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Insights into base-free OsO_4-catalyzed aminohydroxylations employing chiral ligands

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ABSTRACT

Attempts to perform the OsO_4-catalyzed enantioselective base-free aminohydroxylation of β,β-disubstituted enoates are described. Low yields and racemic products were obtained in the presence of standard chiral ligands, suggesting the occurrence of a "Second Cycle" process due to slow hydrolysis of the amino alcohol product from the Os metal center. Support for this hypothesis was provided by the slightly improved enantioselectivity (60:40 er) obtained with an amino alcohol ligand. Based on density functional theory calculations, it is proposed that the lack of significant enantioselectivity is due to a low-energy (3 + 2) oxo/imido cycloaddition transition state without the chiral ligand in the Second Cycle that outcompetes protonolysis in the First Cycle.

1. Introduction

The Os-catalyzed aminohydroxylation reaction [1] provides a direct route to valuable vicinal amino alcohols [2] from simple and abundant alkenes. The discovery of the Sharpless asymmetric aminohydroxylation (SAA) [3] rendered this process enantioselective, greatly increasing its utility in the synthesis of natural products and potential therapeutic agents. However, the SAA is primarily limited to mono- or disubstituted alkenes, can sometimes deliver modest regioselectivity, and requires the cumbersome in situ preparation of relatively unstable *N*-halocarbamates [4]. In 2011, Luxenburger and co-workers introduced a convenient base-free aminohydroxylation procedure that replaced *N*-halocarbamates with more robust *p*-chlorobenzoyloxycarbamates as nitrogen source reagents [5]. We subsequently found that a modification of the Luxenburger protocol enabled highly regioselective aminohydroxylations of several trisubstituted and 1,1-disubstituted alkenes, producing racemic amino alcohols in the absence of a chiral ligand [6]. Enoate substrates were transformed into racemic β-hydroxy amino acids, which could be converted into α,β-dehydroamino acids via stereospecific *anti* dehydrations [7].

β-*tert*-Hydroxy amino acids such as β-OHVal and β-OHIle are components of several important bioactive peptide natural products [8–12]. Prompted by our interest in synthesizing the anticancer peptide yaku'amide A (**1**, Fig. 1) [12,13], we recognized that an enantioselective version of the base-free aminohydroxylation would provide a direct and powerful means of accessing β-*tert*-hydroxy amino acids. Luxenburger and co-workers reported successful enantioselective aminohydroxylations of cinnamates [5], but our attempts with an allylic alcohol substrate [6] and the efforts of McLeod and co-workers using styrene [14] were fruitless. Puzzled by these inconsistencies, we initiated an investigation of the enantioselective synthesis of β-*tert*-hydroxy amino acids utilizing the base-free aminohydroxylation protocol. Herein, we report the results of our study, including calculations that shed some light on the mechanism of this process.

2. Results and discussion

We began by surveying the base-free asymmetric aminohydroxylation (AA) of ethyl 3,3-dimethylacrylate (**2**, Table 1) using standard ligands that have been employed in SAA and Sharpless asymmetric dihydroxylation (SAD) reactions. The product of this transformation, β-OHVal derivative **3**, is a key building block for the total synthesis of **1**. AA reactions utilizing the dimeric cinchona alkaloid ligands $(DHQD)_2PHAL$ and $(DHQD)_2PYR$ were somewhat sluggish, requiring 3–4 days to proceed to completion and affording moderate yields of **3** as a racemic mixture (Table 1, Entries 1 and

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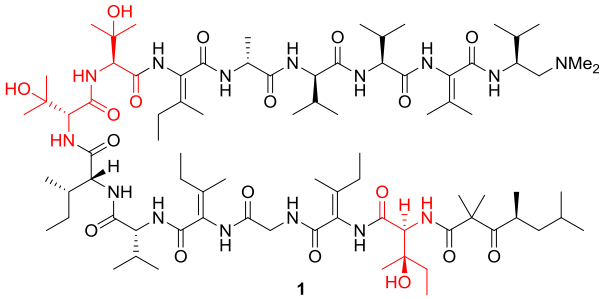
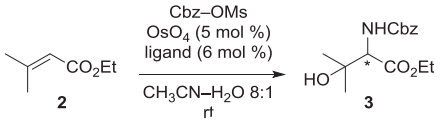


Fig. 1. Yaku'amide A (**1**), with β-hydroxy amino acids shown in red.

Table 1
Attempted AA Reactions with Sharpless Ligands.



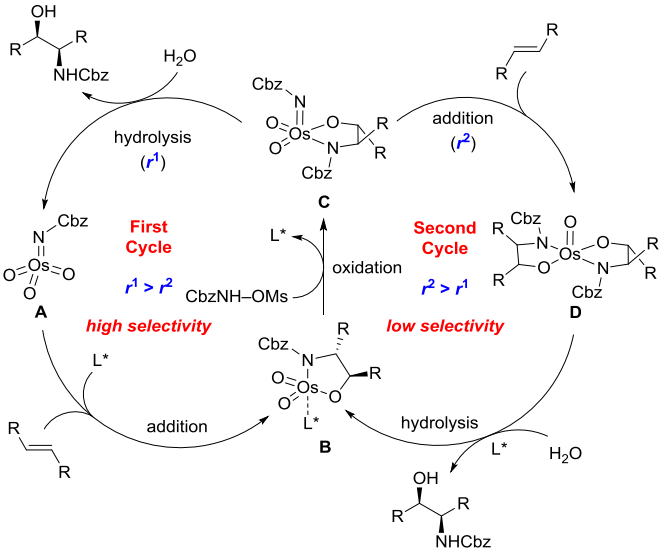
Entry	Ligand	Time (h)	Yield (%)[a]	er[b]
1	$(DHQD)_2PHAL$	72	54	50:50
2	$(DHQD)_2PYR$	96	66	50:50
3	DHQD-CLB	120	66	50:50
4	DHQD-MEQ	120	64	50:50
5	DHQD-PHN	70	28	50:50

[a] Isolated yield.
[b] Determined by chiral HPLC (Chiralcel OD-H, 90:10 hexanes/*i*-PrOH, 1.0 mL/min).

2). Suspecting that the combination of a trisubstituted alkene substrate and a large nitrogen source reagent (Cbz—OMs) might require a smaller ligand, we evaluated the monomeric cinchona alkaloid ligands DHQD-CLB [15], DHQD-MEQ [16], and DHQD-PHN [16]. Unfortunately, reactions employing these ligands also delivered racemic product (Table 1, Entries 3—5). McLeod and co-workers have suggested that the generation of 1 equiv of sulfonic acid during the base-free aminohydroxylation reaction can be problematic [14], as a higher pH is reportedly key to obtaining useful enantioselectivities in SAA and SAD reactions [17]. Accordingly, we attempted the AA with DHQD-MEQ in the presence of a pH 7 buffer. However, a complex mixture was obtained. Performing the reaction under weakly basic conditions yielded copious amounts of benzyl carbamate ($CbzNH_2$), which was presumably derived from hydrolysis of an osmium imido intermediate.

At this point, we wondered if the base-free AA reaction was proceeding through the "Second Cycle" described by Sharpless, Fokin, and co-workers [18]. In the "First Cycle" of aminohydroxylation, the alkene substrate undergoes addition to osmium imido complex **A**, delivering **B** in a ligand-accelerated process (Scheme 1). After oxidation of **B** by the nitrogen source reagent to afford osmium imido complex **C**, hydrolysis releases the imino alcohol product and regenerates **A**. In cases where the rate of hydrolysis (r^1) is slow, **C** can enter the Second Cycle by undergoing addition of a second alkene molecule, yielding complex **D**. In contrast to the First Cycle, the Second Cycle is characterized by (1) no ligand acceleration, (2) the absence of ligand from the Os complex during the addition step, and (3) racemic products. Presumably, the lack of base in our reactions could result in a slowing of the hydrolysis step, thereby shifting the reaction into the Second Cycle.

Sharpless, Fokin, and co-workers found that chiral amino alcohol ligands could effectively mediate enantioselective second-

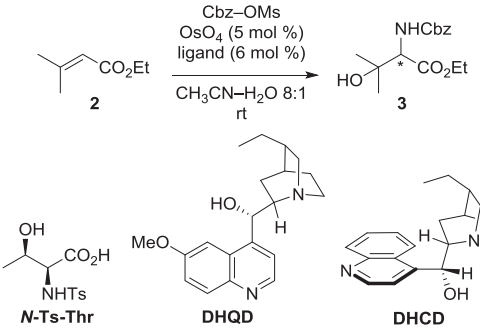


Scheme 1. First and Second Cycles of the SAA reaction.

cycle dihydroxylations and aminohydroxylations, presumably due to their ability to chelate and remain attached to the Os metal center for the duration of the reaction [18]. Accordingly, we evaluated a selection of amino alcohols in the base-free aminohydroxylation of **2** (Table 2). We were disappointed to find that prototypical second-cycle ligand *N*-Ts-Thr furnished **3** in moderate yield as a racemic mixture (Entry 1). Dihydroquinidine (DHQD), the amino alcohol building block for the SAD ligands, also delivered racemic product (Entry 2). Interestingly, the related *Cinchona* alkaloid derivative dihydrocinchonidine (DHCD) afforded scalemic **3** in low yield and 60:40 er (Entry 3). Unfortunately, attempts to optimize this result were not fruitful.

To directly evaluate the possibility of the Second Cycle versus the First Cycle, we executed density functional theory (DFT) calculations using the M06-L/6-31+G(d,p)[LANL2DZ only for Os] level of theory [19]. All structures were optimized in the Gaussian 09 [20] program, and confirmed as minima or transition-state structures by normal-mode vibrational frequency analysis. The SMD continuum

Table 2
AA Reactions with Amino Alcohol Ligands.



Entry	Ligand	Time (h)	Yield (%)[a]	er[b]
1	*N*-Ts-Thr	93	52	50:50
2	DHQD	66	72	50:50
3	DHCD	100	31	60:40

[a] Isolated yield.
[b] Determined by chiral HPLC (Chiralcel OD-H, 90:10 hexanes/*i*-PrOH, 1.0 mL/min).

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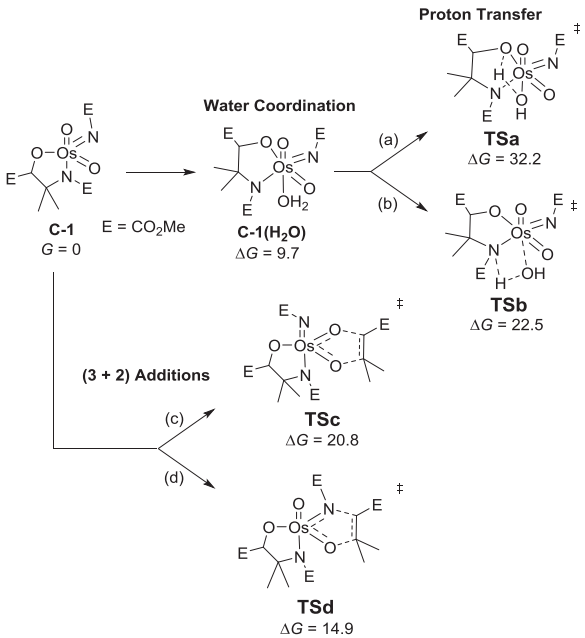
solvent model was used for acetonitrile [21]. Electronic energies were calculated with the def2-TZVP basis set [22], and reported free energies correspond to M06-L/def2-TZVP//M06-L/6-31**[LANL2DZ for Os only]. Extensive conformational evaluation was performed, including consideration of all oxo/imido ligand coordination patterns, and all reported values correspond to the lowest-energy structures identified. We modeled the imido Cbz group as an imido methyl carbamate. The alkene substrate was modeled as methyl 3,3-dimethylacrylate instead of the ethyl ester **2**.

One possible branching point in determining whether the First Cycle or Second Cycle is followed during catalysis involves intermediate **C** (Scheme 1). We considered four major pathways that could diverge from this species: (a) Os-alkoxide water hydrolysis, (b) Os-amido water hydrolysis, (c) *cis*-oxo (3 + 2) alkene cycloaddition, and (d) *cis*-oxo/imido (3 + 2) cycloaddition. The transition-state structures and energies are reported in Scheme 2 and Fig. 2.

Pathway (a) begins with water coordination to the 5-coordinate Os complex **C-1**, which is ~10 kcal/mol endergonic, followed by proton transfer. The $\Delta G^{\ddagger}$ value for this proton transfer is 32.2 kcal/mol (**TSa**, Scheme 2 and Fig. 2) using a single water molecule. While this protonolysis is not viable, as expected, the more basic amido moiety is more easily protonated. The $\Delta G^{\ddagger}$ value for the proton transfer in pathway (b) is only 22.5 kcal/mol (**TSb**). While this barrier might suggest the feasibility of the First Cycle, (3 + 2) cycloaddition is lower in energy. *Cis*-oxo (3 + 2) addition has a $\Delta G^{\ddagger}$ value of 20.8 kcal/mol through **TSc**. The (3 + 2) oxo/imido cycloaddition pathway involving **TSd** leading to an intermediate analogous to **D** in Scheme 1 is the lowest in Gibbs free energy, with a $\Delta G^{\ddagger}$ value of 14.9 kcal/mol. This transition state is 5.9 kcal/mol lower in energy than the transition state of the unobserved dihydroxylation pathway and 7.6 kcal/mol lower than the transition state of the lowest-energy hydrolysis pathway. While these calculations suggest that the reactivity of intermediate **C** provides the key branching point towards the Second Cycle, we did not examine the entire catalytic cycle. We also did not explore water-assisted proton transfer since the entropy penalty for involvement of a second water in 8:1 CH_3CN–H_2O is difficult to model correctly.



Scheme 2. Transition-state structures and free energies comparing water proton transfer pathways and (3 + 2) cycloaddition pathways from intermediate **C-1**. (kcal/mol).

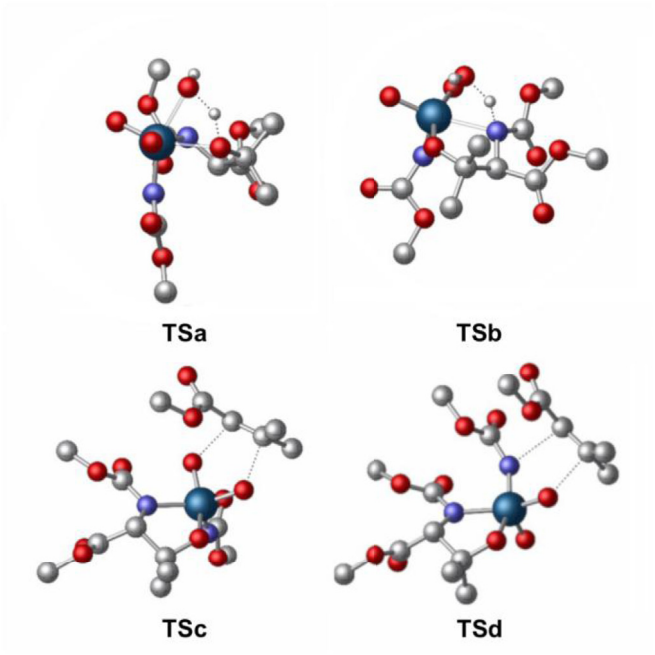


Fig. 2. Transition-state structures for protonolysis and cycloaddition pathways from intermediate **C-1**.

3. Conclusions

We investigated the OsO_4-catalyzed enantioselective base-free aminohydroxylation as a method of constructing β-*tert*-hydroxy amino acids such as β-OHVal and β-OHIle. Aminohydroxylations conducted in the presence of typical SAA ligands were sluggish and afforded racemic products. We suspected that the reactions might be proceeding through the Second Cycle, wherein hydrolysis of the amino alcohol adduct from the Os catalyst is slower than addition of a second alkene substrate. This hypothesis was supported by the fact that a chiral amino alcohol ligand afforded some improvement in enantioselectivity. DFT calculations indicated that the Second Cycle is kinetically preferred over the First Cycle under the base-free reaction conditions. It is currently unclear whether the low enantioselectivity observed with DHCD is due to very small energy differences between the two diastereomeric (3 + 2) transition states involving the chiral ligand or to competition between an enantioselective Second Cycle pathway involving the chiral ligand and a racemic pathway in which the ligand is not bound to the metal. Although these studies have not yet produced a viable enantioselective synthesis of β-*tert*-hydroxy amino acids, it is our hope that the observations detailed herein will prompt a renewed focus on the development of more effective chiral ligands for base-free aminohydroxylations that utilize the Second Cycle. The convenience of the base-free aminohydroxylation protocol, its compatibility with trisubstituted alkenes, and the utility of the β-hydroxy amino acids accessible via this process would render such ligands highly useful to the organic synthesis community.

4. Experimental section

General experimental details. All reagents and solvents were purchased from commercial vendors and used without purification. Flash chromatography was carried out using 60–230 mesh silica gel. ^{1}H NMR spectra were obtained on a 500 MHz spectrometer with chloroform (7.27 ppm) as internal reference. ^{13}C NMR spectra

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were obtained on a spectrometer operating at 125 MHz with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI mass spectrometry.

N*-Cbz-β-OHVal-OEt (3) via asymmetric aminohydroxylation of enoate 2.** The following procedure employing DHCD as the chiral ligand is representative. ***Caution: *OsO_4 is toxic, and exposure to its vapors can damage the eyes, respiratory tract, and skin. Solutions of this reagent should be handled inside fume hoods with extreme care using appropriate personal protective equipment. Aqueous waste containing Os should be collected with other hazardous heavy metals and disposed of in accordance with local environmental regulations.* A solution of benzyl ((methylsulfonyl)oxy)carbamate [23] (94.0 mg, 0.383 mmol, 1.9 equiv) and dihydrocinchonidine (4.2 mg, 0.014 mmol, 0.07 equiv) in CH_3CN (3 mL) at rt was treated with OsO_4 (4 wt % solution in H_2O, 62 μL, 0.0098 mmol, 0.05 equiv), stirred for 10 min, then treated with ethyl 3,3-dimethylacrylate (**2**, 27 μL, 24.9 mg, 0.194 mmol) and H_2O (300 μL). The resulting mixture was stirred at rt for 100 h, treated with sat aq $K_2S_2O_5$ (400 μL), and stirred for an additional 10 min. It was then diluted with H_2O (3 mL) and extracted with EtOAc (6 × 3 mL). The combined organic layers were washed with sat aq $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.5–1% MeOH in CH_2Cl_2 gradient elution) afforded **3** (18.0 mg, 0.609 mmol, 31%) as a light yellow oil. Spectral data were in accordance with previously published data [6]. Compound **3** was obtained in 20% ee as analyzed by HPLC (Chiralcel OD-H, 90:10 hexane/*i*-PrOH, 1.0 mL/min; $t_R = 7.5$ min (major), 9.0 min).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.01.018.

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