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Reversal of Regioselection in the Sharpless Asymmetric Aminohydroxylation of Aryl Ester Substrates

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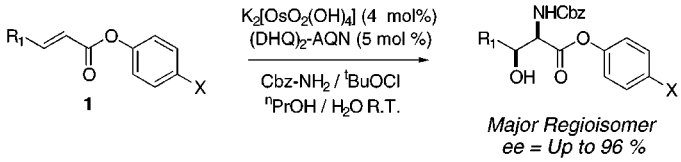
ABSTRACT



The asymmetric synthesis of *β*-hydroxy-α-amino acids is reported which relies on the use of α,*β*-unsaturated aryl ester substrates and the dihydroquinyl alkaloid ligand system $(DHQ)_2$-AQN to control the regio- and enantioselectivity of the asymmetric aminohydroxylation (AA) process. α,*β*-Unsaturated ester substrates of type 1 have a significant effect on the substrate–ligand recognition event which results in a reversal of regioselectivity in the AA reaction.

β-Hydroxy-α-amino acid derivatives frequently occur as constituents of biologically active peptides, precursors to *β*-lactam antibiotics, and synthons for the preparation of several neurologically active natural products. For instance, 3-hydroxyleucine and 3-hydroxylysine derivatives have attracted considerable attention as unusual amino acid components of numerous peptide antibiotics such as azinothricin,[1] telomycin,[2] lysobacin,[3] and the protein kinase C inhibitor (−)-balanol (Figure 1).[4] More recently, 3-hydroxyleucine has been sought after as a key synthon in the synthesis of (+)-lactacystin and its analogues (Figure 1).[5]

In conjunction with our efforts toward the total synthesis of (+)-lactacystin,[5a] we began to explore the asymmetric aminohydroxylation (AA) reaction as an efficient method to access the hydroxyleucine synthon. Numerous approaches to the 3-hydroxyleucine have been reported. However, they lack the flexibility to prepare stereoisomers, require the preparation of a chiral catalyst system, or are prohibitively lengthy and not practical for large scale preparations.[6] In our report on the synthesis of (+)-lactacystin, we discovered that using the AA reaction on a *p*-bromophenyl ester olefinic substrate provided the hydroxyleucine synthon with useful

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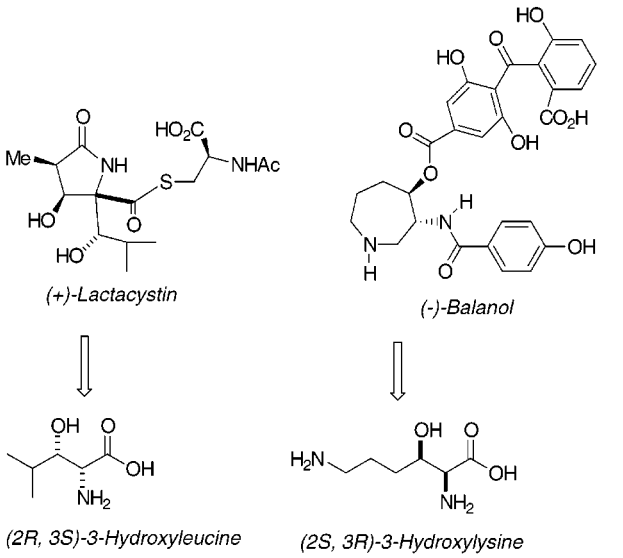

Figure 1. Amino acid components of (+)-lactacystin and (−)-balanol.

levels of regio- and enantioselection. This successful approach constituted the first example of a reversal in the regioselection of the AA reaction with noncinnamate ester substrates. Herein, we describe an efficient approach to the asymmetric synthesis of certain β-hydroxy-α-amino acid derivatives including a further investigation of the hydroxyleucine substrate. This process employs commercially available materials utilizing the Sharpless catalytic asymmetric aminohydroxylation (AA) of aryl ester acrylate substrates.[7] Sharpless and co-workers have previously shown that cinnamates provided the desired β-hydroxy-α-amino ester when the $(DHQ)_2$-AQN ligand is utilized.[8] At the time of our initial investigation, the regiochemical outcome of the AA process for aliphatic olefins of type **1** was unknown with the recently available $(DHQ)_2$-AQN ligand. The recent work of Janda and co-workers[9] with allylic alcohol substrates using the $(DHQD)_2$-PHAL ligand has shown that the steric bulk and the electronic properties of the substituents on either side of the olefinic substrate can be used to control the regiochemistry of the AA reaction. Despite the recent discovery of a method for obtaining β-hydroxy-α-aminocinnamate esters, the development of routes to enantiomerically pure β-alkyl-substituted β-hydroxy-α-amino derivatives using the AA process remains an active area of research. We decided to investigate if this trend of the reversal of regiochemistry was applicable to β-substituted aliphatic acrylate esters in an effort to expand the scope to β-alkyl-substituted β-hydroxy-α-amino derivatives and to further understand the nature of these electronic effects.

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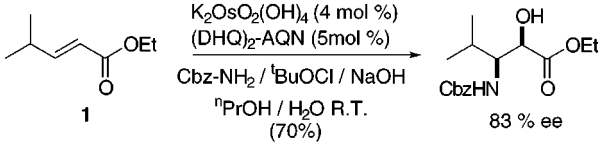
Our initial experiments with aliphatic substrates utilized alkyl esters (**1**, Scheme 1) with the $(DHQ)_2$-AQN ligand.

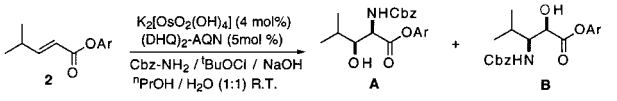
Scheme 1



However, this reaction afforded the undesired α-hydroxy-β-amino ester as the sole regioisomeric product with high levels of enantioselection (83% ee), consistent with literature precedent for substrates of this type with the $(DHQ)_2$-PHAL ligand.[7]

With the presumption that the interactions of the aromatic group of the cinnamates and the $(DHQ)_2$-AQN alkaloid ligand used in the Sharpless investigation contributed to the regiochemical course of the reaction, a series of *p*-substituted aryl esters of type **2** were screened in the AA using the $(DHQ)_2$-AQN ligand (Table 1).[10] These substrates proved to affect the regioselectivity pattern of the AA reaction to provide the β-hydroxy-α-amino ester as the major regio-

Table 1. Reversal of Regioselection with Aryl Ester Substrates



entry	aryl group (Ar)	regioselection (**A** : **B**)[a]	yield of **A** (%)	%ee **A**[b]
1	**2a**	1 : 1	51	10%, **3a**
2	**2b**	4 : 1	53	16%, **3b**
3	**2c**	5 : 1	55	30%, **3c**
4	**2d**	7 : 1 (> 20:1)[c]	60	87% (>99%)[c], **3d**
5	**2e**	5 : 1	58	89%, **3e**
6	**2f**	3 : 1	59	96%, **3f**
7	**2g**	1.4 : 1	50	3%, **3g**
8	**2h**	*NR*[d]		—
9	**2i**	*NR*[d]		—

[a] Ratios of products were determined by ^{1}H NMR (400 MHz) operating at S/N of > 200:1. [b] Determined by chiral HPLC analysis using a Chiracel OD-H column. [c] After 2× recrystallization from EtOH/H_2O (1:1). [c] Starting olefin was recovered with varying amounts of saponification.

isomeric product (Table 1, entries 2−7).[11] The turnover of the regioselection for these aryl esters appears to rely on subtle changes in the substrate−ligand recognition event. To more fully investigate the electronic contributions of the aryl esters on the aminohydroxylation reaction, a series of *p*-substituted aryl esters were surveyed for use in a Hammett-type analysis.[12]

The ready accessibility of the *p*-substituted aryl ester substrates allows for a survey of the electronic characteristics of the AA using a Hammett-type analysis on the data presented in Table 1 (Figure 2). These data clearly suggested

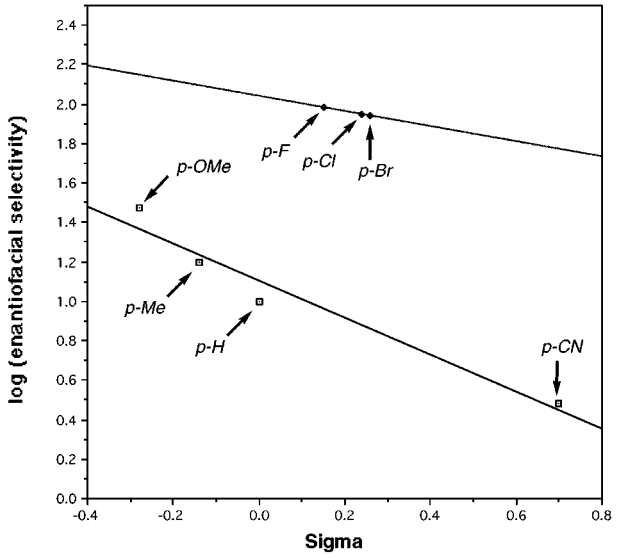


Figure 2. Hammett-type analysis for the aminohydroxylation process.

an empirical correlation between the electronic nature of the aryl ester and the enantioselection of the aminohydroxylation reaction. In general, electron-donating groups provided higher levels of enantioselection than electron-withdrawing groups, which if sufficiently electron withdrawing (e.g., *p*-NO_2, entry 8) rendered the substrate unreactive. Interestingly, the *p*-halo-substituted esters were found to have a unique effect on the AA reaction, providing higher levels of regio- and enantio-selection compared to those of the other substituents. Indeed, the halogens defined a separate linear correlation distinct from that of the other functional groups. This may indicate a subtle change in the substrate−catalyst recognition event. The negative slope associated with both the halo-substituted esters and the other substituents surveyed indicated that electron-donating groups stabilize the developing partial positive charge on the olefinic carbons in the transition state, thus accelerating the reaction rates. The type of halogen atom also seemed to play a key role in the observed regioselection, with the bromine-substituted ester (entry 4) being the optimal substrate for the cases examined. The iodine-substituted ester (entry 9) proved unreactive even after prolonged exposure (48 h) to the reaction conditions. This may indicate a steric preference for penetration of the olefinic substrate into the active site of the catalyst.

The reversal of regioselection may arise from a conformational change induced by the aryl ester functionality. To determine the conformation of the aryl ester substrates in solution, a series of NOE experiments were carried out with substrates **2d** and **1**. These NOE experiments were performed in d_4-methanol to mimic the alcoholic solvent used in the AA reaction. Substrate **2d** exhibited a 6% NOE between the β-olefinic proton and the ortho protons of the aryl ester (H_4 and H_1, respectively, see Figure 3). The observation of this

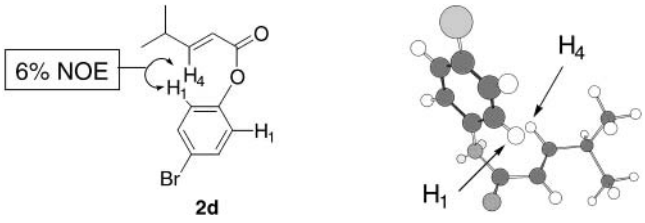
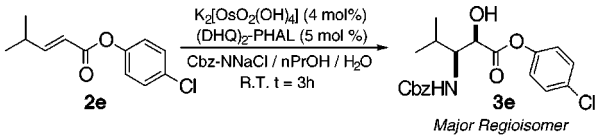


Figure 3. Solution conformation and 3-D minimized view of substrate **2d**.

NOE is indicative of a *s-trans* type conformer which positions the ortho protons of the aryl ester (H_1) in close proximity to the β-olefinic proton (H_4).[13] Not surprisingly, NOE experiments on the ethyl ester substrate (**1**) showed no observable NOE's upon irradiation of either the β-olefinic proton or the methylene protons of the ethyl ester in accord with the literature precedent of Wiberg and co-workers on the conformation of such alkyl esters.[14] Wiberg has shown that the alkyl ester substrates prefer a *s-cis* conformer with a *cis* orientation of the alkyl group relative to the carbonyl moiety. This conformer minimizes dipole−dipole interactions.[14] The altered conformation of the aryl ester substrates might allow for the assembly of a productive π-complex between the osmium bound to the alkaloid ligand, the aryl moiety of the ester, and the anthroquinone ring of the

(10) For the preparation of olefins **2a**−**i** and **4a**−**d**, see the Supporting Information.

(11) To determine the effect of the $(DHQ)_2$-AQN ligand on the regiochemical outcome of the AA, we subjected substrate **2e** to the AA protocol using (DHQ)2−PHAL as the ligand. The AA reaction afforded the α-hydroxy-β-amino ester as the major regiosiomeric product (ratio = 2.5:1).



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(13) Molecular modeling studies with substrate **2d** (Chem 3D Pro, MM2 minimization) indicate an internuclear distance between H_1 and H_4 to be ca. 3.0 Å.

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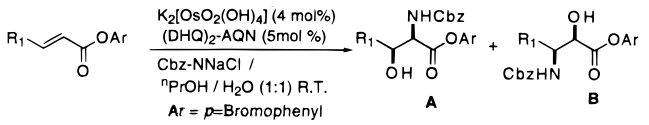
ligand.[15] This orientation of the substrate−catalyst complex may account for the turnover in regioselectivity of the AA and the formation of the β-hydroxy-α-amino ester.

In an effort to expand the scope of the AA, additional *p*-bromo-substituted aryl esters were prepared (Table 2).

Table 2. Aminohydroxylation of *p*-Bromophenyl Ester Substrates



entry	R_1	yield of **A** (%)[a]	regioselection (**A**:**B**)[b]	enantioselection (% ee of **A**)[c]
1	^{i}Pr, **2d**	60	7:1 (>20:1)[d]	87 (>99),[d] **3d**
2	Me, **4a**	40	1:1	2, **5a**
3	H, **4b**	52	4:1	69, **5b**
4	$Cl(CH_2)_3$,**4c**	53	>20:1	82,[e] **5c**
5[f]	$Cl(CH_2)_3$, **4d**	50	4:1	90,[e] **5d**

[a] Yields of isolated product after chromatography on silica gel. [b] Ratios of products were determined by ^{1}H NMR (400 MHz) operating at a S/N of >200:1. [c] Determined by chiral HPLC analysis using a Chiracel OD-H column. [d] After 2× recrystallization from EtOH/ H_2O (1:1). [e] Optical purity determined by ^{1}H NMR of the mandelate ester. [f] Ar = *p*-fluorophenyl.

These included crotonate and acrylate olefins (entries 2 and 3) which, in principle, provide access to the threonine and serine synthons, respectively. The β-substituted acrylate systems (entries 4 and 5) were also included to provide access to unnatural amino acid derivatives as well as a hydroxylysine derivative.

The acrylate ester (entry 3) reacted, as expected, to favor the desired β-hydroxy-α-amino ester with moderate levels of regio- and enantioselection. Unexplainably, the crotonate derivative (entry 2) exhibited no regio- or enantioselection! This surprising result indicates that even subtle variations in the nature of the alkyl groups on the olefin can have a dramatic effect on the selectivity of the AA reaction. Interestingly, the *p*-fluorophenyl ester derivative (entry 5) gave the highest ee (90%) of these substrates but showed a slight decrease in regioselectivity.

The high levels of enantioselection with these aryl ester substrates offset their susceptibility to saponification under the standard conditions of the AA reaction.[7] The degree of saponification can be attenuated by careful monitoring of the reaction; however, yields could be significantly improved by limiting the competing hydrolysis pathway. Attempts to reduce saponification by using the analogous *p*-bromobenzyl esters were less successful as these substrates proved less reactive and afforded generally lower levels of regio- and enantioselection. However, saponification of the *p*-bromophenyl esters was greatly reduced by utilizing an aqueous solution of OsO_4 (4 wt % in H_2O) in the reaction. This allowed the use of a reduced amount of NaOH (1.5 equiv) as it was no longer necessary to in situ generate the OsO_4 from the potassium osmate dihydrate. This procedure was performed using substrate **2d** on a 40 mmol scale, providing **3d** in 60% yield. The regioselectivity and enantioselectivity of the product (**3d**) remained unchanged; hence this protocol is readily scalable to multigram quantities using this procedure.

In summary, the Os(VIII)/$(DHQ)_2$-AQN promoted AA of certain α,β-unsaturated aryl esters provides a useful route to β-alkyl-β-hydroxy-α-amino acid derivatives using a convenient procedure and readily available catalyst system. Presently, the AA process provides efficient access to the important amino acids, 3-hydroxyleucine and 3-hydroxylysine. Further, this study clearly indicates a trend for the reversal of AA regioselection by simple variation of the ester moiety which apparently alters the substrate-ligand recognition event. In that context, this study constitutes a useful observation that subtle alterations of the substrate can be an effective alternative to catalyst modification. It has also been shown that the level of enantioselection is controlled, at least in part, by the electronic properties of the aryl ester functionality on the olefinic substrate. We are currently undertaking further investigations in our laboratories to enhance the scope of this process.

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Supporting Information Available: General experimental procedures and full characterization of compounds **1**−**5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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