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Osmium-Catalyzed Olefin Dihydroxylation and Aminohydroxylation in the Second Catalytic Cycle

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Abstract: Two catalytic cycles operate in the osmium-catalyzed olefin dihydroxylation and aminohydroxylation. Slow hydrolysis of the Os(VI) monoglycolate (or monoazaglycolate in aminohydroxylation) intermediate often results in the addition of another molecule of olefin thereby shunting the catalysis into the second catalytic cycle. As a result, both enantio- and chemoselectivity are reduced. A series of new chelating ligands were devised, which force the catalysis into the second cycle while maintaining enantiocontrol in the olefin addition step. Excellent catalytic turnover and moderate to good enantioselectivity were achieved.

Keywords: alkenes; aminohydroxylations; asymmetric catalysis; dihydroxylations; osmium

Introduction

The cornerstone for catalytic aminohydroxylation was laid in 1975 with the discovery that the *tert*-alkylimido complex of osmium(VIII) adds to olefins and that reductive cleavage of the resulting osmium(VI) azaglycolate yields the corresponding mono-, di-, or trisubstituted *cis*-amino alcohols.[1] The first catalytic version of this reaction was developed soon afterwards, utilizing chloramine-T as both the nitrogen source and the oxidant.[2] It was not until 1996, however, that the crucial importance of a high water content for achieving optimal turnover rates without any additives was recognized, enabling the first catalytic asymmetric aminohydroxylation of an olefin using an excess of chloramine-T and catalytic amounts of $K_2OsO_2(OH)_4$ in the presence of chiral *Cinchona* alkaloid ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$.[3] Given that the vicinal amino alcohol moiety is found in a vast number of natural products and synthetic drugs, it was not surprising that a general method for stereoselective introduction of this functionality into the olefin backbone quickly found many applications.

However, in spite of the great deal of effort that has been devoted to make asymmetric aminohydroxylation (AA) as reliable, versatile and convenient to use as its asymmetric dihydroxylation (AD) counterpart, several problems have limited its utility. Chief among those are (1) selectivities (chemo-, regio-, and enantio-), (2) substrate scope, and (3) catalyst activity. Of these, chemoselectivity is the most serious, for up to 70% of corresponding vicinal diol can be produced in unfavorable cases.[4]

Insights into the mechanism of the AD process provided a foundation for understanding the aminohydroxylation reaction. Most important was the realization that the two processes share a potential for having multiple catalytic cycles, and that these cycles must intersect since both dihydroxylation and aminohydroxylation are simultaneously observed in many cases.

An overall mechanistic pathway for aminohydroxylation, in analogy to that of dihydroxylation,[5,6] is outlined in Scheme 1. Osmium(VIII) trioxoimido species **I** can add to an olefin generating the Os(VI) azaglycolate complex **II**. This step is presumably strongly accelerated by the chiral ligand L, accounting the for asymmetric induction in the process. Complex **II** is then reoxidized to the pivotal Os(VIII) azaglycolate **III**. This species completes the first cycle by hydrolysis, or enters the second cycle by oxidizing another olefin to give bis(azaglycolate) complex **IV**. We propose that the five-coordinate nature of **III** (in contrast to the four-coordinate **I**) provides sufficient electron density at the metal center to allow olefin oxidation to proceed without external ligand. (Indeed, chiral ligands such as those derived from DHQ and DHQD, even in five-fold excess relative to osmium, have no effect on the rate, yield, chemo-, regio- or stereo-

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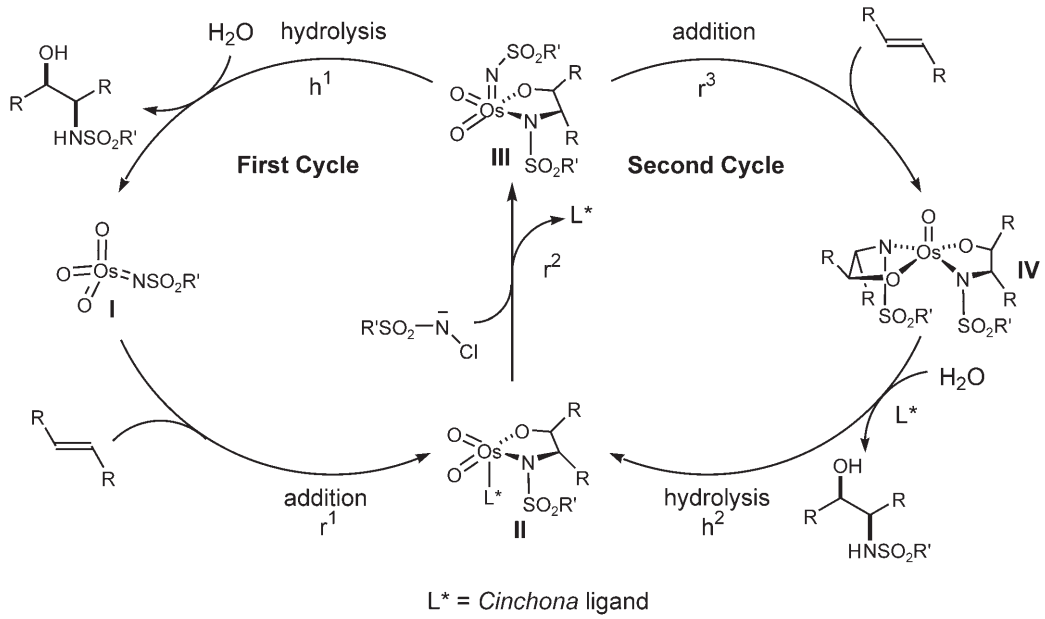

Scheme 1. Two catalytic cycles in aminohydroxylation of olefins.

chemical outcome of the reaction.) Hydrolysis of **IV** restores **II**, completing the second cycle.

An important insight is that for aminohydroxylation reactions, *hydrolysis steps, (h^1 and h^2), are the turnover-limiting events in either catalytic cycle.* This has been demonstrated in several ways, one example being the general observation that aminohydroxylation of a mixture of two olefins invariably proceeds at the same rate as the *slower* substrate alone.[4] In these cases, the resting state of the osmium catalyst is the azaglycolate complex of the slowest substrate, with the overall reaction rate determined by the rate of its hydrolysis.

The second cycle in the Upjohn dihydroxylation [in which the oxidant is an Os(VIII) trioxoglycolate species] was shown to result in low enantiomeric excess of the product diols.[6] This does not mean that it will necessarily be deleterious to aminohydroxylation; indeed, it appears to be the dominant catalytic mechanism for "special " reactions which exhibit unprecedented efficiency (*vide infra*), as well as for dihydroxylation of olefins at low pH with added citric acid.[7]

In the last few years, we have discovered that certain classes of olefins undergo rapid and nearly quantitative conversion to the expected products, vicinal diols or amino alcohols, in the absence of the alkaloid ligand, even with very low catalyst loadings.[7,8] This is in sharp contrast to other olefins, whose turnover is crucially dependent on the ligand-acceleration effect.[9] We grouped these reactions under the general terms "special D" and "special A". Unsaturated carboxylates constitute an extreme example,[10] with turnover rates among the highest observed for any dihydroxylation reported to date.

When "special A" substrates are subjected to the standard conditions for either the osmium-catalyzed dihydroxylation or aminohydroxylation process, only racemic products are formed, even when an enormous excess of the chiral ligand is added. This and other available evidence strongly suggest that these olefins turn over almost exclusively in the second catalytic cycle, in which osmium(VI) bis(azaglycolate) is the most stable intermediate. According to our current mechanistic hypothesis, the resident carboxylate groups ($-COO^-$) in this complex facilitate the rate-determining step, hydrolysis, thereby accounting for the dramatically increased reactivity of these substrates.

In support of the hypothesis that the second cycle is important in aminohydroxylation processes, the osmium(VI) azaglycolate complex **V** (an example of general structure **IV**, Scheme 1) from the catalytic aminohydroxylation of cyclohexene was isolated.[4] The X-ray crystal structure of **V** is shown in Scheme 2. The complex has the expected square-pyramidal structure that is consistent with solution-phase NMR data. Note that, in comparison to the Os(VI) bis(glycolate) species that occupies the same position in the AD second cycle, complex **V** has much greater steric hindrance along the path by which water must approach the only open coordination site of osmium to initiate hydrolysis. The approach of water may also be slowed by the hydrophobic pocket created by the two tosyl groups that point "down" and around the vacant coordination site. These features are consistent with the observation that catalytic aminohydroxylation is generally slower than dihydroxylation, and with the hypothesis that hydrolysis is turnover-limiting.

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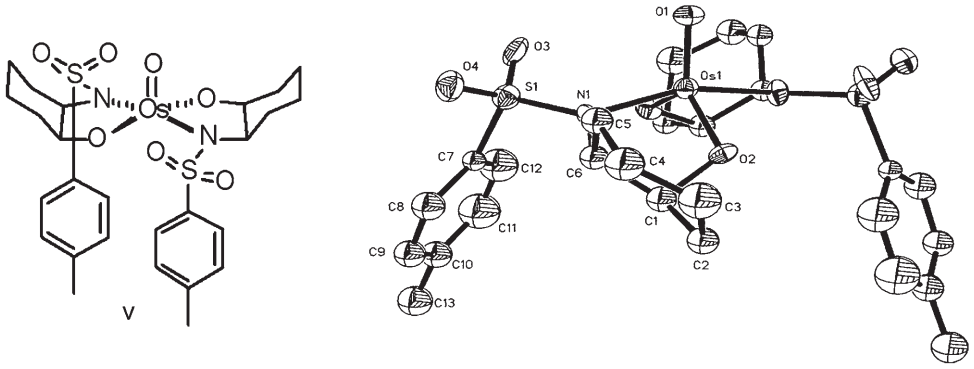
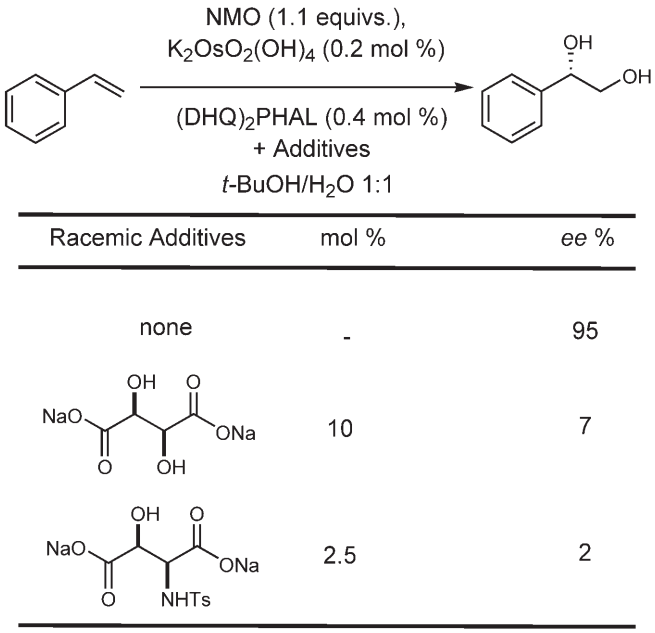


Scheme 2. X-ray crystal structure of osmium bis(azaglycolate) complex **V**.

Although every attempt has been made to avoid the second cycle in the "traditional", *Cinchona* alkaloid-based dihydroxylation and aminohydroxylation, deleterious as it is to enantioselectivity, the enticing possibilities it offers for a new way to control osmium(VIII) catalysis became clear immediately after it was discovered. While the early attempts to design a 2nd cycle ligand were not successful, the recent jump in the effectiveness of the "special A" systems sets the stage for the development of new catalytic processes which take advantage of the unique features of the 2nd catalytic cycle. The idea is simple: the azaglycolate ligand resident on **III** can, in principle, contribute to selectivity in the oxidative addition of the second olefin molecule. As long as the resulting diol or amino alcohol can be hydrolytically released in the next step, the catalysis can be confined to the 2nd cycle. Hence, a successful second cycle ligand should a) be chiral and capable of controlling stereochemistry in the olefin oxidation step r^3; b) aid in the hydrolytic release (h^2) of the diol from the initial Os(VI) product complex (**IV**); and c) not itself be hydrolytically removable from the osmium coordination sphere.[11]

Herein, we offer our account of the development of the first ligands that effect asymmetric osmium-catalyzed dihydroxylation and aminohydroxylation proceeding in the second catalytic cycle.



Racemic Additives	mol %	*ee* %
none	-	95
	10	7
	2.5	2

Scheme 3. Effect of racemic additives on enantioselectivity of asymmetric dihydroxylation (AD) of styrene.

Results and Discussion

The dihydroxylation of styrene under the Upjohn conditions[12] has been chosen as a simple model for screening carboxylate-containing molecules as potential osmium binding ligands. The following two experiments confirmed the viability of our approach.

First, we found that addition of racemic *N*-toluenesulfonyl-2-amino-3-hydroxysuccinate had a marked effect on the level of enantioselectivity achieved in asymmetric dihydroxylations of styrene (Scheme 3). In the absence of any additives, the *R*-configured diol product (95% *ee*) was obtained. However, the inherent, substantial enantioselectivity was destroyed by even small amounts of added racemic hydroxysuccinate salts. Thus, in the presence of 2.5 mol% of *N*-toluenesulfonyl-2-amino-3-hydroxysuccinate, only racemic diols were formed. Even a tartrate salt, albeit to a lesser extent, had an impact at the enantioselectivity of the process. This finding suggests that *N*-toluenesulfonyl-2-amino-3-hydroxysuccinic acid has higher binding constants for osmium than its vicinal diol counterpart, the tartrate, and the *Cinchona* alkaloids, and it is capable of shunting the dihydroxylation process almost exclusively into a 2nd, non-enantioselective catalytic cycle.

Second, aminohydroxylation of stilbene, which does not proceed to any appreciable extent in *tert*-butyl alconol/water (1:1), proceeded to completion in less

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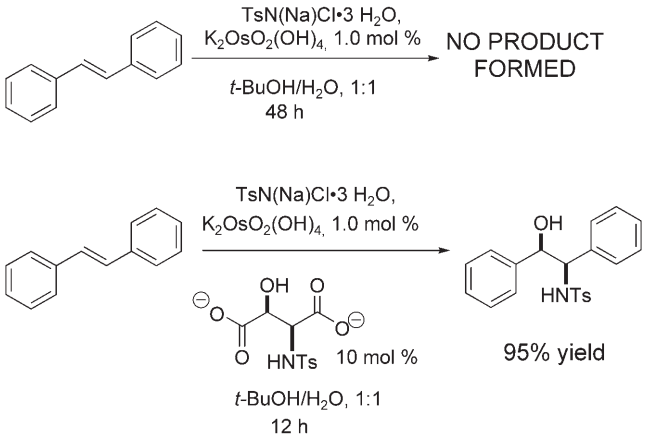

Scheme 4. Aminohydroxylation of styrene: effect of a hydroxysulfonamide ligand. See Supporting Information for details.

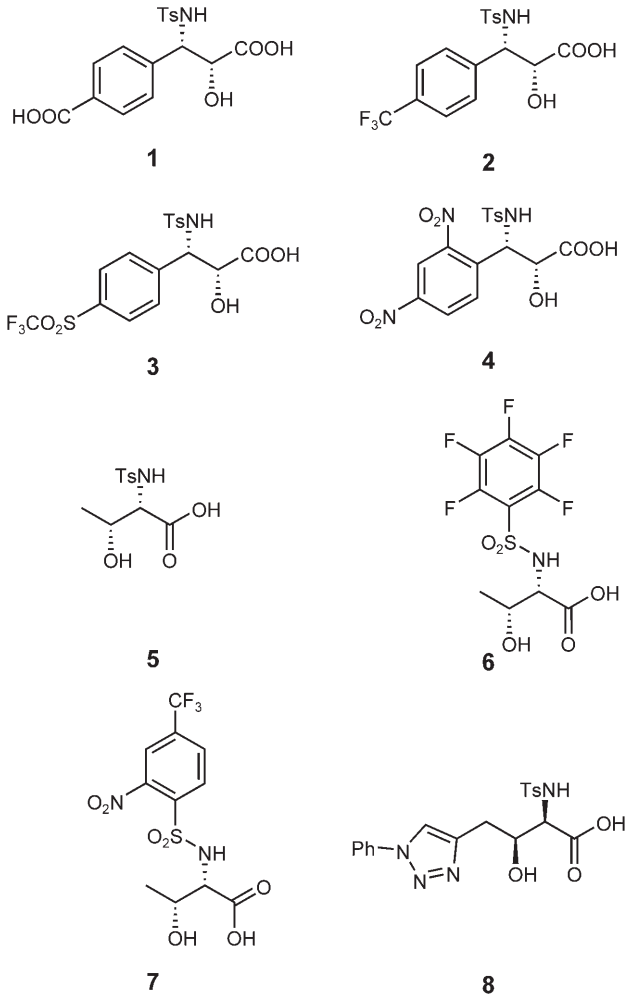

Figure 1. 2nd cycle ligands used in this study.

than 12 h when 5 mol% of *N*-toluenesulfonyl-2-amino-3-hydroxysuccinate was added to the mixture (Scheme 4). Neither its dimethyl ester, nor the *N*-methyl-*N*-toluenesulfonyl analogue had an effect on the reaction. This was the first example of a 1,2-hydroxysulfonamide derivative acting as a 2nd cycle aminohydroxylation ligand.

We, therefore, focused our initial search for the 2nd cycle ligand on the *N*-sulfonyl-α,β-hydroxyamino acids. Readily available starting materials and simple synthetic strategies for the introduction of vicinal hydroxysulfonamide moiety in enantiomerically enriched form allowed the preparation of a library of *N*-(sulfonyl)-isophenylserine and *N*-sulfonylthreonine derivatives (a representative subset is shown in Figure 1).

The effects of these new ligands were first tested in the dihydroxylation of styrene under the Upjohn conditions. Although ligand **1**, derived from *p*-carboxy-substituted *N*-(4-*t*oluenesulfonyl)-isophenylserine, resulted in low enantioselectivity (13% *ee*; Table 1, entry 1), introduction of a more electron-withdrawing trifluoromethyl substituent in the *para*-position (ligand **2**) led to higher enantioselectivity (30% *ee*; Table 1, entry 2). Use of an analogous *para*-trifluoromethylsulfonyl derivative **3** resulted in further improvement of enantioselectivity (44% *ee*; Table 1, entry 3), as did replacement of the *para*-carboxylate group with two nitro substituents in the 2- and 4-positions (58% *ee*; Table 1, entry 4). A similar trend was observed with 2-vinylnaphthalene, methyl cinnamate and methyl (*para*-nitro)cinnamate as substrates (Table 1). Only racemic diols were obtained when methyl esters of ligands **1**–**4** were employed, thus confirming that a free carboxylate was an essential component of a 2nd cycle ligand.

Further investigations have shown that when applying *N*-sulfonylthreonine derivatives as ligands, modification of the substituents on the sulfonamide group ($R\text{-}SO_2NH$-) had only a minor effect on the stereochemical outcome of the reaction. Incorporation of electron-withdrawing groups did not necessarily increase enantioselectivity (Table 1, entry 12 vs. entry 11; entry 18 vs. entry 17). Decreased *ee*s in dihydroxylation of all cinnamate derivatives were observed when an *ortho*-nitro substituent was introduced (ligand **7**), which might be explained by a more crowded environment at the osmium coordination sphere created by an *ortho* substituent which sterically hinders the approach of an olefin.

Next, the effects of these new second cycle ligands on the osmium-catalyzed aminohydroxylation of styrene and methyl cinnamate were tested. We were pleased to find that both substrates were converted to the corresponding hydroxysulfonamides in high yields, albeit with modest *ee* values ranging from 14 to 84% (Table 2). Importantly, and in contrast to the AA with alkaloid ligands, significantly lower loading of osmium catalyst was required (1.0 mol% as opposed to 4–5 mol%), and no diol formation was ob-

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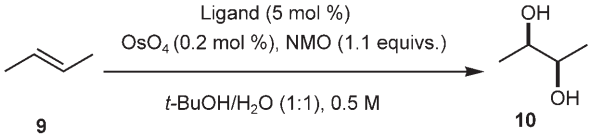
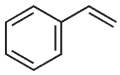
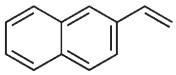
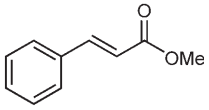
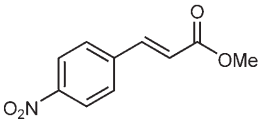
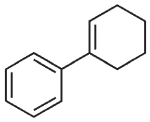
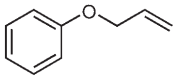
Table 1. Osmium-catalyzed dihydroxylation of olefins with second cycle ligands.[a]



Entry	Olefin	Ligand	Yield [%]	*ee* [%] (absolute configuration)[b]
1		**1**	74	13 (*R*)
2		**2**	87	30 (*R*)
3		**3**	90	44 (*R*)
4		**4**	89	58 (*R*)
5		**1**	92	8 (*R*)
6		**2**	88	55 (*R*)
7		**3**	98	70 (*R*)
8		**4**	93	69 (*R*)
9		**2**	96	54 (2*S*,3*R*)
10		**3**	98	70 (2*S*,3*R*)
11		**5**	93	51 (2*R*,3*S*)
12		**6**	91	59 (2*R*,3*S*)
13		**7**	94	37 (2*R*,3*S*)
14		**8**	95	55 (2*S*,3*R*)
15		**2**	93	49 (2*S*,3*R*)
16		**3**	89	61 (2*S*,3*R*)
17		**5**	92	70 (2*R*,3*S*)
18		**6**	90	65 (2*R*,3*S*)
19		**7**	89	35 (2*R*,3*S*)
20		**8**	90	52 (2*S*,3*R*)
21		**4**	92	74 (1*R*,2*R*)
22		**4**	90	42 (*S*)

[a] All reactions were performed on a 1 mmol scale at 0.5 M concentration in *t*-BuOH/H_2O (1:1) with 1.1 equivs. NMO and 0.2 mol % of OsO_4. The progress was monitored by GC, and *ee* values were determined by HPLC [diols from styrene, Chiralcel OB, 10 % *i*-PrOH/hexane, 13.4 min (*R*), 16.9 min (*S*); diols from 2-vinylnaphthalene, Chiralcel OJ, 8 % *i*-PrOH/hexane, 21.8 min (*R*), 25.6 min (*S*); diols from methyl cinnamate, Chiralcel OB, 10 % *i*-PrOH/hexane, 20.2 min (2*R*,3*S*), 21.6 min (2*S*,3*R*); diols from methyl *p*-nitrocinnamate, Chiralcel OG, 20 % *i*PrOH/hexane, 12.1 min (2*S*,3*R*), 18.3 min (2*R*,3*S*); diols from 1-phenyl-1-cyclohexene, Chiralcel OJ, 2 % *i*-PrOH/hexane, 26.7 min (*S*,*S*), 37.6 min (*R*,*R*); diols from allyl phenyl ether, Chiralcel OD, 10 % *i*-PrOH/hexane, 18.9 min (*R*), 37.6 min (*S*)].

[b] The absolute configurations of diols were assigned by comparison with authentic samples.

served. The products were isolated as white solids, visually free of osmium contamination. In the aminohydroxylation of styrene, ligands bearing electron-withdrawing substituents gave higher levels of enantioselectivity (Table 2, entry 2, 3 vs. 1). Threonine derivative **6** gave the highest *ee* of 70 % for the major regioisomer (Table 2, entry 5). On the contrary, in the aminohydroxylation of methyl cinnamate, threonine-derived ligands gave lower level of asymmetric induction comparing to the *N*-(4-*t*oluenesulfonyl)-isophenylserine derivatives (Table 2, entries 9 and 10 vs. 7 and 8).

Conclusions

In summary, a series of *N*-sulfonyl-α,β-hydroxyamino acid-based ligands has been synthesized and studied in osmium-catalyzed dihydroxylation and aminohydroxylation of olefins. Although enantioselectivity

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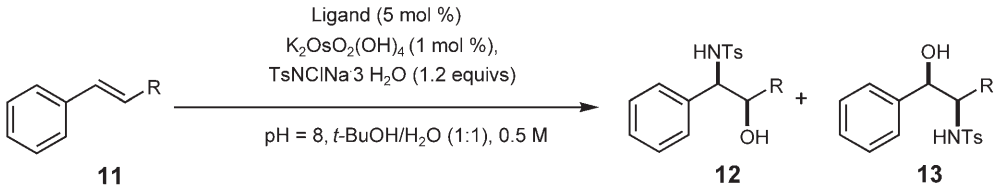
Table 2. Osmium-catalyzed aminohydroxylation of olefins with second cycle ligands.



Entry	R	Ligand	Yield [%]	Ratio (**12:13**)	*ee* of **12** (absolute configuration)[b]	*ee* of **13** (absolute configuration)[b]
1	H	**1**	90	1:1.0	24 (*S*)	18 (*R*)
2	H	**2**	92	1:2.0	55 (*S*)	54 (*R*)
3	H	**4**	92	1:2.0	43 (*S*)	55 (*R*)
4	H	**7**	94	1:2.0	72 (*S*)	40 (*R*)
5	H	**6**	92	1:2.0	84 (*S*)	70 (*R*)
6	H	**8**	92	1.1.8	44 (*R*)	13 (*S*)
7	COOMe	**2**	94	1:2.0	54 (*2S,3R*)	54 (*2R,3S*)
8	COOMe	**4**	94	1:2.0	49(*2S,3R*)	20 (*2R,3S*)
9	COOMe	**6**	90	1:3.0	14(*2S,3R*)	40 (*2R,3S*)
10	COOMe	**7**	89	1:3.0	15 (*2S,3R*)	19 (*2R,3S*)
11	COOMe	**8**	91	1:3.0	37 (*2R,3S*)	27 (*2S,3R*)

[a] The regioisomers were separated by reversed-phase preparative liquid chromatography and the *ee* values were determined for each regioisomer separately [R = H, **12**: Chiralcel OG (30% *i*-PrOH in hexane), 5.3 min (*R*), 7.2 min (*S*); **13**: Chiralpak AS (15% *i*-PrOH in hexane), 17.7 min (*R*), 24.0 min (*S*); R = $COOCH_3$, **12**: Chiralcel OG (30% *i*-PrOH in hexane), 11.2 min (2*R*,3*S*), 14.4 min (2*S*,3*R*); **13**: Chiralpak AD (20% *i*-PrOH in hexane), 8.4 min (2*S*,3*R*), 14.6 min (2*R*,3*S*)].

[b] The absolute configuration of the products was assigned by comparison with authentic samples.

was good to moderate, excellent catalytic turnover, resulting in high yields, was observed. Much lower loading of osmium catalyst was required, and no diol by-products were detected in the aminohydroxylation reactions. Products were isolated free of osmium contamination. Further studies on kinetics and mechanism of olefin aminohydroxylation in the presence of the second cycle ligands as well as combinatorial approaches for new ligand discovery are ongoing in our laboratory.

Experimental Section

Typical Dihydroxylation Procedure as Exemplified for Methyl 4-Nitrocinnamate

Methyl 4-nitrocinnamate (207 mg, 1 mmol) and *N*-(4-toluenesulfonyl)-L-threonine (13.6 mg, 5 mol%) were dissolved in a *t*-BuOH/H_2O mixture (1:1, 2 mL). NMO (50 wt% in water, 228 μL, 1.1 mmol) and OsO_4 (0.1 M in acetonitrile, 20 μL, 0.002 mmol) were added successively. The pH was adjusted to 5 by addition of 2 N H_2SO_4 (150 μL), and the reaction mixture was stirred vigorously for 24 h, at which time the pH was adjusted to 5 again. After an additional 12 h (>95% conversion by liquid chromatography), 1 mL saturated solution of Na_2SO_3 was added. The reaction mixture was stirred for another 5 min before *t*-BuOH was evaporated. The residue was diluted with 100 mL ethyl acetate and washed with 15 mL HCl (2 M) and 2×20 mL saturated $NaHCO_3$ solution sequentially. After drying with $MgSO_4$ and evaporation of the solvents, methyl (2*R*,3*S*)-(+)-2,3-dihydroxy-3-(*p*-nitrophenyl)-propionate was obtained in 70% *ee* (HPLC: Chiralcel OG, 20% *i*-PrOH/hexane). The reaction time can be reduced to about 24 h by maintaining constant pH using a pH-stat. A 10 mmol scale reaction, performed under these conditions, afforded product as white solid in 75% yield (1.8 g) and 70% *ee*. Recrystallization from ethanol produced needle-shaped crystals in 57% yield and 81% *ee*.

Typical Aminohydroxylation Procedure as Exemplified for Styrene

(2*R*,3*S*)-*N*-(4-Toluenesulfonyl)-2,4-dinitroisophenylserine (212 mg, 0.5 mmol) and sodium bicarbonate (42 mg, 0.5 mmol) were dissolved in *t*-BuOH/H_2O (1:1, 20 mL). Styrene (1.040 g, 10 mmol), chloramine-T trihydrate (2.870 g, 10 mmol), and $K_2OsO_2(OH)_4$ (36 mg, 0.1 mmol) were then added successively. The reaction mixture was stirred at room temperature for 20 h, at which point LC-MS analysis indicated 90% conversion. Sodium sulfite (100 mg) was added, and the mixture was stirred for an additional hour. It was then extracted (ethyl acetate, 3×25 mL), dried over anhydrous sodium sulfate, and concentrated to yield an amorphous solid. Flash chromatography purification afforded a mixture of regioisomers **12:13** (32:68, determined by ^{1}H NMR) as a white crystalline product (2.5 g, 86%). Regioisomers were separated by preparative HPLC [CH_3CN/H_2O, 30:70, 0.1% trifluoroacetic acid (TFA), YMCC18 column, 100 mg scale]. Enantiomeric excess was determined

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by chiral HPLC and the absolute configuration was established by comparing optical rotation with authentic samples. (*S*)-**12**, 43% *ee* (Chiralcel-OG, *i*-PrOH/hexane, 30:70, 1.5 mL min^{-1}) and (*R*)-**13**, 55% *ee* (Chiralcel-AS, *i*-PrOH/hexane, 30:70, 1.5 mL min^{-1}).

X-Ray Crystallographic Study

The synthesis and X-ray crystallographic study of complex **V** can be found in the Supporting Information. Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-267259. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

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