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Reversal of Regioselection in the Asymmetric Aminohydroxylation of Cinnamates

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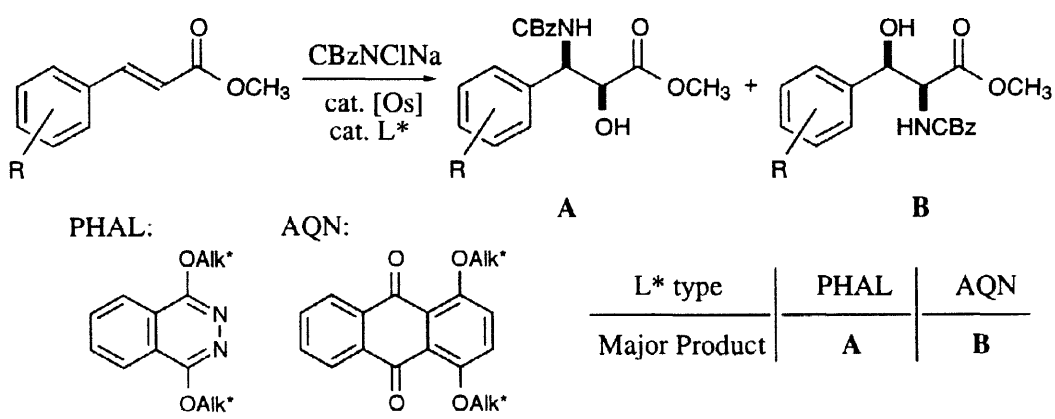
Abstract

Use of cinchona ligands with an anthraquinone (AQN) core, in place of the usual phthalazine (PHAL) core, in the asymmetric aminohydroxylation of cinnamates causes dramatic reversal of the regioselection, so that phenyl serines are obtained in high enantiomeric excess. Hence, the regioselectivity outcome (i.e. isoserine vs. serine) is controlled by the ligand and not the substrate.

Keywords: Amino acids and derivatives; Amino alcohols; Asymmetric reactions; Catalysis

The asymmetric aminohydroxylation (AA) is a one-step stereospecific conversion of olefins to protected β-aminoalcohols using catalytic amounts of an osmium source and chiral ligands based on cinchona alkaloids.[1] Three different types of *N*-haloamine salts were found to deliver the nitrogen heteroatom while also serving as the ultimate oxidant. The fact that sulfonamides,[2] amides,[3] and carbamates[4] can be used, simplifies catalysis optimization and leaves a certain flexibility when planning a reaction sequence with the AA products. The most significant method for a synthetic chemist surely is the carbamate modification, since numerous deprotection methods for reductive (CBz), acidic (*t*-BOC), and nucleophilic (Teoc) removal are known.[5]



Scheme. AA of cinnamates [Alk* = dihydroquininyl (DHQ) or -quinidinyl (DHQD)]

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The aminohydroxylation works particularly well for *E*-3-substituted acrylate esters [*E*-RCH=CHCOOR', R = aryl or alkyl]. In recent studies[3] on the *N*-bromoacetamide-based AA, we noted that the anthraquinone ligands $(DHQ)_2AQN$ and $(DHQD)_2AQN$[6] imposed a regioselectivity pattern different from that seen with their more commonly used PHAL-analogs. For example, in the transformation of styrenes, the amide-based AA's preference for placing the nitrogen on the terminal nonbenzylic carbon is accentuated using the AQN-ligands.[3] In pursuing this phenomenon and using *N*-chloro-*N*-sodio *carbamates* for the AA of *cinnamates*, we now report that the serine regioisomers **B** (Scheme) are strongly favored using the AQN-ligands (c.f. PHAL-ligands which give the isoserine isomers **A**[1,4a,4c]).

Table
Asymmetric Aminohydroxylation of Methyl Cinnamates Using CBzNClNa.[a]

Entry	R	B:A[b]	$(DHQ)_2AQN$ *Ee* (yield)/% of (2*R*,3*S*)-**B**[c]	$(DHQD)_2AQN$ *Ee* (yield)/% of (2*S*,3*R*)-**B**[d]
1	H	79:21	95 (58)	92 (62)
2	4-F	82:18	91 (67)	92 (68)
3	4-Cl	77:23	91 (58)	92 (54)
4	4-Br	80:20	89 (51)	89 (52)
5	4-Me	78:22	93 (n. d.)[e]	96 (52)
6	4-MeO	78:22	94 [f](67)	93 (65)
7[g]	2,6-$(MeO)_2$	75:25	91 (50)	91 (51)
8[h]	4-BnO	66:34	87 (40)	87 (40)

a) See text for reaction conditions; CBz = Benzyloxycarbonyl. b) Determined by ^{1}H-NMR. c) Products obtained using $(DHQ)_2AQN$. *Ee*'s were determined on chiral stationary HPLC columns (Chiralcel OD-H or Chiralpak AS, Daicel). d) Products obtained using $(DHQD)_2AQN$. e) Not determined. f) HPLC analysis of the minor regioisomer [(2*R*,3*S*)-**A**] revealed an *ee* of 91%. g) Regioisomers were inseparable by chromatography. h) Ethyl cinnamate was used in place of methyl cinnamate.

The table reveals the outcome for eight variously substituted cinnamates.[7] All the results are good, even for the 2,6-disubstituted case in entry 7. While the "serine-regioselection" is lower (**B**:**A** ≈ 4:1) than in the "isoserine-regioselection" (**A**:**B** ≈ 7:1) with the PHAL-ligands, it is still very useful, especially since high asymmetric induction is observed (>90% *ee*) and with one exception (entry 7), the minor regioisomer **A** was easily removed by chromatography on silica gel. Due to the high overall yield of the AA regioisomers in all cases, the serine type products were isolated in yields up to 68% (entry 2). Electron poor cinnamates proved less suitable with the AQN ligand system. For example, the AA of methyl 3-nitrocinnamate gave a

1:1 mixture of regioisomers and significant amounts of the diol by-product. On the other hand, changing the aromatic substituent for an aliphatic one, led to only a slight drop in the regioselectivity. Thus, methyl *trans*-2-octenoate afforded a 75:25 mixture favoring the 3-*n*-pentylserine regioisomer [using $(DHQD)_2AQN$ gave (2*S*,3*R*)-**B**, with *n*-pentyl in place of the aryl, in 93% *ee*].

In a typical experiment, a reaction flask immersed in a water bath was charged with sodium hydroxide (3.05 mmol of a commercial 1.022 N solution) and diluted with water (4.5 mL) in a dark fume hood. Part of this alkaline solution (*c.* 0.5 mL)[4b] was transferred into a vial to dissolve $K_2[OsO_2(OH)_4]$ (14.7 mg, 0.04 mmol). With vigorous stirring, *n*-propanol (4 mL) and benzyl carbamate (0.469 g, 3.1 mmol) were added to the flask, followed by dropwise addition of freshly prepared *t*-butyl hypochlorite (0.331 g, 0.346 mL, 3.05 mmol). After five minutes, an *n*-propanol solution (3.5 mL) of $(DHQD)_2AQN$ (34.3 mg, 0.04 mmol) (Aldrich cat. no.: 45,671-3) and methyl cinnamate (0.162 g, 1 mmol), and the aqueous $K_2[OsO_2(OH)_4]$ solution were added. After 1.5 h, the solution was quenched with 0.5 g sodium bisulfite. After the usual workup,[4a] 0.206 g (62% yield, 92% *ee*) of the pure (2*S*,3*R*)-*N*-benzyloxycarbonyl-3-phenylserine methyl ester[8] (**B**, entry 1, R=H) was isolated via chromatography on silica gel (hexane/EtOAc = 5:1, **A** elutes before **B**).

The reason for the difference between PHAL and AQN ligand classes for the AA of cinnamates is unknown. However, the substrate *orientation* within the binding pockets of these two different ligand classes is obviously altered in such a way that opposite regioselection results, but remarkably, without affecting the sense or the degree of the enantiofacial selectivity. Mechanistic understanding aside, the AA now provides a simple method to functionalize cinnamates and other olefins through direct introduction of an N,O-vicinal set of heteroatoms in a single step. These *cis*-additions are stereospecific, proceed with high asymmetric induction, and now also allow selective access to either of the aminoacid regioisomers.

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7. All products were characterized by means of NMR, MS, melting point, optical rotation, and HPLC.
8. (2*S*,3*R*)-**B**, R=H: M.p. 107-108°C; $[\alpha]_D^{25}$ = -26.9 (c = 1 in 95% EtOH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.23 (m, 10 H), 5.55 (d, *J* = 8.5 Hz, 1H), 5.38 (s, 1H), 4.99 (s, 2H), 4.59 (dd, *J* = 2.5, 9.1 Hz, 1H), 3.75 (s, 3H), 2.56 (br s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 171.1, 158.9, 139.5, 136.1, 128.5, 128.2, 128.1, 127.9, 126.2, 125.9, 73.7, 67.0, 59.7, 52.7; HRMS calcd. for $C_{18}H_{19}NO_5$ $(M + Na)^+$: 352.1161, found: 352.1152; HPLC: Chiralcel OD-H, 0.46 cm x 25 cm, hexane/*i*-PrOH 85/15, 0.6 mL/min, 210 nm, 30.1 min (2*R*,3*S*), 33.7 min (2*S*,3*R*). The absolute configuration of this compound was determined by hydrogenolytic removal of the CBz-group, followed by comparison of the resulting aminohydroxyester's optical rotation with the literature value; T. Beulshausen, U. Groth, U. Schöllkopf, *Liebigs Ann. Chem.* **1991**, 1207-1209.