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DIASTEREOSELECTIVITY IN THE OSMIUM-CATALYZED DIHYDROXYLATION OF ALLYLIC AMIDES AND CARBAMATES

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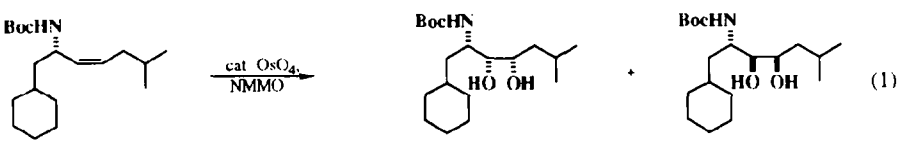
Abstract: The stereochemistry of the osmium-catalyzed dihydroxylation of a series of chiral allylic amides and carbamates has been studied. The diastereoselectivity of these reactions was found to be dependent upon the solvent and the nitrogen protecting group as well as the geometry and substitution pattern of the olefin substrate. In contrast to the erythro selectivity observed with allylic alcohols, osmylations of the allylic amides and carbamates in this study were threo selective. Stoichiometric osmylations were consistently more selective than the corresponding catalytic reactions. Control experiments suggest this is due to the presence of a second catalytic cycle based upon an osmium glycolate catalyst which accumulates as the reaction proceeds to completion. Double diastereoselective dihydroxylations of allylic carbamates were also briefly examined.

Introduction

π-Facial diastereoselection in the addition reactions of chiral, allylically functionalized alkenes is a phenomenon of both synthetic and theoretical importance.[2] Recent work in a number of laboratories with a wide range of substituted allylic alkenes has resulted in a variety of synthetically useful transformations[3] as well as contributed to our fundamental understanding of the factors which govern the stereoselectivity of these processes.[4]

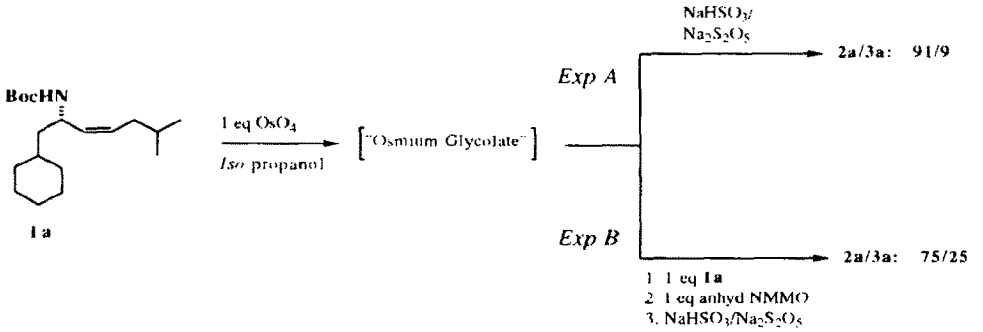
Although the π-facial diastereoselection of alkenes containing allylic heteroatoms has, in general, been well studied, the reactions of allylic amines have only recently come under scrutiny. The emergence of the allylic amine substrate in this context has mainly been due to its role in the stereocontrolled synthesis of various amino-alcohols and amino-polyols related to amino-sugars,[5] unusual amino-acids[6] and peptidomimetic enzyme inhibitors.[7] As a result, a growing body of data concerning the stereochemistry of allylic amine epoxidation,[8] dihydroxylation,[9] oxygenation,[10] hydroboration[11] and halogenation[12] has begun to appear in the literature. With this in mind, we now report the results of our study of the stereochemistry of the osmium-catalyzed dihydroxylation of a series of chiral, allylic secondary amides and carbamates.

Results

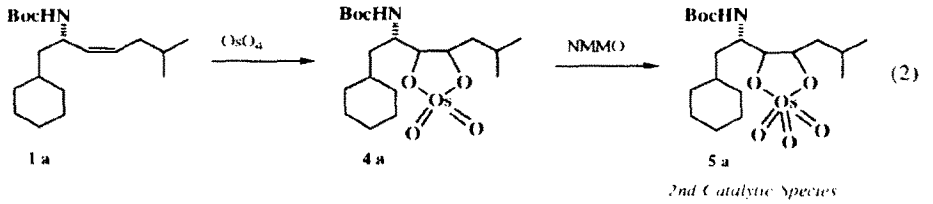


Our interest in this area grew out of a need to optimize the dihydroxylation of **1a** as an approach to the synthesis of the protected dihydroxyethylene dipeptide isostere **2a**.[13] Under standard conditions[14] (eq 1), the process was essentially unselective. Fortunately, simply changing the solvent to *iso*-propanol and limiting the amount of water to that associated with the stoichiometric oxidant (*N* methyl-morpholine *N*-oxide hydrate, NMMO) improved the selectivity of the reaction for the desired threo diastereomer **2a** to a respectable 82/18.[15]

Scheme 1. Stoichiometric and Two Cycle Catalytic Experiments.



In the course of our optimization studies, we observed that at low conversions the threo/erythro ratio of the product was quite high (*ca.* 8-9/1) and that this ratio deteriorated as the reaction proceeded to completion. In order to gain insight into the origin of this behavior, a stoichiometric osmylation of **1a** was performed (Scheme 1, Exp A) and found to give the threo diastereomer in a greatly increased 91/9 ratio. A likely explanation for this conversion-dependant reduction in selectivity was suggested by the recent work of Sharpless and co-workers.[16] In the course of their development of the cinchona alkaloid-based asymmetric dihydroxlation (A.D.) technology, Sharpless identified a second catalytic cycle based upon osmium glycolate species such as **5a**. These complexes apparently arise when oxidation of the osmium adduct **4a** successfully competes with its hydrolysis (eq 2).[17]



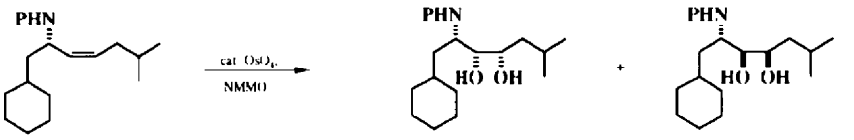
(2)

Experiment B was performed to test the validity of the osmium-glycolate hypothesis.[16] As shown in Scheme 1, osmylation of **1a** under anhydrous conditions (to insure minimal hydrolysis of the putative osmium-glycolate **4a**) followed by oxidation with anhydrous NMMO and treatment with a second equivalent of **1a** led to the isolation of a 75/25 mixture of diastereomers **2a** and **3a**. This corresponded to a second dihydroxylation reaction which proceeds with a 60/40 threo/erythro selectivity. Based upon this experiment it seems likely that a complex related to **5a** could be responsible for the reduced selectivity of the catalytic reaction relative to the stoichiometric counterpart. Unfortunately, adoption of procedures developed by Sharpless to suppress this second catalytic cycle did not improve the selectivity of the catalytic reaction.[16, 18]

As an alternate approach to improving the selectivity, a series of substrates with different nitrogen protecting groups was surveyed (Table 1). Although our initial choice of protecting group proved to be optimal, two interesting trends were observed. As is evident from entries 1-3, carbamate protected allylic amines gave experimentally identical selectivities regardless of steric bulk. Conversely, amide protecting groups displayed significant steric effects. Acetamide **1d** (entry 4) gave poor selectivity while the more bulky trichloroacetamide **1e**[19] gave an improved threo/erythro ratio of 75/25 (entry 5). The highly hindered pivalamide substrate **1f** was

osmylated with a selectivity (entry 5) comparable to that observed with the carbamate substrates. In the three cases examined, stoichiometric osmylations were more selective than the corresponding catalytic reactions.[20] From these data, it appears that carbamate derivatives are the substrates of choice for threo selective osmium-catalyzed dihydroxylations of (Z)-allylic amines.

Table 1. Effect of Nitrogen Protecting Group on Diastereoselectivity.



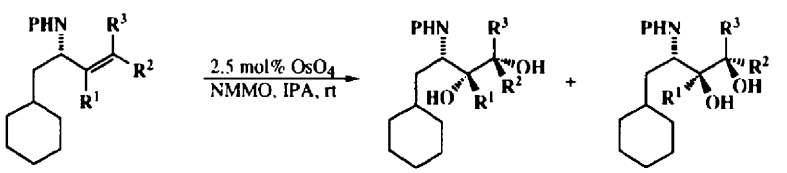
1 2 threo 3 erythro

Entry	Substrate	P	Product	2/3, Cat[a]	2/3, Stoich[b]
1	**1a**	*t*-BuOC(O)	**2a/3a**	82/18	91/9
2	**1b**	BnOC(O)	**2b/3b**	80/20	–
3	**1c**	EtOC(O)	**2c/3b**	82/18	–
4	**1d**	MeC(O)	**2d/3d**	60/40	75/25
5	**1e**	$Cl_3C(O)$	**2e/3e**	75/25	–
6	**1f**	*t*-BuC(O)	**2f/3f**	83/17	89/11

[a] 2.5 mol% OsO_4, 2.5 equiv NMMO, *iso*-propanol, 0 °C to rt, 18 hr, 75-80% yield of a mixture of **2/3**.
[b] 1.0 equiv OsO_4, *iso*-propanol, 0 °C to rt, 4 h.

Since no systematic study of the effects of olefin substitution on the diastereoselective osmium-catalyzed dihydroxylation of allylic amine derivatives has been reported, we also examined a series of *tert*-butyl carbamate protected allylic amines under our optimized conditions. As shown in Table 2, only the previously mentioned (Z)-olefin **1a** (entry 1) gave good simple diastereoselectivity. Not surprisingly, the corresponding (*E*)-isomer **1g** reacted with poorer selectivity (entry 2); the major isomer, again, was the threo diol **2g**. The 1,1-disubstituted substrate **1h** (entry 3) reacted with a slight preference for the threo isomer (*vide infra*) as did the monosubstituted olefin **1i**.

Table 2. Effect of Olefin Substitution and Geometry on Diastereoselectivity



1a,g-i **2a,g-i** threo **3a,g-i** erythro

Entry	Substrate	R^1	R^2	R^3	Product	2/3
1	**1a**	H	H	*i*-Bu	**2a/3a**	82/18
2	**1g**	H	*i*-Bu	H	**2g/3g**	66/35
3	**1h**	Me	H	H	**2h/3h**	57/43[a]
4	**1i**	H	H	H	**2i/3i**	60/40

[a]Stereochemistry tentatively assigned by analogy.

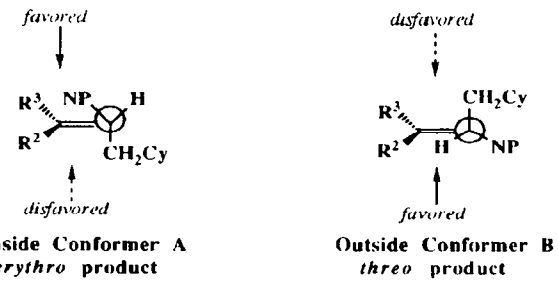
Sharpless A.D. conditions[18b] were also examined but double diastereoselective[21] dihydroxylation was successful only in the case of (*E*)-substrate **1g**.[22] Use of a quinidine-derived ligand gave the threo diastereomer **3g** in a matched pair reaction (86/14) while the corresponding erythro diastereomer could be selectively generated (75/25) in the mismatched case by use of a quinine-derived ligand. Use of these conditions with the other substrates in Table 2 gave selectivities that were either unchanged or reduced when compared to the simple OsO_4 catalyzed reactions.

Discussion

The consistent threo selectivity observed for the allylic carbamates and amides in this study is somewhat unusual since very few examples of threo selective osmylations involving olefins bearing allylic heteroatoms have been reported.[23] The vast majority of reported examples show moderate to excellent erythro selectivity depending upon the exact nature of the substrate.[20,23,24] Indeed, previous examples of osmium-catalyzed dihydroxylations of acyclic allylic amides have also been erythro selective reactions (selectivites ranging from 60/40 to 80/20, erythro/threo).[9] Although any rigorous mechanistic or theoretical examination of this system is fraught with dangers, the trends for the diastereoselectivity in the osmylation of allylic carbamates and amides may be rationalized through a consideration of the "inside alkoxy" or "perpendicular" transition state model for stereoselective transformations of olefins containing allylic heteroatoms.[3c,4a,23,25]

Based on the above transition state models, the two lowest energy conformations for electrophilic addition to **1a-i** are proposed to be conformers **A** and **B** (figure). The OsO_4L species is envisioned to attack antiperiplanar to the σ-donating, and sterically bulky, cyclohexylmethyl substituent. Additionally, the electronic deactivation of the olefin is minimized in **A** and **B** since efficient overlap between the electron withdrawing, σ* orbital of the C-N bond and the π-system of the olefin is avoided.

Figure. Conformational Analysis of *Threo*-Selectivity



Inside Conformer A ***erythro*** **product**

Outside Conformer B ***threo*** **product**

Calculations by Houk[4a,b] indicate that, in the absence of strong steric considerations, "inside" conformer **A** is the more stable structure, since the deactiviting C-N bond is nearly coplanar with the olefin. But, as the steric demands of the system increase, it is expected that "outside" confomer **B** would begin to predominate by virtue of reduced $A^{1,3}$ interactions with the olefin R^2 substituent (NP-R^2 *vs* H-R^2).[4a,23] As shown in the figure, the "inside" conformer **A** would lead to an erythro amino-diol while the "outside" species **B** would provide the threo product.

An examination of the data for allylic amide osmylation (data from this study as well as that from previous work in other labs[9]) within the context of this model proves particularly illustrative. For the relatively unhindered (*E*)-allylic amides,[26] the electronic stablility of **A** appears to slightly outweigh the steric liabilities and

leads to a marginally erythro selective reaction. However, upon moving to a more hindered (*Z*)-allylic amide, increased $A^{1,3}$ interactions induce a crossover to a threo selective reaction via conformer **B**. As the steric bulk of the amide protecting group increases (Table 1 entries 4-6), conformer **A** is destablized further, leading to a corresponding increase in threo selectivity.

Apparently, the carbamate substituents are quite bulky regardless of the steric nature of their alkoxy moieties and, thereby, force the molecule to consistently adopt the outside conformation **B**. As demonstrated by entries 2-4 in Table 2, the carbamate function is large enough to slightly disfavor the inside conformation even when the R^2 substituent of the olefin is hydrogen. Consequently, electronic factors never completely overcome the steric interactions and, although the threo selectivity decreases significantly for these substrates, crossover to an erythro selective process in the carbamate series is not observed.

Conclusions

As a result of our investigations the following conclusions may be drawn with respect to the diastereoselectivity of the osmium-catalyzed dihydroxylation of allylic amides and carbamates: 1) threo amino-diols are the major products of the osmylation of allylic carbamates; 2) (*Z*)-allylic amides are also threo selective with substrates containing bulky amide groups giving the best ratios; 3) as a result of the apparent *in situ* generation of a second, poorly selective osmium glycolate catalyst, stoichiometric osmylations give consistently higher diastereoselectivities than the corresponding catalytic reactions; 4) the perpendicular transition state model may be used to rationalize the general trends for the observed diastereoselectivites. It is hoped that these observations will be of use to those interested in the synthesis of amino-diols as well as to those interested in the stereocontrolled functionalization of alkenes bearing allylic substituents.

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EXPERIMENTAL

General. Solvents and reagents were obtained from commercial sources and were used as received without further purification. Reaction temperatures refer to bath temperatures. Gas chromatograms were recorded on a Hewlet Packard HP 5890 instrument equipped with an Alltech AT-1 column. Determinations of enantiomeric purity based on chiral HPLC were made on a Spectra Physics SP8800 instrument using a Regis Pirkle Covalent D-2-napthylalanine column. ^1H and ^{13}C NMR were recorded on a GE QE300 spectrometer at 300 MHz and 74.8 MHz respectively and are referenced to internal TMS (0.00 ppm). All allylic amine substrates and amino-diol products were characterized spectroscopically (^1H and ^{13}C NMR, IR, and MS). All diastereomer ratios were determined by GC analysis of crude reaction products. The stereochemistry of diols **2,3a-g** were assigned by correlation with the free amino-diol compound. Diols **2i** and **3i** are known compounds and the stereochemistry was assigned by comparison to literature data.[13] The stereochemistry of diols **2h** and **3h** has not been rigorously established and has been tentatively assigned by ^1H NMR and chromatographic (GC, TLC) comparison to the related diols **2i** and **3i**.

Represenatative Procedure for Synthesis of Boc-Protected Allylic Amines: (2*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-amino-1-cyclohexyl-6-methyl-3(*Z*)-heptene (1a).[27] A 500 mL round bottom flask equipped with a nitrogen inlet, an addition funnel, a thermometer, and a magnetic stirbar was charged with isoamyltriphenylphosphonium bromide (44.2 g, 0.11 mol, 1.3 equiv) and tetrahydrofuran (100 mL). The suspension was cooled with an ice/methanol bath to an internal temperature of −10°C before being treated with solid potassium *tert*-butoxide (13.8 g, 0.123 mol, 1.5 equiv). The reaction mixture turned deep red and was stirred at 10°C for 6 h. The mixture was then treated with a tetrahydrofuran (50 mL) solution of (*S*)-*N*-(BOC)-cyclohexylalaninal[26] (20.9 g, 0.082 mol, 1.0 equiv) in a dropwise fashion over a 0.5 h period (internal temperature was maintained below 0°C). The reaction was judged complete after 0.5 h by GC analysis for disappearance of starting material. The mixture was poured into ice cold 20% aqueous citric acid (200 mL) and allowed to warm to room temperature. The mixture was extracted with heptane (300 mL) and the organic layer was washed with 90/10 dimethylformamide/water solution (3 X 150 mL). The resulting heptane extracts were concentrated to give **1a** (18.0 g, 71%, 35:1 mixture of *Z*:*E* isomers) as an off white, waxy solid. mp 55°C. $[\alpha]^{25}_{D}$ = +48.8 (c = 1, CH_3OH). GC retention time: 5.75 min, 100°C-250°C/20°C/min. TLC. R_f = 0.70, 50/50 EtOAc/Heptane, Ce^{IV}. ^1H NMR ($CDCl_3$): δ 5.45 (d of t, 1H, *J* = 10.8, 7.5, 1.5 Hz) 5.18 (q of t, 1H, *J* = 15.0, 9.0, 7.5, 1.5 Hz), 4.50-4.30 (overlapping multiplets, 2H), 2.03 (t, 2H, *J* = 9.0, 7.5 Hz), 1.80 - 1.55 (multiplet, 7H), 1.43 (s, 9H), 1.30-1.10 (m, 7H), 0.91 (d, 3H, *J* = 3.0 Hz), 0.85 (d, 3H, *J* = 3.0 Hz). ^{13}C NMR ($CDCl_3$) δ 131.80, 130.76, 78.57, 45.41, 44.2, 36.79, 34.17, 33.53, 33.51, 31.75, 28.59, 28.45, 28.25, 26.57, 26.28, 22.41, 22.33, 22.14. IR ($CDCl_3$): 3346, 2975, 2899, 1703, 1517, 1458, 1370 cm^{-1}. LRMS *m/z* 310 (M+1), 271 (100), 254, 210. HRMS (FAB) Calc'd for $C_{19}H_{36}NO_2$: 310.2745; Found: 310.2835.

Representative Conversion of (1a) to Amide or Carbamate Protected Allylic Amines (1b-f): (2*S*)-*N*-(Trimethylacetyl)-2-amino-1-cyclohexyl-6-methyl-3(*Z*)-heptene (1f). A 1L 3 neck round bottom flask was charged with **1a** (12.0 g, 0.04 mol, 1.0 equiv) and treated with a 4/1 (v/v) solution of acetic acid/hydrochloric acid (200 mL) and stirred for 1 h. At this time no starting material was evident by TLC or GC analysis. The solution was diluted with water (200 mL) and ice was added. The pH of the solution was carefully adjusted above 12 with 50% aqueous sodium hydroxide. Once cooled, the mixture was extracted with dichloromethane (2 x 200 mL) and the combined organic layers were washed with water (150 mL) and brine (150 mL) before being dried (sodium sulfate) and concentrated to a thick oil. The oil was immediately dissolved in dichloromethane (150 mL) and treated with triethylamine (5.0 g, 0.06 mol, 1.5 equiv) and trimethylacetyl chloride (3.28 g, 0.04, 1.0 equiv). The stirred mixture was then treated with a catalytic amount of *N*,*N*-dimethylamino-pyridine (ca. 300 mg) and allowed to stir for 2.5 h. GC showed no remaining free amine and the reaction was poured into a stirred solution of 10% citric acid (200 mL). The organic layer was removed and washed with an additional portion of 10% citric acid (150 mL), water (150 mL) and finally brine (150 mL). The resulting reddish solution was dried (sodium sulfate) and concentrated to give **1f** as an off-white solid (6.9 g, 81%). GC retention time: 6.76 min, 100°C-250°C/20°C/min. TLC: R_f = 0.56, 50/50 EtOAc/Heptane, Ce^{IV}. ^1H NMR ($CDCl_3$) δ 5.49 (1H, d of t of d, *J* = 12.0, 10.5, 7.5, 1.5 Hz), 5.38 (1H, broad d), 5.20 (1H, t of t, *J* = 12.0, 9.0, 1.5, 1.0 Hz), 4.78 (1H, m), 2.07 (2H, t of d, *J* = 9.0, 7.5, 1.0 Hz), 1.80-1.60 (7H, m), 1.43 (1H, m), 1.30-1.20 (6H, m), 1.16 (9H, s), 0.89 (6H, d, *J* =7.5 Hz).^{13}C NMR ($CDCl_3$) δ 200.2, 131.69, 130.98, 44.30, 43.60, 38.49, 34.37, 33.46, 33.19, 28.50, 27.55, 26.46, 26.17, 22.29. IR (KBr) 3440, 3300, 2960, 2920, 2870, 2850, 1625, 1530. LRMS *m/z* 293 (M), 278, 250, 222, 210, 196, 102, 57 (100). HRMS (FAB) Calc'd for $C_{19}H_{35}NO$: 293.2719; Found: 293.2718

General Osmium-Catalyzed Dihydroxylation Procedure: Preparation of (2*S*, 3*R*, 4*S*)-*N*-(*tert*-butyloxycarbonyl)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (2a). A 250 mL round bottom flask was charged with an *iso*-propanol solution (32 mL) of **1a** (5.0 g, 0.016 mol, 1.0 equiv). The solution was treated with *N*-methyl-morpholine-*N*-oxide hydrate (3.4 g, 0.025 mol, 1.5 equiv) and cooled to 0°C with an ice bath. The solution was then treated with a 0.125 M toluene solution of osmium tetroxide (0.6 mL, 0.8 mmol, 0.05 equiv). The cooling bath was removed after 15 min and the solution was allowed to stir at room temperature for 18 h after which time no starting material remained by GC and TLC analysis. The dark mixture was diluted with ethyl acetate (75 mL) and poured into aqueous 10% bisulfite (30 mL). After stirring for 1 h, the aqueous layer was removed and washed with an additional portion of ethyl acetate (50 mL). The combined organic layers were washed with 10% aqueous citric acid (100 mL) and brine (75 mL) before being dried (sodium sulfate) and concentrated to give a mixture of **2a/3a** as a light brown solid. The solid was recrystallized by dissolving in ethanol (50 mL) and treating with water (20 mL); after 12 h, the solid precipitate was isolated by filtration and shown to be >95% diastereomerically pure **2a** by HPLC. The solid was then dissolved in hot heptane and cooled to room temperature to induce precipitation. The resulting white solid was isolated to give **2a** (3.3 g, 60%) as a white powder which showed no detectable osmium residues by ICP atomic

absorbtion analysis. mp 128-129°C. $[\alpha]^{25}_D$ = -55.0 (c = 8, MeOH). GC retention time: **2a**, 7.22 min; **3a** 7.32 min; 100°C-250°C/20°C/min. TLC: R_f = **2a**, 0.67; **3a** 0.44; 50/50 EtOAc/Heptane, Ce^{IV}. ^1H NMR ($CDCl_3$): δ 4.81 (1H, d, J = 9.9 Hz), 4.02 (1H, m), 3.34 (1H, m), 3.17 (1H, d, J = 9.0 Hz), 2.0 - 1.6 (7H, m), 1.5-1.2 (10H, m), 1.45 (9H, s), 0.95 (3H, d, J = 7.5 Hz), 0.87 (3H, d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 157.60, 80.02, 77.45, 69.09, 47.90, 42.00, 39.67, 34.19, 33.69, 32.75, 28.33, 28.22, 26.43, 26.22, 26.09, 24.31, 23.97, 21.22. IR ($CDCl_3$): 3640, 3620-3240, 3000-2480, 2240, 1680 cm^{-1}. LRMS m/z 344 (M+1), 226, 201, 170 (100), 140, 126, 57. Anal. Calc'd for $C_{19}H_{37}NO_4$: C, 66.47; H, 10.79; N, 4.08; Found: C, 66.82; H, 10.61; N, 4.12.

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15. Use of other, more traditional solvents such as acetone or ^{t}BuOH gave lower selectivities and were somewhat erratic in nature. Other stoichiometric oxidants such as trimethylamine-N-oxide, ^{t}BuOOH, chlorate, and potassium ferricyanide (see below) gave either reduced selectivity (TMMNO: 1/1threo/erythro) or reduced chemical yields. Use of a 60% aqueous solution of NMMO also gave a slightly lower threo/erythro ratio of 71/29. Addition of water to reactions otherwise identical to the optimized conditions also adversely affected the diastereoselectivity.
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19. Although the electron withdrawing nature of the trichloroacetamide group undoubtedly affects the selectivity of dihydroxylation, the manner in which such factors manifest themselves is not apparent based upon our observations.
20. Similar dIscrepAncies in diastereoselectivity between stoichiometric and catalytic osmylation of allylic alcohols have been reported by Kishi with the difference for (*Z*)-isomers being particularly distinct, *c.f.* Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943.
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22. Paz and Sardina[9f] recently reported the Sharpless A.D. based double diastereoselective dihydroxylation of methyl (2*S*)-2-[*N*-(9'-phenylfluoren-9'-yl)amino]-5-(carbamoyloxy)-3-(*E*)-pentenoate. In contrast to our results with (*S*)-*N*-Boc-allylic amines, these workers found that the quinine ligands gave threo selectivity (2/1) while the quinidine ligands gave erythro selectivity (1/2.6): the simple diastereoselectivity was 1/1. Here again, the nitrogen protecting group appears to be playing a crucial role in determining the diastereoselectivity.
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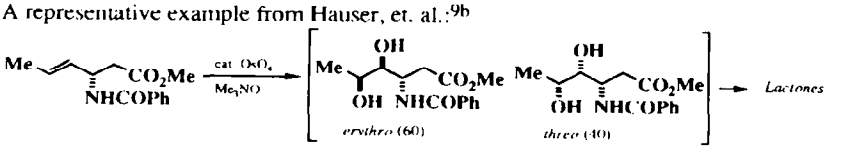
26. A representative example from Hauser, et. al.:[9b]



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