, respectively.

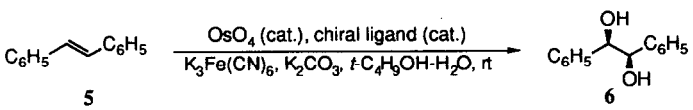


3 **4** **1** **2**

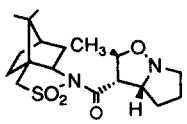
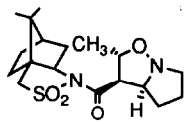
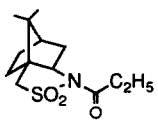
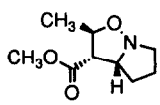
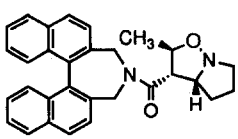
The ligand effect was examined for the OsO_4-catalyzed asymmetric dihydroxylation of (*E*)-stilbene (**5**) in the presence of reoxidant of $K_3Fe(CN)_6$.[5] To a mixture of the chiral isoxazolidine ligand (0.3 equiv), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), and (*E*)-stilbene in *t*-BuOH–H_2O (1:1) was added a 2.0 M toluene solution of OsO_4 (1 mol%) with vigorous stirring, and the mixture was stirred at room temperature for 1 day. After usual workup, *syn*-1,2-diphenyl-1,2-ethanediol (**6**) was obtained in over 99% yield, and the enantiomeric excess of **6** was determined on the basis of ^1H NMR analysis in the presence of Eu(tfc)$_3$ or HPLC analysis on CHIRALCEL OJ.

The representative results of the OsO_4-catalyzed oxidation of (*E*)-stilbene in the presence of various ligands are shown in Table 1. Remarkable rate acceleration was observed, when isoxazolidines **1**, **2**, and **8** were used as ligands. The dihydroxylation of (*E*)-stilbene **5** in the presence of isoxazolidine ligand **1** was completed within 5 h to give (*R*,*R*)-**6** quantitatively with 73% ee, while the dihydroxylation without the ligand proceeds slowly. It is noteworthy that the opposite enantioselectivity was obtained by using chiral ligand **2**. *N*-(Propanoyl)bornane-10,2-sultam (**7**) did not accelerate the oxidation, and no remarkable enantioselection was observed. These results indicate that the isoxazolidine structure is essential for high enantioselectivity.

Table 1. Enantiomeric Excess of the Dihydroxylation of (*E*)-Stilbene (**5**)



5 **6**

entry	ligand		yield, %[a]	ee, %[b]	config.
1		**1**	100	73	R,R
2		**2**	100	73	S,S
3		**7**	73	2	R,R
4		**8**	93	10	R,R
5[c]		**9**	59	62[d]	—

[a]GC yield. [b]Enantiomeric excess was determined by ^1H NMR analysis in the presence of Eu(tfc)$_3$. [c]The relative configration of **9** is not decided except for isoxazolidine ring. [d]Determined by HPLC analysis on CHIRALCEL OJ, eluted with 2% EtOH in *n*-hexane (1 mL / min).

Isoxazolidine **8** gave low selectivity (10% ee), however, isoxazolidine **9** bearing the bulky amide substituent gave noteworthy selectivity (62% ee). These results indicate that bulky substituents at C-3 position of isoxazolidines play an important role for enantioselection.

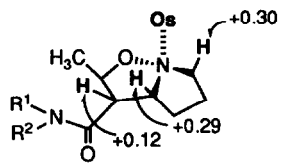
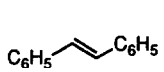
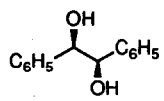
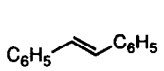
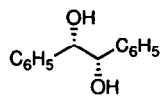
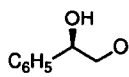
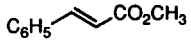
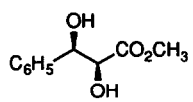
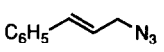
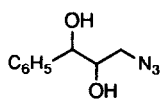
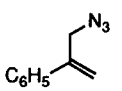
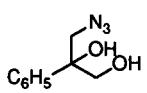
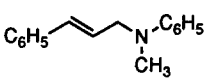
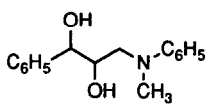


Figure 1. Downfield shifts (ppm) of **1** upon complexation with OsO_4

Coordination of osmium to the nitrogen atom of isoxazolidines is indicated by NMR study. Addition of osmium tetroxide to a solution of ligand **1** in acetone-d_6 resulted in dramatic change in the ^1H and ^{13}C NMR spectra. The noticeable downfield shifts of ^1H NMR (270 MHz) absorptions are shown in Figure 1.

Table 2. Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins by Using Isoxazolidine Ligand **1**

entry	substrate	product	yield, %	ee, %[a]	config.[b]
1			99	73[c]	R,R
2[d]			99	73[c]	S,S
3			99	22	R
4			43	40	2S,3R
5			99	32	—
6			99	33	—
7			99	30	—

[a] Enantiomeric excess was determined by HPLC analysis. [b] The absolute configuration of diol was determined by comparison of optical rotation with the literature value. [c] Enantiomeric excess was determined by ^1H NMR analysis in the presence of $Eu(tfc)_3$. [d] Chiral isoxazolidine **2** was used.

The representative results of the oxidation of olefins with the osmium catalyst bearing **1** are shown in Table 2. Various olefins are converted into the corresponding diols in over 99% yields except for methyl cinnamate (43%). Allylamines and allyl azides, which are prepared readily by palladium-catalyzed reactions of allyl esters,[6] can be converted into the corresponding chiral amino and azido diols in 99% yields with moderate enantiomeric excess.

Isoxazolidines **1** and **2** are found to be good ligands for asymmetric dihydroxylation of olefins. Since various chiral isoxazolidines are prepared readily by cycloaddition of nitrones with olefins, structural modification of chiral nitrogen ligands can be performed readily. Hence, highly enantioselective catalytic dihydroxylation will be explored.

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