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The Use of pH to Influence Regio- and Chemoselectivity in the Asymmetric Aminohydroxylation of Styrenes

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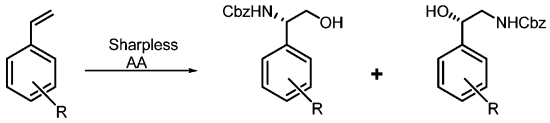
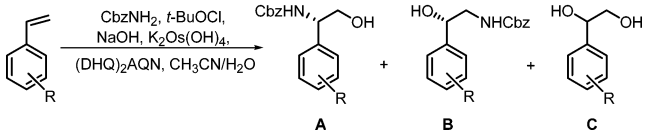
ABSTRACT



The pH-controlled Sharpless asymmetric aminohydroxylation (AA) of styrenes provides 1-aryl-2-amino ethanols (regioisomer B) with high enantio-, chemo-, and regioselectivity. As existing AA protocols typically give regioisomer A as the major reaction product when using carbamate nitrogen sources, this method is a convenient alternative for the selective production of regioisomer B.

The asymmetric aminohydroxylation (AA) is a useful reaction for producing the ubiquitous β-amino alcohol moiety. As developed by Sharpless and co-workers, this reaction typically utilizes osmium, a chiral ligand, and a nitrogen source in the generation of 1,2-*N*-protected amino alcohols from alkenes.[1] With α,β-unsaturated ester substrates the regioselectivity of the reaction can be controlled with appropriate experimental conditions, and the enantioselectivites are typically excellent.[2] Styrene derivatives have also been investigated as AA substrates; however, the regiochemical outcome of the AA with these substrates has been much less predictable. The ratio of regioisomeric products in the AA of styrenes is known to be influenced markedly by solvent, nitrogen source, substrate, and ligand.[3] In particular, the 2-aryl-2-amino ethanol regioisomer (**A** in Scheme 1) is typically the major product in such reactions.

Scheme 1



Although there is a report on the production of useful levels of the 1-aryl-2-amino ethanol regioisomer (**B** in Scheme 1) in the amide derived AA,[4] it has not been possible to obtain this **B** regioisomer with high regio- and enantioselectivities with easily deprotected carbamate nitrogen sources. In fact, it has been noted by Sharpless and co-workers that with carbamate nitrogen sources regioselectivity of the **B** isomer

(1) (a) Li, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454. (b) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326−329.

(2) (a) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507−2510. (b) Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949−1952. (c) Han, H.; Cho, C.-W.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565−1569.

(3) (a) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207−1217. (b) O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519−2526. (c) Goossen, L. J.; Liu, H.; Dress, K. R.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1080−1083. (d) Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221−2223. (e) Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 3667−3670.

(4) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1997**, *36*, 1483−1486.

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is inversely correlated with enantiselectivity.[3a] We now report a method utilizing pH control to override other variables in the AA reaction of styrenes to selectively provide the **B** regioisomer with good enantiomeric ratios (ers).[5]

We required a convenient method to generate a variety of 1-aryl-2-amino ethanol derivatives for our program in the synthesis of compounds that influence apoptosis. Investigation of styrene derivatives as substrates for the AA revealed that the pH was changing during the course of the reaction. As it is known that the asymmetric dihydroxylation is facile at pH >10,[6] we conducted our AA studies in the presence of a phosphate buffer, allowing for precise control of pH. When the reaction was buffered between pH 7.5 and 8.5, we found that the **B** regioisomer was preferentially formed irrespective of the nature of the styrene substrate, the solvent, or the ligand.

The dependence of chemo- and regioselectivity on pH is depicted graphically in Figure 1 for styrene. The reactions

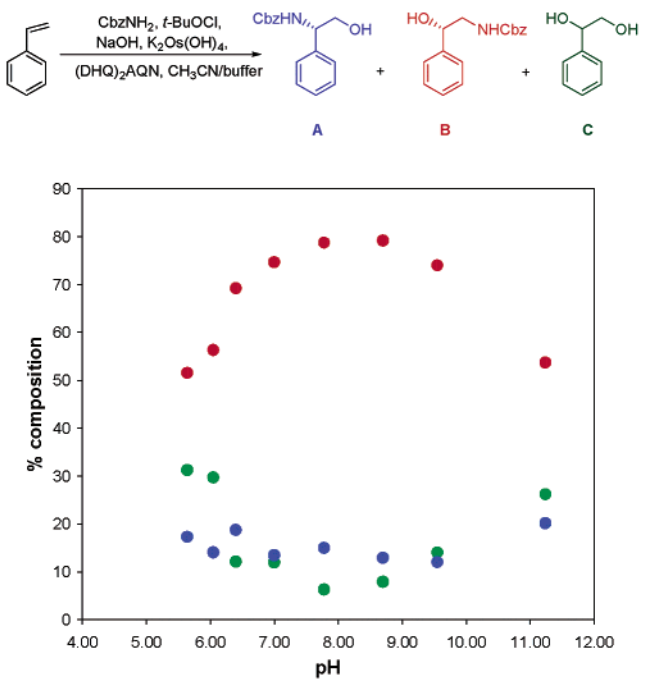


Figure 1. Reaction mixture composition for the aminohydroxylation of styrene in the pH range from 5.5 to 11.3. The ratio of products was determined by integration of the ^{1}H NMR of the crude reaction mixture.

were performed in a 2:1 mixture of acetonitrile/0.5 M phosphate buffer with a variety of pH values. As illustrated in Figure 1, pH values in the range of 7.5−8.5 are optimal for obtaining high yields of the **B** regioisomer; formation of the **A** regioisomer and of the diol side product are maximally suppressed at this pH.

The regioselectivity of the AA is known to be influenced by the nature of the alkaloid ligand used. With this in mind, the common $(DHQ)_2AQN$, $(DHQ)_2PHAL$, and $(DHQ)_2PYR$ ligands were examined, as well as some less common alkaloid ligands. These reactions were performed in phosphate buffer (pH 7.5−7.7) with *p*-acetoxystyrene as the substrate. As summarized in Table 1, the **B** regioisomer was preferentially formed for almost all ligand/solvent combinations. Even under $(DHQ)_2PHAL$/*n*-PrOH conditions (Table 1, entry 5), a combination known to give a strong preference for regioisomer **A**,[3a,b,e] the buffered AA gave **B** as the predominant product. In general, the AQN-based ligands with acetonitrile gave the best yield, regioselectivity, and enantioselectivity in this buffered asymmetric aminohydroxylation (Table 1, entries 1 and 16).

Table 1. Ligand Effect on the Regiomeric Composition in the Buffered Aminohydroxylation of *p*-Acetoxystyrene

entry	ligand	solvent/buffer (1:1)	ratio **A**:**B**[a]	yield of **B**[b]	er of **B**[c] (*S*:*R*)
1	$(DHQ)_2AQN$	CH_3CN	1:10	82	87:13
2	$(DHQ)_2AQN$	*n*-propanol	1:4	57	75:25
3	$(DHQ)_2AQN$	THF	1:4	53	58:42
4	$(DHQ)_2PHAL$	CH_3CN	1:5	52	85:15
5	$(DHQ)_2PHAL$	*n*-propanol	1:2	42	79:21
6	$(DHQ)_2PYR$	CH_3CN	1:3	38	70:30
7	$(DHQD)_2BcPHAL$	CH_3CN	1:1	44	26:74
8.	$(DHQD)_2PHALPh_2$	CH_3CN	1:4	71	12:88
9	DHQD-MEQ	CH_3CN	1:5	56	45:55
10	DHQD-CLB	CH_3CN	1:5	53	45:55
11	$(DHQD)_2PYR(^iPr)$	CH_3CN	1:3	30	50:50
12	$(DHQD)_2PYR$	CH_3CN	1:3	45	50:50
13	$(DHQD)_2PYR(Naph)$	CH_3CN	1:3	43	47:53
14	$(DHQD)_2PYR(OMe)_3$	CH_3CN	1:2	42	41:59
15	$(DHQD)_2PYR(Morph)$	CH_3CN	1:5	60	50:50
16	$(DHQD)_2AQN$	CH_3CN	1:10	78	11:89

[a] Determined from ^{1}H NMR of the crude reaction mixture. [b] Isolated yield after chromatography on silica gel. [c] Ratios determined by chiral SFC. Stereochemistry assigned from optical rotation and comparison to known compounds.

A range of *p*-acetoxystyrene substrate concentrations was evaluated under the buffered AA conditions. Substrate concentrations greater than 80 mM led to significant diol formation, up to 30% at 160 mM. Similar effects of concentration on chemoselectivity have been previously observed in the AA.[7]

The effect of temperature on the reaction outcome was determined to be minimal, as the regio-, chemo-, and enantioselectivities were essentially the same over a range of temperatures. However, the reaction proceeded much more rapidly at higher temperatures. Indeed, at 40 °C the reaction was complete in 5 to 7 min (Figure 2).

Substitution of the carboxybenzylcarbamate (Cbz) nitrogen source with *tert*-butylcarbamate (Boc) or *n*-butylcarbamate

(5) For recent studies on the pH dependence of the asymmetric dihyroxylation see: (a) Krief, A.; Castillo-Colaux, C. *Synlett* **2001**, 501−504. (b) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421−434.

(6) Dobler, C.; Mehltretter, G.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3026−3028.

(7) Wuts, P. G. M.; Anderson, A. M.; Goble, M. P.; Mancini, S. E.; VanderRoest, R. J. *Org. Lett.* **2000**, *2*, 2667−2669.

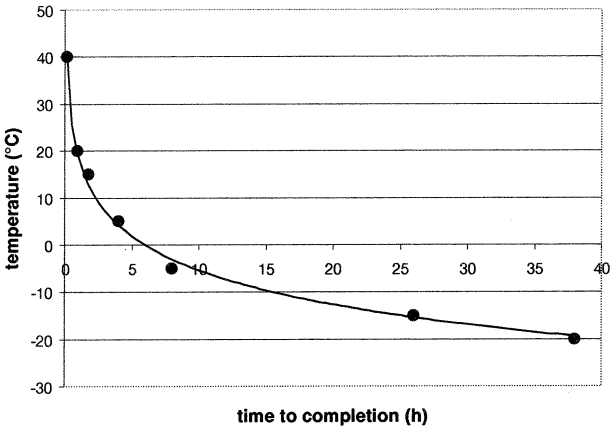


Figure 2. Effect of reaction temperature on the rate of aminohydroxylation of *p*-acetoxystyrene.

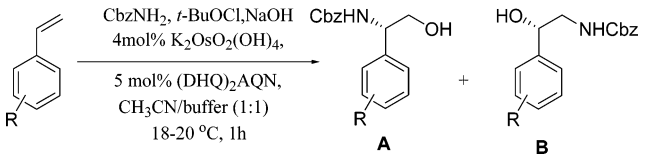
had little effect on regio-, chemo-, or enantioselectivity, although the reaction was faster with *n*-butyl carbamate as the nitrogen source.[8] In addition it was found that the ligand and catalyst loading could be reduced 5-fold (to 1% and 0.8%, respectively) with no diminution in regio- or enantioselectivity, and with a slight improvement in chemoselectivity. As the pK_a of *N*-halogenated carbamate salts is known to be dependent on the solvent-to-water ratio,[9] all experiments were performed with a constant ratio of solvent to buffer. In addition, the formation of the dihydroxylated byproduct can be diminished by careful loading of *t*-BuOCl, as the presence of unreacted hypochlorite results in accelerated dihydroxylation.

With optimized experimental conditions in place, the regio-, chemo-, and enantioselectivity of the AA was investigated for a variety of styrene substrates. The results (Table 2) show that the desired **B** regioisomer is obtained in good yields and modest-to-good enantioselectivity on differently substituted styrenes. In general, enantiomeric ratios in the 85:15 range are observed for all para- and meta-substituted substrates; lower ers are observed for the ortho-substituted styrene (Table 2, entry 10). In all cases the regioisomers could be easily separated by chromatography on silica gel. These buffered reaction conditions are a complement to existing experimental protocols that selectively generate the **A** regioisomer, and are a marked improvement upon those that utilize carbamate nitrogen sources to access the **B** regioisomer.

A kinetic investigation revealed that under the reaction conditions regioisomer **B** is the dominant product in the early stages of the reaction (Figure 3). At a certain point (30 min for the *p*-acetoxystyrene substrate) the rate of formation of the **A** regioisomer starts to become significant. Further

(8) For use of less sterically challenged nitrogen sources in the asymmetric aminohydroxylation see: Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810−2813.
(9) (a) Menard, H.; Lessard, J. *J. Chem. Eng. Data* **1978**, *23*, 64−65. (b) Bachand, C.; Driguez, H.; Paton, J. M.; Touchard, D.; Lessard, J. *J. Org. Chem.* **1974**, *39*, 3136−3138.

Table 2. Results of the pH-Controlled Aminohydroxylation



entry	R	ratio **A**:**B**[a]	yield **B**[b]	er of **B** (*S*:*R*)[c]
1	H	1:8	72	88:12
2	*p*-OAc	1:10	85	85:15
3	*p*-OCH_3	1:8	64	85:15
4	*p*-OtBu	1:10	70	85:15
5	*p*-OTBDMS	1:10	70	87:13
6	*p*-OTs	1:21	76	88:12
7	*p*-COOH	1:12	81	74:26
8	*p*-NO_2	1:5.4	58	85:15
9	*m*-OCH_3	1:8	58	86:14
10	*o*-OCH_3	1:9	54	61:39
11	*m*-NO_2	1:3.5	47	85:15

[a] Determined from ^{1}H NMR of the crude reaction mixture. [b] Isolated yield after chromatography on silica gel. [c] Ratios determined by chiral SFC. Stereochemistry assigned from optical rotation and comparison to known compounds.

experimentation confirmed that the presence of regioisomer **A** leads to the formation of even greater amounts of regioisomer **A**. For instance, when purified regioisomer **A** is added at the start of the aminohydroxylation, the regiomeric composition of the products shifts from 1:10 (**A**:**B**) to 1:1.6 (**A**:**B**); initial addition of purified regioisomer **B** had little effect on the reaction outcome (see Supporting Information for details).

Described herein is a simple method to access the **B** regioisomer in the aminohydroxylation of styrenes with high yields and good enantioselectivites with carbamate nitrogen

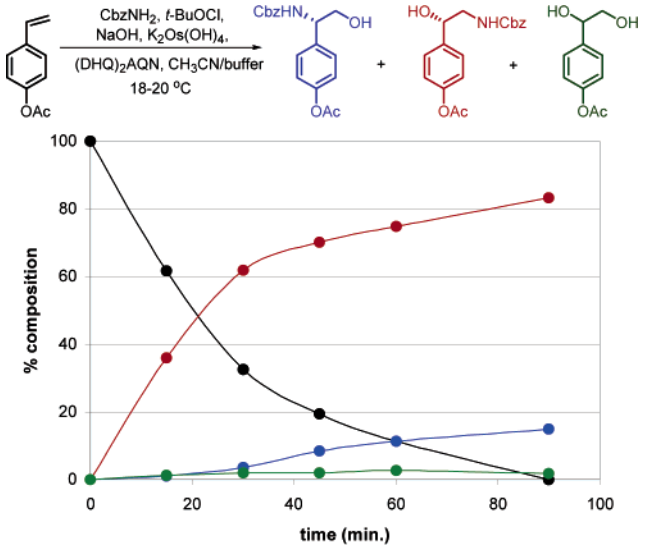


Figure 3. Product formation as a function of time in the buffered asymmetric aminohydroxylation of *p*-acetoxystyrene.

sources. Further mechanistic investigations into the influence of pH on regioselctivity in the AA are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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