From Styrenes to Enantiopure α-Arylglycines in Two Steps

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Abstract: Direct enantioselective synthesis of (*R*)- and (*S*)-*N*-Cbz- or *N*-BOC-protected α-arylglycinols from styrenes via catalytic *asymmetric* aminohydroxylation, with enantioselectivities up to 99% and isolated yields up to 80%, is described. In a subsequent oxidation step, these glycinols yield the corresponding carbamate-protected α-arylglycines.

The biological importance of enantiopure α-amino acids drives the search for ever more efficient synthetic routes to these compounds.[1] An interesting class of α-amino acids are the arylglycines which are found in a wide range of bioactive compounds such as amoxicillins,[2] nocardicins,[3] cephalecins,[4] and glycopeptide antibiotics[5] (e.g., vancomycin). Despite the relatively simple structures of aryl glycines, their nonracemic syntheses have been plagued by the ease of base-catalyzed epimerization involving the α-methine proton in synthetic intermediates. A number of research groups have achieved *asymmetric* syntheses of this class of amino acids.[6]

Results and Discussion

The catalytic *asymmetric* aminohydroxylation (AA) reaction provides either (*R*)- or (*S*)-α-aryl-Cbz- or BOC-protected amino alcohols from commercially available styrenes (Scheme 1). The enantioselectivities are generally excellent and a subsequent oxidation step yields the corresponding α-arylglycine.

The osmium-catalyzed *asymmetric* aminohydroxylation (AA) reaction first emerged as a process in which the nitrogen source was the chloramine salt of a sulfonamide.[7] These original sulfonamide-based AA procedures, although efficient, lack substrate scope. For example, styrenes are conspicuously absent from the list of olefins which succeed in these systems. The replacement of sulfonamides by alkyl carbamates[8] or by amides[9] has greatly improved the AA in both scope and selectivity. Styrenes, very poor substrates under the sulfonamide-based AA conditions, became excellent substrates under the carbamate-based conditions. In fact, as in the catalytic asymmetric dihydroxylation (AD), styrenes are among the best substrates for this new carbamate-based AA process, and they also obey the same face selection rule established for the AD reaction.[10] Additionally, reactions with all styrene derivatives studied to date exhibit the desirable phenomenon of ligand-accelerated catalysis (LAC).[11] We report here the results of applying the carbamate AA process with a wide range of substituted styrenes. Enantioselectivities of up to 99% and yields of up to ∼80% for the major regioisomer (typically the one with the benzylic NHR group) make styrenes excellent substrates for the new carbamate-based AA reaction.[8]

Effective experimental conditions for styrenes in the AA process using benzyl carbamate[12] employ 4 mol % $K_2OsO_2(OH)_4$, 5 mol % alkaloid ligand $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, 3.1 equiv of BnOC(O)NNaCl and *n*-PrOH/H_2O (∼1.5:1) at 25 °C. The results are summarized in Table 1, and although largely self-explanatory, they are deserving of a few comments.

The regioselectivity is seen to be highly dependent on the nature of the styrene as well as the choice of ligand, solvent, and ligand−solvent combination. Phthalazine ligands such as $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ in *n*-PrOH (alcoholic solvents) favor the benzylic amine (**A**) over the benzylic alcohol regioisomer (**B**) (Scheme 1) (all entries in Table 1 and entries 1, 9, and 13 in Table 2). In acetonitrile, the ratio of benzylic amine to benzylic alcohol (**A**/**B**) decreases significantly (entries 2 and 10 in Table 2) and in one case actually reverses (entry 6, Table 2). The recently introduced anthraquinone (AQN) ligands[13] appear to strongly favor this reversal of regioselectivity, and when used in conjunction with the CH_3CN/H_2O solvent system, the ratio of **B**/**A** reaches its zenith (entries 4, 8, 12, and 15 in Table 2).[14] Unexpectedly however, the enantioselectivities for the **B** regioisomers in Table 2 proved to be poor [ranging

(1) Williams, R. M. In *The Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Ed.; Organic Chemistry Series; Pergamon Press: Oxford, 1989.

(2) Meyer, E. M.; Boesten, W. H. J.; Schoemaker, H. E.; van Balken, J. A. M. In *Biocatalysis in Organic Synthesis;* Tramper, J., van der Plas, H. C., Linko, P., Eds.; Elsevier: Amsterdam, 1985; p 135.

(3) Townsend, C. A.; Brown, A. M. *J. Am. Chem. Soc.* **1983,** *105,* 913.

(4) Spencer, J. L.; Flynn, E. H.; Roeske, R. W.; Sriv, F. Y.; Chaivette, R. R. *J. Med. Chem.* **1966,** *9,* 746.

(5) Rama Rao, A. V.; Gurjar, M. K.; Laxma Reddy, K.; Rao, A. S. *Chem. Rev.* **1995,** *95,* 2135.

(6) (a) Williams, R. M.; Hendric, J. A. *Chem. Rev.* **1992,** *92,* 889 and references therein. (b) Vernier, J. M.; Hegedus, L. S.; Miller, D. *J. Org. Chem.* **1992,** *57,* 6914. (c) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997,** *119,* 6452 and references therein. (d) Boger, D. L.; Borzilleri, R. M.; Nukui, S. *J. Org. Chem.* **1996,** *61,* 3561. (e) Kunz, H.; Sager, W. *Angew. Chem., Int. Ed. Engl.* **1987,** *26,* 557. (f) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996,** *118,* 4910. (g) Donnell, M. J. O.; Bennett, W. D. *Tetrahedron* **1988,** *44,* 5389.

(7) (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996,** *35,* 451. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996,** *35,* 2831 (c) G. Li.; Sharpless, K. B. *Acta Chem. Scand.* **1996,** *50,* 649.

(8) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996,** *35,* 2813.

(9) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem.* **1993**, *109,* 1580.

(10) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994,** *94,* 2483.

(11) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995,** *34,* 1059.

(12) Benzyl carbamate should be recrystallized from water before use.

(13) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996,** *35,* 448. Both $(DHQ)_2AQN$ and $(DHQD)_2AQN$ are commercially available (Aldrich).

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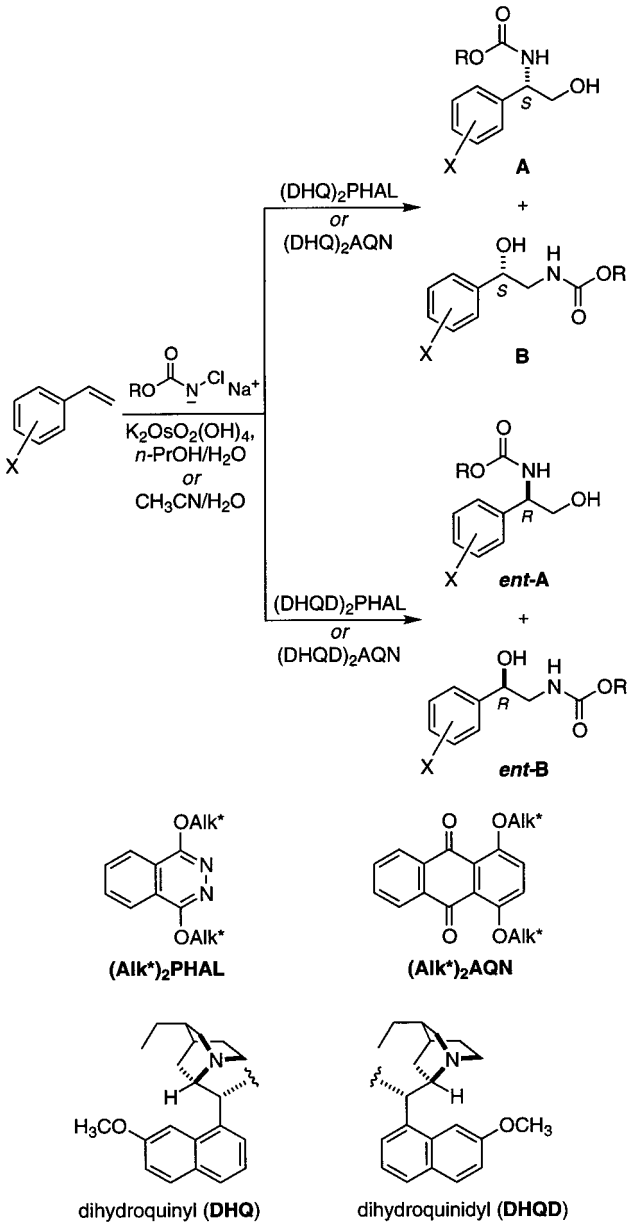
Scheme 1. AA Reactions of Substituted Styrenes (X = alkyl, halogen, phenyl, OR′, NO_2, CF_3, CN) Using Carbamates (R = benzyl, *tert*-butyl)



from ca. 80% enantiomeric excess (ee) to 0% ee]. In fact, regioselectivity and enantioselectivity seem to be inversely correlated (e.g., for entry 15, Table 2, **A**/**B** = 20:80 and **B** = 58% ee, whereas for entry 8, Table 2, **A**/**B** = 1:50 and **B** = 0% ee). Hence, the carbamate AA does not offer a useful route from styrenes to the **B** regioisomers in enantiopure form. Fortunately, the recently reported amide AA provides the **B** regioisomers (important adrenergic drugs[15]) with high regio- and enantioselectivities.[9]

The absolute configurations of several of these amino alcohols were determined by comparison with authentic samples of both regioisomers.[16] For the substrates studied, the enantiofacial selectivity of the AA reaction is solely determined by the ligand (i.e., DHQ-type vs DHQD-type), so that for a given ligand the enantiofacial selectivity is the same for both regioisomers. The configurations of the other entries in the tables are provisionally assigned by analogy.

Initially, the *tert*-butyl carbamate-based AA reactions were carried out in the same way as the benzyl carbamate-based reactions, but the results were disappointing. Poor chemoselectivity (i.e., substantial diol formation) and low yields were observed (entries 1−3, Table 3). Solvent variation (e.g., EtOH or *t*-BuOH instead of *n*-PrOH) gave no improvement. In CH_3CN/H_2O (1:1), formation of diol was suppressed, however, at the expense of regioselectivity. We were assuming that a higher water content could only be advantageous, because it should accelerate the hydrolysis step in the catalytic cycle and thereby suppress the involvement of the rate and selectivity damaging *second cycle*.[17] But we soon realized that the higher water concentrations, at least in this particular case (i.e., styrenes and *t*-alkyl carbamate-based chloramine salts), also leads to competing hydrolysis of the putative ROCON═OsO_3 complex, affording OsO_4 which of course leads to dihydroxylation. This side reaction is suppressed when the percentage of solvent water is reduced. The best results were obtained with 4 mol % of $K_2OsO_2(OH)_4$ and 6 mol % ligand[18] at 0 °C with a 2:1 ratio of *n*-PrOH/water as the solvent. Under these conditions, good regioselectivities and excellent enantioselectivities were realized (Table 3).

Compared to the benzyl carbamate series, the *tert*-butyl carbamate series still affords slightly poorer regioselectivities and yields, but the enantioselectivities approach 100% in each case. Both the Cbz- and BOC-AA reactions are fast, independent of the substituents present on the styrene. We assume that for styrenes the catalytic process is dominated by turnover in the enantioselective and, hence, desirable "first cycle".[17]

Results from preparative scale applications of the standard (benzyl carbamate) and the "modified" (*tert*-butyl carbamate) procedures are shown in Scheme 2 for 4-(benzyloxy)styrene and 3,5-dimethoxystyrene, respectively. In these two cases, working on this larger scale greatly simplified isolation and purification of the AA product. In the benzyl carbamate example, the workup simply involved diluting the reaction

(14) The presence of electron-withdrawing or electron-donating groups in the aromatic ring can also influence the regioselectivity. The data in Table 1 for closely related cases (e.g., entries 3, 10, and 11) suggest that electron donating substituents favor isomer **A**, but the results in entries 13−18 indicate that such simple rationales for regioselectivity trends will be of little help in this system.

(15) (a) Ruffolo, R. R., Jr. *Tetrahedron* **1991,** *47,* 9953. (b) Brown, R. F. C.; Donohue, A. C.; Jackson, W. R.; McCarthy, R. D. *Tetrahedron* **1994,** *50,* 13739. (c) Zaponakis, G.; Katerinopoulos, H. E. *Tetrahedron Lett.* **1996,** *37,* 3045.

(16) (a) Commercially available (*S*)-(+)-2-phenylglycinol (Aldrich) and (*R*)-(−)-2-phenylglycinol (Acros) were converted to their Cbz derivatives. The optical rotations and the chiral HPLC behavior were compared with those for the AA products (entry 1, Table 1) obtained from $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, respectively. For (*S*)-*N*-Cbz-phenylglycinol (commercial): $[\alpha]^{25}_D = +31.0°$ (*c* = 1, 95% EtOH); HPLC Chiracel AD, 15% *i*-PrOH/hexane, 0.7 mL min^{-1}, 254 nm, 12.0 min. Product **1A** [$(DHQ)_2PHAL$ derived]: $[\alpha]^{25}_D = +29.0°$ (*c* = 0.5, 95% EtOH); HPLC Chiracel AD, 15% *i*-PrOH/hexane, 0.7 mL min^{-1}, 254 nm, 12.0 min. For (*R*)-*N*-Cbz-phenylglycinol (commercial): $[\alpha]^{25}_D = -31.4°$ (*c* = 1, 95% EtOH); HPLC Chiracel AD, 15% *i*-PrOH/hexane, 0.7 mL/min, 254 nm, 16.5 min. Product ***ent*-1A** [$(DHQD)_2PHAL$ derived, entry 1, Table 1]: $[\alpha]^{25}_D = -28.3°$ (*c* = 0.5, 95% EtOH); HPLC Chiracel AD, 15% *i*-PrOH/hexane, 0.7 mL min^{-1}, 254 nm, 16.5 min. (b) An authentic sample of (1*R*)-1-(3-pyridyl)-2-aminoethanol (kindly provided by Dr. John Chung of Merck) was converted to its Cbz derivative. The optical rotation and the chiral HPLC retention time were compared with the AA product of entry **18** (Table 1) obtained from $(DHQD)_2PHAL$. For the Cbz derivative of (1*R*)-1-(3-pyridyl)-2-aminoethanol (Merck sample): $[\alpha]^{25}_D = +9.7°$ (*c* = 1.123, 95% EtOH); HPLC Chiracel AD, 15% *i*-PrOH/hexane, 0.7 mL min^{-1}, 254 nm, 24.1 min. For AA product ***ent*-18B** [$(DHQD)_2PHAL$ derived] (43% ee): $[\alpha]^{25}_D = +4.3°$ (*c* = 0.295, 95% EtOH); HPLC Chiracel AD, 15% *i*-PrOH/hexane, 0.7 mL min^{-1}, 254 nm, 24.1 min *R*, 28.6 min *S*.

(17) See ref 7b for explanation and discussion of the "first and second cycle" phenomena in these catalytic AA systems.

(18) By using high ligand concentration at low temperature, the ligand acceleration is increased, which indirectly reduces the hydrolysis of the osmium−imido complex formed in the catalytic cycle.

Table 1. AA Reactions Using BnOC(O)NNaCl as the Nitrogen Source

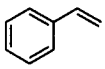
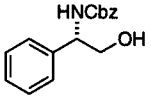
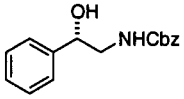
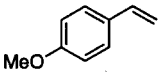
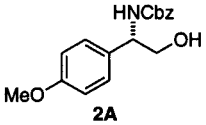
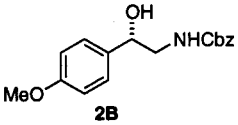
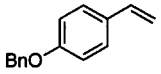
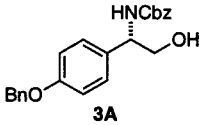
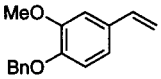
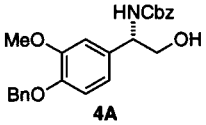
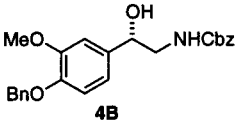
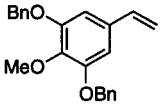
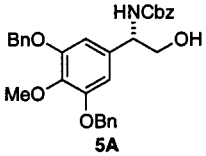
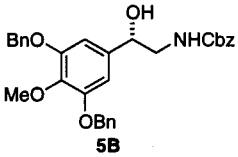
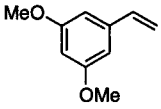
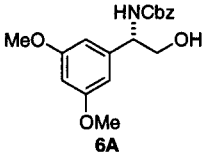
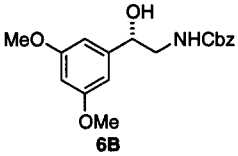
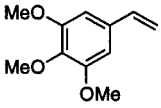
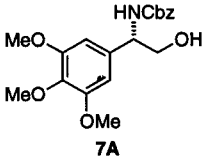
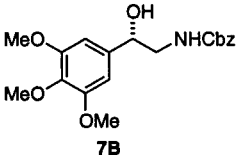
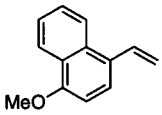
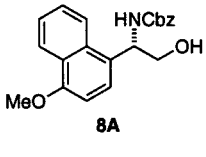
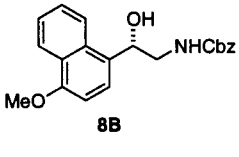
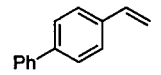
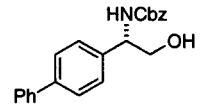
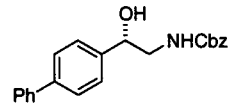
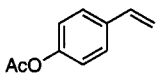
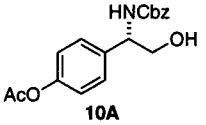
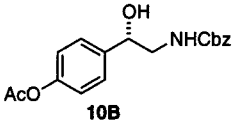
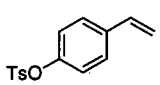
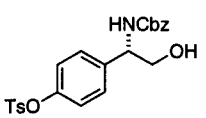
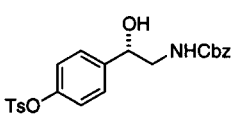
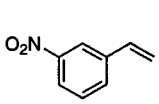
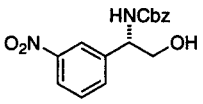
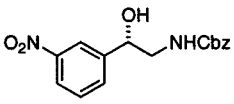
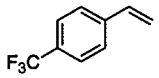
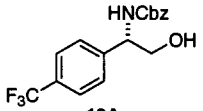
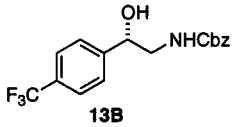
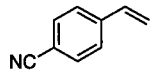
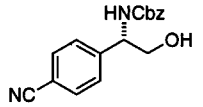
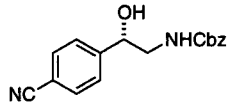
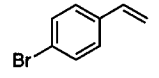
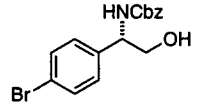
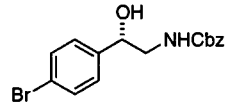
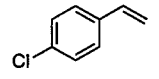
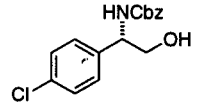
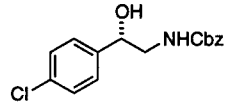
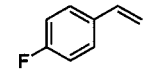
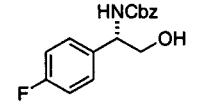
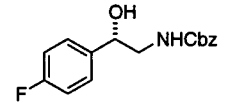
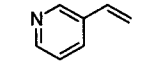
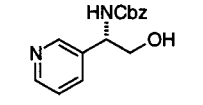
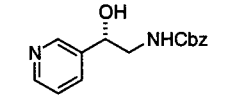
entry	substrate [a]	product A [b]	product B [b]	yield A % [c]	A : B [d]	%ee, A (DHQ)$_2$PHAL [e]	%ee, *ent*-A (DHQD)$_2$PHAL [e,f]
1		 **1A**	 **1B**	40	55 : 45	93	–90
2		 **2A**	 **2B**	64	66 : 33	93	–98
3		 **3A**	 **3B**	76	88 : 12	97	–93
4		 **4A**	 **4B**	70	77 : 23	98	–94
5		 **5A**	 **5B**	68	88 : 12	91	–98
6		 **6A**	 **6B**	68	75 : 25	90	–94
7		 **7A**	 **7B**	65	75 : 25	95	–94
8		 **8A**	 **8B**	67	83 : 17	92	–84
9		 **9A**	 **9B**	70	91 : 9	74 (88) [g]	–51 (83) [g]
10		 **10A**	 **10B**	35	50 : 50	82	–89
11		 **11A**	 **11B**	42	50 : 50	83	–81

Table 1 (Continued)

entry	substrate [a]	product **A** [b]	product **B** [b]	yield **A** % [c]	**A** : **B** [d]	%ee, **A** $(DHQ)_2PHAL$ [e]	%ee, ***ent*-A** $(DHQD)_2PHAL$ [e,f]
12		 **12A**	 **12B**	59	74 : 26	92	–90
13		 **13A**	 **13B**	63	75 : 25	90	–83
14		 **14A**	 **14B**	62	75 : 25	94	–95
15		 **15A**	 **15B**	64	80 : 20	94	–90
16		 **16A**	 **16B**	70	86 : 14	93	–90
17		 **17A**	 **17B**	53	66 : 33	94	–86
18		 **18A**	 **18B**	35 [h]	50 : 50	96	–94

[a] All reactions were performed on a 2.0 mmol scale using 4% $K_2OsO_2(OH)_4$, 5% ligand, and *n*-PrOH/water (1.5:1) at 25 °C for 1 h. [b] The products shown are the major enantiomers from reactions using $(DHQ)_2PHAL$ as the ligand. [c] Isolated yield of **A** using $(DHQ)_2PHAL$. [d] Ratio of benzylic amine (**A**) to benzylic alcohol (**B**) regioisomers determined by ^1H NMR. [e] Determined by HPLC (Chiralcel AD column). [f] The "negative" ee values are used to make it clear at a glance that with $(DHQD)_2PHAL$ as ligand, the mirror image isomer dominates (i.e., ***ent*-A** > **A**). [g] The ee values after one crystallization. [h] Yield based on 80% conversion after 10 h.

mixture with water to cause precipitation of both product regioisomers (**3**), isolation of the resulting solid by filtration, and, finally, trituration with cold *n*-PrOH to leave 14.5 g (90%) of the product regioisomers **3** (**A**/**B** = 80:20).[19] In the *tert*-butyl carbamate example, precipitation of the product was induced by concentration of the reaction mixture to ca. one-third its volume on a rotary evaporator. Filtration of the resulting slurry gave 11.3 g (86%) of the product regioisomers **21** (**A**/**B** = 66:33).[19] Thus, in both cases the usual extractive workup, even the initial quenching with sodium sulfite, is omitted. Perhaps the most important advantage of these large scale procedures is that the excess carbamate (and/or its *N*-chloro salt) remains in the filtrate.

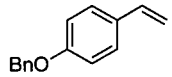
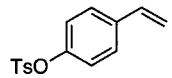
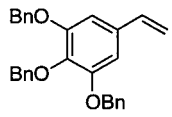
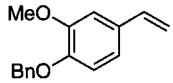
The second, and final step, in this route to α-arylglycines is the oxidation of the protected amino alcohol to the corresponding amino acid. Direct oxidation of the primary alcohol to the desired carboxylic acid was first accomplished using a standard periodic acid/catalytic RuO_4 system (Scheme 3),[20] but in some cases this gave poor yields. TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical)-catalyzed NaOCl oxidation[21] proved to be more reliable (Table 4). Of great practical importance, the oxidation step works equally well on the crude mixture of the two regioisomers (Table 4), with isomer **A** yielding the protected amino acid and isomer **B** the protected amino ketone. The amino acid is easily separated from the amino ketone by simple acid−base extraction; hence, chromatography is avoided altogether in this two-step sequence.[22] In most of the cases, 70−86% yields were obtained and no epimerization was detected.[23a,b]

(19) Products were isolated as a mixture of regioisomers.

(20) (a) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988,** *53,* 5187. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985,** *50,* 1560. (c) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981,** *46,* 3936.

(21) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987,** *52,* 2559. (b) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torri, S. *J. Org. Chem.* **1990,** *55,* 462. (c) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985,** *50,* 1332.

Table 2. Influence of Ligand and Solvent on Regioselectivity in the AA Reaction of Four Styrene Derivatives

entry	substrate [a]	ligand	solvent	A : B [b]
1		$(DHQ)_2PHAL$	*n*-PrOH/H_2O	88 : 12
2		$(DHQ)_2PHAL$	CH_3CN/H_2O	75 : 25
3		$(DHQ)_2AQN$	*n*-PrOH/H_2O	33 : 66
4		$(DHQ)_2AQN$	CH_3CN/H_2O	25 : 75
5		$(DHQ)_2PHAL$	*n*-PrOH/H_2O	50 : 50
6		$(DHQ)_2PHAL$	CH_3CN/H_2O	14 : 86
7		$(DHQ)_2AQN$	*n*-PrOH/H_2O	17 : 83
8		$(DHQ)_2AQN$	CH_3CN/H_2O	< 1 : 50
9		$(DHQ)_2PHAL$	*n*-PrOH/H_2O	88 : 12
10		$(DHQ)_2PHAL$	CH_3CN/H_2O	50 : 50
11		$(DHQ)_2AQN$	*n*-PrOH/H_2O	33 : 66
12		$(DHQ)_2AQN$	CH_3CN/H_2O	23 : 77
13		$(DHQ)_2PHAL$	*n*-PrOH/H_2O	77 : 23
14		$(DHQ)_2AQN$	*n*-PrOH/H_2O	33 : 66
15		$(DHQ)_2AQN$	CH_3CN/H_2O	20 : 80

[a] All reactions were performed on a 1.0 mmol scale using 4% $K_2OsO_2(OH)_4$, 5% ligand, and the solvent given in the table at 25 °C for 1 h. [b] Ratio of benzylic amine **A** to benzylic alcohol **B** regioisomers determined by ^1H NMR.

In optimizing this reaction it was found that one equivalent of TEMPO was needed. When a catalytic amount of TEMPO was employed, a chlorinated aromatic derivative was isolated as the major product (presumably the TEMPO scavenges any chlorine which is liberated during the reaction provided that ca. 1 equiv is present). In these (Table 4) and several other cases[23c] examined to date, the configurational integrity of the stereogenic center is maintained during the oxidation. However, it remains to be seen if that center survives with even more electron-deficient aromatic rings than those in the present work. If one encounters this problem, the slightly acidic, catalytic RuO_4/H_5IO_6 oxidation method could be superior to the TEMPO/NaOCl method.

In conclusion, the catalytic asymmetric aminohydroxylation (AA) reaction proves to be a powerful tool for the enantioselective one-step synthesis of *N*-Cbz- or *N*-*t*-BOC-protected[24] α-arylglycinols from styrenes, in good yields and excellent enantioselectivities. The subsequent oxidation of these arylglycinols to the corresponding α-arylglycines is a convenient and highly efficient synthetic route to this important class of amino acids.

Experimental Section

Materials and Methods. Solvents were reagent grade and used without purification. Commercial reagents were used without purification unless noted otherwise. Benzyl carbamate was purchased from Aldrich and recrystallized from water. *tert*-Butyl carbamate and Cbz-Cl were purchased from Lancaster and Aldrich, respectively. $K_2OsO_2(OH)_4$ was purchased from Colonial Metals. [The crystal form or degree of hydration or both for the $K_2OsO_2(OH)_4$ seems to be crucial for success when it is *added directly* to the reaction mixture, and $K_2OsO_2(OH)_4$ purchased from other companies was not always successful. The problem seems to be that the material from some suppliers fails to dissolve. This source of difficulties can be overcome by our observation that all forms of $K_2OsO_2(OH)_4$ dissolve readily in dilute aqueous NaOH, but not in pure water. This has led to one of the catalyst addition scenarios (vide infra) where a small aliquot of the aqueous NaOH solution intended for titration of the chloramine proton is used to dissolve the $K_2OsO_2(OH)_4$. However, even these alkaline catalyst solutions appear to be unstable and should not be kept longer than 30 min before use.] The ligands $(DHQ)_2PHAL$, $(DHQD)_2PHAL$, $(DHQ)_2AQN$, and $(DHQD)_2AQN$ were obtained from Aldrich or prepared according to literature procedures.[13] Clorox brand aqueous sodium hypochlorite solutions (4−6%) were used. *tert*-Butyl hypochlorite was freshly prepared according to the *Organic Syntheses* procedure and stored over anhydrous $CaCl_2$ at ∼4 °C.[25]

Styrenes **1**, **2**, **4**, **9**, **12**, **13**, and **15**−**17** (Table 1) were purchased from Aldrich. Olefin **14** (Table 1) was purchased from Acros. Styrene **5** was kindly provided by Professor Dale Boger. We thank Ken Davenport of Hoechst Celanese for a generous gift of styrene **10** (Table 1). Styrene **18** (Table 1) was a gift from John Chung of Merck, and **6**−**8** (Table 1) were synthesized from the corresponding aldehydes (Aldrich) by the Wittig reaction. Styrenes **3** and **11** (Table 1) were prepared from *p*-hydroxybenzaldehyde in two steps: benzylation or tosylation of the phenolic hydroxyl group and Wittig olefination of the aldehyde. When necessary, the styrenes were purified by distillation, crystallization, or chromatography; however, most commercial samples were used as obtained.

Melting points were determined on a Thomas-Hoover Capillary Melting Point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00 ppm) for ^1H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. Optical rotations were measured with a Perkin-Elmer model 241 polarimeter in 95% EtOH. High-resolution mass spectra were obtained on VG-ZAB-2 SE spectrometer. Flash column chromatography was performed on Merck Kieselgel 60 (230−400 mesh). Analytical thin-layer chromatography was performed with precoated glass-backed plates (Merck Kieselgel 60 F_{254}). HPLC was performed on a Chiralcel AD column (25 cm × 4.6 mm i.d.), and the products were detected at 254 nm.

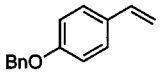
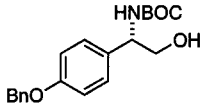
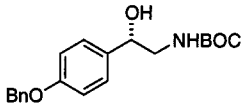
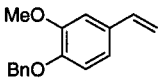
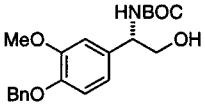
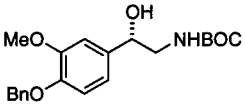
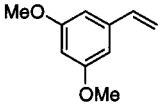
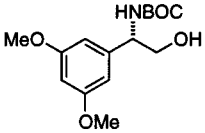
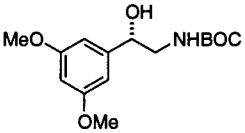
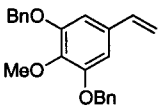
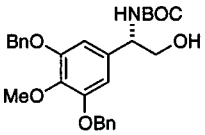
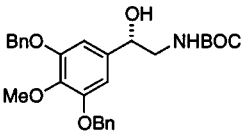
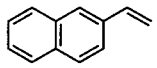
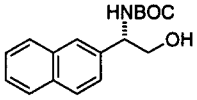
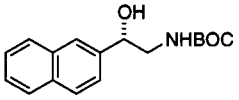
(22) Since the two regioisomers are oxidized to very different compounds (i.e., a carboxylic acid and a ketone, respectively), they need not be separated if the amino acid is the desired product. The crude mixture is oxidized and the ketone is removed from the much less soluble *N*-protected amino acid by trituration, by crystallization, or by the classical sequence: base-extraction/washing/release by acidification (see preparation of **25** and **26** in the Experimental Section).

(23) (a) To determine their enantiomeric purity, the amino acids were reduced back to the amino alcohols and their ee values compared with those of the original amino alcohols (e.g., amino acid **27** was converted to the protected amino alcohol acid **7A**, in a three-step sequence: (i) H_2/Pd−C, MeOH; (ii) LAH, THF, reflux; (iii) Cbz-Cl, $NaHCO_3$, CH_2Cl_2). (b) The amino acids **29** and **30** were reduced back to the corresponding protected amino alcohols **12A** and **13A** with borane−tetrahydrofuran complex in THF. The ee values were identical with those of the original amino alcohols derived from the AA reaction. (c) The *N*-Cbz-protected (*S*)-4-methoxyphenylglycinol was oxidized using a catalytic amount of ruthenium trichloride and 4.1 equiv of periodic acid in $CH_3CN/CCl_4/H_2O$ (1:1:0.15) at room temperature, in this case an approximately quantitative yield was obtained without any epimerization (Li, G.; Sharpless, K. B. unpublished results).

(24) We have now successfully developed a new nitrogen source for the AA reaction, 2-(trimethylsilyl)ethyl carbamate, which is complementary to the benzyl and *tert*-butyl carbamates (K. Barry Sharpless, K. Laxma Reddy, and Klaus R. Dress, manuscript in preparation).

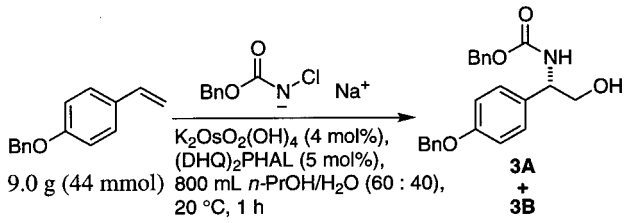
(25) We strongly recommend freshly prepared *tert*-butyl hypochlorite (Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1983; Collect. Vol. V, p 183). This material can be stored for up to 2 months at roughly 4 °C under dry conditions. Some commercially obtained samples of *tert*-butyl hypochlorite gave substandard enantioselectivities and lower yields.

Table 3. AA Reactions Using *t*-BuOC(O)NNaCl as the Nitrogen Source

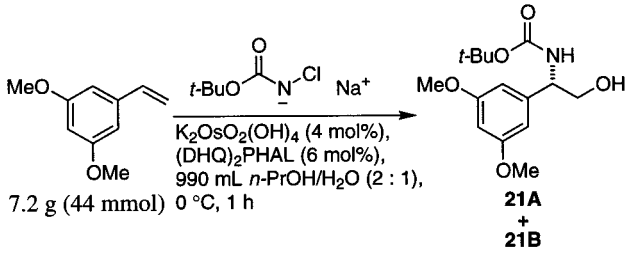
entry	substrate [a]	product **A** [b]	product **B** [b]	yield **A** % [c]	**A : B** [d]	%ee, **A** $(DHQ)_2PHAL$ [e]	%ee, ***ent*-A** $(DHQD)_2PHAL$ [e,f]
1		 **19A**	 **19B**	68	83 : 17	99	–96
2		 **20A**	 **20B**	65	75 : 25	99	–95
3		 **21A**	 **21B**	60	75 : 25	97	–95
4		 **22A**	 **22B**	70	89 : 11	98	–96
5		 **23A**	 **23B**	70	88 : 12	98	–97

[a] All reactions were performed on a 1.0 mmol scale using 4% $K_2OsO_2(OH)_4$, 6% ligand, and *n*-PrOH/water (2:1) at 0 °C for 1 h. [b] The products shown are the major enantiomers from reactions using $(DHQ)_2PHAL$ as the ligand. [c] Isolated yield of regioisomer **A** using $(DHQ)_2PHAL$. [d] The ratio of benzylic amine **A** to benzylic alcohol **B** determined by ^1H NMR. [e] The BOC groups were replaced by Cbz groups, and ee values were determined by HPLC (Chiralcel AD column). [f] The "negative" ee values are meant to emphasize that with $(DHQD)_2PHAL$ as ligand the mirror image isomer dominates (i.e., ***ent*-A** > **A**).

Scheme 2. Large Scale AA Reactions



Yield (both isomers): 14.5 g, 90%; regioselectivity 80 : 20; ee of major regioisomer (**3A**): 94%

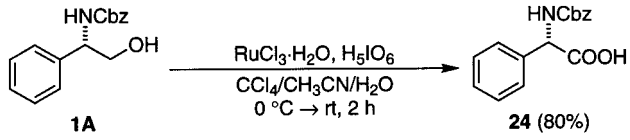


Yield (both isomers): 11.3 g, 86%; regioselectivity 75 : 25; ee of major regioisomer (**21A**): 97%

The benzyl carbamate AA reactions in Table 1 were carried out on a 2 mmol scale and those in Table 2 on a 1 mmol scale. The *tert*-butyl carbamate AA reactions in Table 3 were performed on a 1 mmol scale.

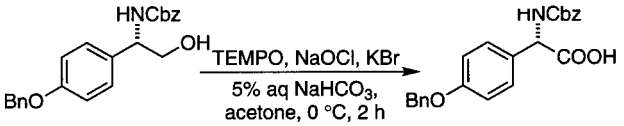
General Procedure for the Benzyl Carbamate-Based AA. All benzyl carbamate reactions (entries 1−19 in Table 1) were performed as described here for 4-(benzyloxy)-3-methoxystyrene (entry 4, Table 1).

Scheme 3. RuO_4-Catalyzed Oxidation of α-Arylglycinols to the Corresponding α-Arylglycines



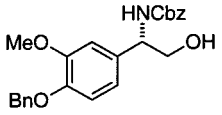
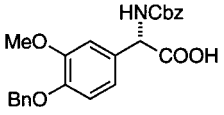
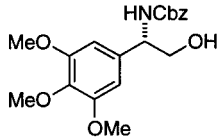
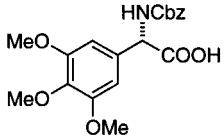
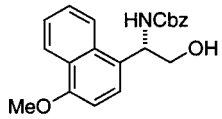
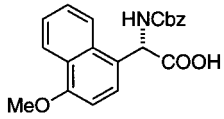
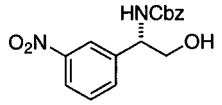
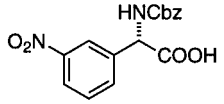
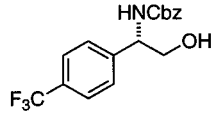
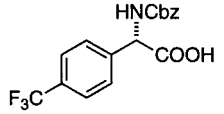
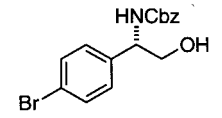
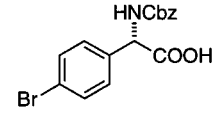
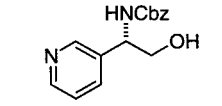
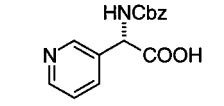
(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-(benzyloxy)-3-methoxyphenyl)-2-hydroxyethylamine (4A and 4B) [$(DHQ)_2PHAL$]. A 50 mL round-bottomed flask was charged with benzyl carbamate (0.940 g, 6.20 mmol) and *n*-PrOH (8 mL). To this stirred solution was added a freshly prepared aqueous solution of NaOH (0.244 g, 6.1 mmol in 15 mL water), followed by *tert*-butyl hypochlorite[25] (0.7 mL, 0.662 g, 6.1 mmol). After 5 min a solution of $(DHQ)_2PHAL$ (80 mg, 0.10 mmol, 5 mol %) in *n*-PrOH (7 mL) was added; the reaction mixture should be homogeneous at this point. 4-(Benzyloxy)-3-methoxystyrene (0.480 g, 2.0 mmol, dissolved in 10 mL of *n*-PrOH) was then added, followed by $K_2OsO_2(OH)_4$ (29.4 mg, 0.08 mmol, 4 mol %). The light green solution was stirred at 25 °C and became light yellow after 1 h, indicating completion. The reaction mixture was then cooled in an ice-bath, and the reaction was quenched by the addition of a saturated aqueous sodium sulfite solution (20 mL) and stirred for 15 min. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with water (20 mL), brine (50 mL), dried over

Table 4. TEMPO-Catalyzed Oxidation of α-Arylglycinols to the Corresponding α-Arylglycines *without Prior Purification To Remove the Regioisomer*



20 g (53 mmol)
3A : 3B (80 : 20)

25 (14.6 g, 86%)

aminoalcohol	amino acid	yield (%)[a]
 **4A : 4B** (77 : 23)	 **26**	71
 **7A : 7B** (75 : 25)	 **27**	75
 **8A : 8B** (83 : 17)	 **28**	78
 **12A : 12B** (74 : 26)	 **29**	82
 **13A : 13B** (75 : 25)	 **30**	77
 **15A : 15B** (80 : 20)	 **31**	86
 **18A : 18B** (50 : 50)	 **32**	61

[a] Based on the regioisomer **A** content of the starting mixture.

anhydrous $MgSO_4$, and concentrated to afford the crude mixture of regioisomers (**A**/**B** = 77:23) and benzyl carbamate. Flash chromatography (SiO_2, 5 × 25 cm, 15−35% EtOAc/hexane gradient elution) provided regioisomer **4B** (0.16 g, 17% yield, 22% ee) as a colorless solid and the desired product **4A** (0.54 g, 70%, 98% ee) as a colorless solid. For **4B:** R_f = 0.6 (EtOAc/hexane = 4:6); mp 96−97 °C; $[\alpha]^{25}_D$ = +6.4° (c = 0.5, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (m, 10H), 6.91 (s, 1H), 6.82−6.80 (m, 2H), 5.18 (br t, 1H), 5.13 (s, 2H), 5.09 (s, 2H), 4.75−4.72 (m, 1H), 3.85 (s, 3H), 3.54−3.48 (m, 1H), 3.31−3.25 (m, 1H), 2.77 (br s, 1H, OH, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 149.6, 147.7, 137.1, 136.4, 134.9, 128.6, 128.2, 127.9, 127.3, 118.1, 113.8, 109.6, 73.1, 71.0, 66.9, 55.9, 55.8, 48.5; HRMS calcd for $C_{24}H_{25}NO_5$ $(M + Na)^+$ 430.1630, found 430.1646; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.4 mL min^{-1}, 254 nm, 45.2 min (*S*), 49.2 min (*R*). For **4A:** R_f = 0.5 (EtOAc/hexane = 4:6); mp 144−145 °C; $[\alpha]^{25}_D$ = +38.4° (c = 0.5, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.28 (m, 10H), 6.84 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 6.75 (dd, J = 8.2, 1.9 Hz, 1H), 5.4 (d, J = 6.2 Hz, 1H), 5.1 (m, 4H), 4.8 (br s, 1H), 3.85 (br s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 149.8, 147.8, 137.0, 136.2, 128.6, 128.5, 128.2, 127.9, 127.8, 127.2, 127.1, 118.5, 114.0, 110.5, 71.0, 67.0, 66.4, 56.8, 56.0; HRMS calcd for $C_{24}H_{25}NO_5$ $(M + Na)^+$ 430.1630, found 430.1640; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 40.5 min (*S*), 67.2 min (*R*).

Preparative Scale (44 mmol) Procedure for the Benzyl Carbamate-Based AA (described for 4-(benzyloxy)styrene) Giving 3A and 3B [$(DHQ)_2PHAL$]: A 1-L round-bottomed flask, equipped with a magnetic stir bar was charged with aqueous NaOH [315 mL, prepared by dissolving 5.4 g (135 mmol) in 330 mL of water and then removing a 15 mL portion of solution. This 15 mL of aqueous NaOH is used to dissolve the $K_2OsO_2(OH)_4$ salt providing the pink catalyst solution to be added shortly.[26] To this stirred solution, benzyl carbamate (20.5 g, 135 mmol in 173 mL of *n*-PrOH) and freshly prepared *tert*-butyl hypochlorite (15.2 mL, 14.4 g, 133 mmol) were added sequentially. After about 5 min of stirring, $(DHQ)_2PHAL$ (1.76 g, 2.2 mmol, 5 mol % in 151 mL of *n*-PrOH) was added; it is important to note that the reaction mixture is homogeneous at this point. 4-(Benzyloxy)styrene (9.0 g, 44 mmol, in 150 mL of *n*-PrOH) was then added, followed by the above-described $K_2OsO_2(OH)_4$ solution (0.636 g, 1.73 mmol in 15 mL of aqueous NaOH, vide supra). The reaction mixture was stirred at 20 °C for 1 h (during this time the green solution became light yellow) and then diluted with cold water (1 L) and maintained at 0 °C for 2 h while the product precipitated. The resulting white solid was collected by filtration, washed with cold water (300 mL) and then with cold *n*-PrOH (100 mL), and dried in vacuo to afford **3** as mixture of regioisomers (14.5 g, 90% yield, **3A/3B** = 80:20; **3A,** 94% ee).[27]

(1*S*)-*N*-(Benzyloxycarbonyl)-1-phenyl-2-hydroxyethylamine (1A) [$(DHQ)_2PHAL$]: mp 98−99 °C; $[\alpha]^{25}_D$ = +29.0° (c = 1.0, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 (m, 10H), 5.46 (br s, 1H), 5.0 (dd, J = 12.3, 20.0 Hz, 2H), 4.84 (br, 1H), 3.87 (br s, 2H), 2.01 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 139.1, 136.2, 128.8, 128.5, 128.2, 127.8, 126.6, 67.0, 66.4, 57.0; HRMS calcd for $C_{16}H_{19}NO_4$ $(M + H)^+$ 272.1287, found 272.1299; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.7 mL min^{-1}, 254 nm, 12.0 min (*S*), 16.5 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-methoxyphenyl)-2-hydroxyethylamine (2A) [$(DHQ)_2PHAL$]: mp 111−112 °C; $[\alpha]^{25}_D$ = +45.2° (c = 0.5, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 7.2 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.44 (d, J = 6.7 Hz, 1H), 5.08 (m, 2H), 4.7 (br s, 1H), 3.8 (br s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

(26) Since the rate of dissolution of powdered $K_2OsO_2(OH)_4$ in the reaction medium has been observed to vary widely depending on the supplier and/or age of the material, the outcome of the reaction has occasionally been unsatisfactory. *Therefore, this modification of our original procedure,*[8,9] *in which the $K_2OsO_2(OH)_4$ salt is dissolved in a portion of the aqueous NaOH immediately before use, is now recommended (especially if catalyst-insolubility problems are suspected). All forms of $K_2OsO_2(OH)_4$ seem to dissolve rapidly in water containing a little NaOH.* However, this trick can only be used easily in the carbamate and amide AA processes where the hydroxide ion is needed anyway to titrate the acidic proton of the RCON*H*X species. In other cases (e.g., the AD), the pH of reactions containing unneutralized hydroxide becomes too high and catalyst turnover almost stops.

δ 159.1, 156.5, 136.3, 131.2, 128.5, 128.2, 127.8, 114.1, 113.9, 67.0, 66.3, 56.6, 55.4; HRMS calcd for $C_{17}H_{19}NO_4$ $(M + H)^+$ 302.1392, found 302.1382; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.7 mL min^{-1}, 254 nm, 14.6 min (*S*), 22.2 min (*R*).

(1*R*)-*N*-(Benzyloxycarbonyl)-1-(4-(benzyloxy)phenyl)-2-hydroxyethylamine (*ent*-3A) [(DHQD)$_2$PHAL]: mp 120−121 °C; $[\alpha]^{25}_D = -35.6°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.25 (m, 10H), 7.2 (d, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 5.36 (d, $J = 12.4$ Hz, 1H), 5.08 (m, 4H), 4.78 (br, 1H), 3.84 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.4, 136.8, 136.2, 128.6, 128.5, 128.2, 128.0, 127.7, 127.4, 115.1, 70.0, 67.0, 66.5, 56.5; HRMS calcd for $C_{23}H_{23}NO_4$ $(M + Na)^+$ 400.1525, found 400.1535; HPLC Chiralcel AD, 30% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 14.0 min (*S*), 25.8 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(3,5-bis(benzyloxy)-4-methoxyphenyl)-2-hydroxyethylamine (5A) [(DHQ)$_2$PHAL]: mp 117−118 °C; $[\alpha]^{25}_D = +30.6°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.3 (m, 15H), 6.52 (s, 2H), 5.4−5.36 (br s, 1H), 5.09 (s, 6H), 4.7−4.6 (br s, 1H), 3.9 (s, 3H), 3.8−3.6 (m, 2H), 1.9 (br s, 1H, OH, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 152.7, 138.9, 136.9, 136.2, 134.6, 128.5, 128.2 (br), 127.9, 127.4, 106.3, 71.1, 67.0, 66.3, 60.9, 56.9; HRMS calcd for $C_{31}H_{31}NO_6$ $(M + Cs)^+$ 646.1206, found 646.1187; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 34.8 min (*S*), 63.5 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(3,5-dimethoxyphenyl)-2-hydroxyethylamine (6A) [(DHQ)$_2$PHAL]: mp 109−110 °C; $[\alpha]^{25}_D = +32.6°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 5H), 6.4 (d, $J = 1.9$ Hz, 2H), 6.35 (d, $J = 1.9$ Hz 1H), 5.48 (d, $J = 7.0$ Hz, 1H), 5.09 (m, 2H), 4.7 (br s, 1H), 3.89 (m, 2H), 3.75 (s, 6H), 1.8 (br s, 1H, OH, D_2O exchangeable); ^{13}C NMR (100 MHz $CDCl_3$) δ 161.1, 156.4, 141.6, 136.2, 128.5, 128.2, 104.7, 99.5, 67.1, 66.4, 57.2, 55.4; HRMS calcd for $C_{18}H_{21}NO_5$ $(M + Na)^+$ 354.1317, found 354.1311; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 24.1 min (*S*), 30.0 min (*R*).

(1*R*)-*N*-(Benzyloxycarbonyl)-1-(3,4,5-trimethoxyphenyl)-2-hydroxyethylamine (*ent*-7A) [(DHQD)$_2$PHAL]: mp 96−97 °C; $[\alpha]^{25}_D = -27.8°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.47 (s, 2H), 5.53 (d, $J = 6.8$ Hz, 1H), 5.1 (s, 2H), 4.7 (br s, 1H), 3.85−3.80 (m, 11H), 1.96 (br s, 1H, OH, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 153.4, 137.2, 136.2, 135.1, 128.5, 128.2, 103.4, 102.6, 67.0, 66.2, 60.8, 57.2, 56.0; HRMS calcd for $C_{19}H_{23}NO_6$ $(M + Na)^+$ 384.1423, found 384.1415; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 28.0 min (*S*), 35.6 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-methoxynaphthyl)-2-hydroxyethylamine (8A) [(DHQ)$_2$PHAL]: mp 146−147 °C; $[\alpha]^{25}_D = +7.75°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, $J = 8.1$ Hz, 1H), 8.0 (d, $J = 7.6$ Hz, 1H), 7.52 (m, 2H), 7.34 (m, 6H), 6.73 (d, $J = 8.0$ Hz, 1H), 5.53 (br s, 1H), 5.1 (br s, 1H), 3.99−3.90 (br s, 5H), 2.4 (br s, 1H, OH, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 155.4, 136.3, 131.6, 128.5, 128.1, 127.1, 126.3, 126.1, 125.3, 123.7, 122.8, 122.5, 103.9, 67.0, 65.7, 55.6, 52.9; HRMS calcd for $C_{21}H_{21}NO_4$ $(M + Na)^+$ 374.1368, found 374.1360; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 20.9 min (*S*), 26.5 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-biphenyl)-2-hydroxyethylamine (9A) [(DHQ)$_2$PHAL]: mp 164−165 °C; $[\alpha]^{25}_D = +46.8°$ ($c = 0.5$, 95% EtOH, 80% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6−7.3 (m, 14H), 5.5 (d, $J = 7.2$ Hz, 1H), 5.1 (dd, $J = 8.2$, 2.0 Hz, 1H), 4.8 (br s, 1H), 3.8 (br s, 2H), 2.0 (br s, 1H, OH, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 140.6, 140.3, 138.6, 136.2, 128.7, 128.4, 128.0, 127.9, 127.2, 127.0, 126.9, 126.3, 66.7, 65.4, 56.8; HRMS calcd for $C_{22}H_{21}NO_3$ $(M + Na)^+$ 370.1419, found 370.1411; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 20.4 min (*S*), 26.2 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-acetoxyphenyl)-2-hydroxyethylamine (10A) [(DHQ)$_2$PHAL]: mp 153−154 °C; $[\alpha]^{25}_D = +30.8°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 5H), 7.24 (d, $J = 8.2$ Hz, 2H), 6.68 (d, $J = 8.2$ Hz, 2H), 5.6 (br s, 1H), 5.07 (dd, $J = 8.2$, 20.4 Hz, 2H), 4.7 (br s, 1H), 3.76 (m, 2H), 2.2 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 156.3, 150.0, 137.2, 136.2, 128.5, 128.2, 127.7, 121.9, 115.4, 67.0, 66.1, 56.4, 21.1; HRMS calcd for $C_{18}H_{19}NO_5$ $(M + Na)^+$ 352.1161, found 352.1167; HPLC Chiralcel AD, 30% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 10.6 min (*S*), 13.3 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-((4-(*p*-toluenesulfonyl)oxy)-phenyl)-2-hydroxyethylamine (11A) [(DHQ)$_2$PHAL]: mp 143−144 °C; $[\alpha]^{25}_D = +24.0°$ ($c = 0.4$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, $J = 8.3$ Hz, 2H), 7.28 (m, 7H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.9 (d, $J = 8.3$ Hz, 2H), 5.7 (br s, 1H), 5.04 (m, 2H), 4.7 (br s, 1H), 3.74 (m, 2H), 2.4 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 148.9, 145.5, 138.5, 132.3, 129.8, 128.5, 128.4, 128.2, 128.1, 127.9, 122.5, 67.1, 65.7, 56.2, 21.7; HRMS calcd for $C_{23}H_{23}NO_6S$ $(M + Cs)^+$ 574.0300, found 574.0316; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 58.3 min (*S*), 90.6 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(3-nitrophenyl)-2-hydroxyethylamine (12A) [(DHQ)$_2$PHAL]: mp 85−86 °C; $[\alpha]^{25}_D = +28.6°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.2 (br s, 1H), 8.13 (d, $J = 8.2$ Hz, 1H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.5 (t, $J = 8.2$, 8.1 Hz, 1H), 7.34 (m, 5H), 5.78 (br s, 1H), 5.09 (m, 2H), 4.9 (br s, 1H), 3.90−3.84 (m, 2H), 2.07 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 148.4, 141.9, 135.0, 133.1, 129.6, 128.6, 128.3, 128.1, 122.7, 121.6, 67.2, 65.4, 56.2; HRMS calcd for $C_{16}H_{16}N_2O_5$ $(M + Na)^+$ 339.0957, found 339.0949; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 25.2 min (*S*), 34.2 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-(trifluoromethyl)phenyl)-2-hydroxyethylamine (13A) [(DHQ)$_2$PHAL]: mp 142−143 °C; $[\alpha]^{25}_D = +18.2°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, $J = 8.1$ Hz, 2H), 7.4 (d, $J = 8.1$ Hz, 2H), 7.3 (m, 5H), 5.5 (br s, 1H), 5.1 (dd, $J = 11.8$, 22.8 Hz, 2H), 4.8 (br s, 1H), 3.92−3.86 (m, 2H), 1.8 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 143.9, 129.3, 128.3, 128.0, 127.8, 126.9, 126.3, 125.2, 66.8, 64.9, 56.6; HRMS calcd for $C_{17}H_{16}F_3NO_3$ $(M + Na)^+$ 362.0980, found 362.0988; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 12.4 min (*S*), 23.3 min (*R*).

(1*R*)-*N*-(Benzyloxycarbonyl)-1-(4-cyanophenyl)-2-hydroxyethylamine (*ent*-14A) [(DHQD)$_2$PHAL]: mp 90−91 °C; $[\alpha]^{25}_D = -34.8°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, $J = 7.9$ Hz, 2H), 7.35 (d, $J = 7.9$ Hz, 2H), 7.24 (m, 5H), 5.8 (br s, 1H), 5.0 (m, 2H), 4.8 (br s, 1H), 3.84−3.76 (m, 2H), 2.4 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 145.2, 135.9, 132.4, 128.6, 128.4, 128.2, 127.5, 118.6, 111.4, 67.2, 65.4, 56.6; HRMS calcd for $C_{17}H_{16}N_2O_3$ $(M + Na)^+$ 319.1059, found 319.1050; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 24.0 min (*S*), 54.2 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-bromophenyl)-2-hydroxyethylamine (15A) [(DHQ)$_2$PHAL]: mp 133−134 °C;

$[\alpha]^{25}_D = +33.6°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 (d, $J = 8.2$ Hz, 2H), 7.4 (m, 5H), 7.15 (d, $J = 8.2$ Hz, 2H), 5.7 (br s, 1H), 5.1 (m, 2H), 4.7 (br s, 1H), 3.8−3.7 (m, 2H), 2.3 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 136.0, 131.8, 131.6, 128.5, 128.3, 127.6, 121.7, 67.1, 65.9, 56.4; HRMS calcd for $C_{16}H_{16}BrNO_3$ $(M + Na)^+$ 372.0211/374 $(M + 2)^+$, found 372.0220/374 $(M + 2)^+$; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 15.9 min (*S*), 29.2 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-chlorophenyl)-2-hydroxyethylamine (16A) [(DHQ)$_2$PHAL]: mp 115−116 °C; $[\alpha]^{25}_D = +37.2°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3−7.1 (m, 9H), 5.6 (br s, 1H), 5.08 (dd, $J = 12.0$, 21.0 Hz, 2H), 4.7 (br s, 1H), 3.8−3.7 (m, 2H), 1.9 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 136.1, 128.9, 128.7, 128.5, 128.3, 128.0, 127.2, 67.1, 66.0, 56.3; HRMS calcd for $C_{16}H_{16}ClNO_3$ $(M + Na)^+$ 328.0716/330 $(M + 2)^+$, found 328.0707/330 $(M + 2)^+$; HPLC Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 12.2 min (*S*), 19.0 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-fluorophenyl)-2-hydroxyethylamine (17A) [(DHQ)$_2$PHAL]: mp 107−108 °C; $[\alpha]^{25}_D = +32.6°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (m, 7H), 7.0 (t, $J = 8.4$ Hz, 2H), 5.5 (br s, 1H), 5.08 (dd, $J = 12.1$, 21.0 Hz, 2H), 4.8 (br s, 1H), 3.8 (m, 2H), 2.0 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 ($J = 245$ Hz), 156.4, 136.1, 135.0 (br), 128.6, 128.3 ($J = 7$ Hz), 115.6 ($J = 22$ Hz), 67.1, 66.1, 56.4; HRMS calcd for $C_{16}H_{16}FNO_3$ $(M + Na)^+$ 312.1012, found 312.1017; HPLC Chiralcel AD, 30% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 15.4 min (*S*), 25.8 min (*R*).

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(3-pyridyl)-2-hydroxyethylamine (18A) [(DHQ)$_2$PHAL]: mp 117−118 °C; $[\alpha]^{25}_D = +22.6°$ ($c = 0.23$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5−8.4 (m, 2H), 7.6 (d, $J = 7.5$ Hz, 1H), 7.3 (m, 5H), 7.2 (m, 1H), 5.8 (d, $J = 7.0$ Hz, 1H), 5.08 (m, 2H), 4.8 (br s, 1H), 3.93−3.84 (m, 2H), 2.5 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 148.6, 148.1, 135.4, 134.8, 128.6, 128.3, 128.2, 123.6, 67.1, 65.5, 54.8; HRMS calcd for $C_{15}H_{16}N_2O_3$ $(M + Na)^+$ 295.1059, found 295.1055; HPLC Chiralcel AD, 30% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 8.4 min (*S*), 11.3 min (*R*).

General Procedure for the *tert*-Butyl Carbamate-Based AA. All *t*-butyl carbamate reactions (entries 1−5 in Table 3) were performed as described here for 3,5-dimethoxystyrene (entry 3, Table 3).

(1*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-(3,5-dimethoxyphenyl)-2-hydroxyethylamine (21A) [(DHQ)2PHAL]: A solution of *tert*-butyl carbamate (0.364 g, 3.1 mmol, 3.05 eq) in *n*-PrOH (4.0 mL) was sequentially treated with NaOH (0.122 g, 3.05 mmol in 7.5 mL water) and *t*-BuOCl[24] (0.35 mL, 0.33 g, 3.05 mmol). After 5 min of stirring, the solution was cooled to 0 °C and a solution of $(DHQ)_2PHAL$ (0.048 g, 0.12 mmol, 6 mol % dissolved in 4 mL of *n*-PrOH) was added; the reaction mixture should be homogeneous at this point. A solution of 3,5-dimethoxystyrene (0.164 g, 1.0 mmol dissolved in 7.0 mL of *n*-PrOH) was then added followed by $K_2OsO_2(OH)_4$ (0.0148 g, 0.08 mmol, 4 mol %). The reaction mixture was stirred for 1 h at 0 °C, the light green solution turned light yellow, and the reaction was quenched with saturated aqueous sodium sulfite (10 mL). The two phases were separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (25 mL), dried over anhydrous $MgSO_4$, and concentrated to afford the crude product contaminated with its regioisomer and *tert*-butyl carbamate. Flash chromatography (2.5 × 5 cm, 15−25%, EtOAc/hexane gradient elution) of this crude material provided regioisomer **21B** (0.065 g, 20% yield, 4% ee) as colorless syrup and **21A** (0.195 g, 60% yield, 97% ee) as colorless solid. For **21B**: $R_f = 0.55$ (EtOAc/hexane = 1:2); $[\alpha]^{25}_D = +2.2°$ ($c = 0.65$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, $J = 1.9$ Hz, 2H), 6.37 (t, $J = 2.2$ Hz, 1H), 4.90 (br s, 1H), 4.76 (br s, 1H), 3.78 (s, 6H), 3.46 (m, 1H), 3.24 (m, 1H), 3.10 (br, 1H, OH, D_2O exchangeable), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.1, 144.4, 103.7, 99.8, 79.9, 74.0, 55.4, 48.3, 28.4; HRMS calcd for $C_{15}H_{23}NO_5$ $(M + Na)^+$ 320.1474, found 320.1485; HPLC BOC group was removed and replaced by a Cbz protecting group, Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 26.9 min (*S*), 32.0 min (*R*). For **21A:** $R_f = 0.5$ (EtOAc/hexane = 1:2); mp 97−98 °C; $[\alpha]^{25}_D = +44.6°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, $J = 1.8$ Hz, 2H), 6.35 (d, $J = 1.8$ Hz, 1H), 5.23 (br s, 1H), 4.7 (br s, 1H), 3.8−3.7 (br s, 8H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 156.0, 142.0, 104.6, 99.3, 79.9, 66.6, 56.9, 55.2, 28.3; HRMS calcd for $C_{15}H_{23}NO_5$ $(M + Na)^+$ 320.1414, found 320.1467; HPLC BOC group was removed and replaced by a Cbz protecting group, Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 24.1 min (*S*), 30.0 min (*R*).

Preparative Scale (44 mmol) Procedure for the *tert*-Butyl Carbamate-Based AA (described for 3,5-dimethoxystyrene) Giving 21A and 21B. The same procedure described on a 1.0 mmol scale was followed for this 44.0 mmol scale reaction using the following quantities of reagents: NaOH (5.4 g in 332 mL of H_2O), *tert*-butyl carbamate (16.0 g in 176 mL of *n*-PrOH), *t*-BuOCl (16.5 mL), $(DHQ)_2PHAL$ (2.2 g in 176 mL of *n*-PrOH), 3,5-dimethoxystyrene (7.2 g in 308 mL *n*-PrOH), and $K_2OsO_2(OH)_4$ (0.651 g). After the reaction was complete, *n*-PrOH (about 500 mL) was removed by rotary evaporation (bath at ca. 40 °C) and the resulting solution was cooled to 0 °C. The product which precipitated was isolated by filtration and then dissolved in ca. 150 mL of ethyl acetate. After this solution was passed through a small pad of silica gel, it was concentrated to give the products **21A/21B** (11.3 g, 86% yield, **21A:21B** = 75:25, **21A** 97% ee).

(1*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-(4-((benzyloxy)phenyl)-2-hydroxyethylamine (19A) [(DHQ)$_2$PHAL]: mp 129−130 °C; $[\alpha]^{25}_D = +57.2°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5H), 7.2 (d, $J = 8.6$ Hz, 2H), 6.9 (d, $J = 8.6$ Hz, 2H), 5.2 (br s, 1H), 5.0 (s, 2H), 4.7 (br s, 1H), 3.79 (br s, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.2, 136.9, 131.8, 128.6, 128.0, 127.7, 127.4, 115.1, 80.0, 70.0, 66.9, 56.3, 28.3; HRMS calcd for $C_{20}H_{25}NO_4$ $(M + Na)^+$ 344.1862, found 344.1875; HPLC BOC group was removed and replaced by a Cbz protecting group, Chiralcel AD, 30% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 14.0 min (*S*), 25.8 min (*R*).

(1*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-(4-(benzyloxy)-3-methoxyphenyl]-2-hydroxyethylamine (20A) [(DHQ)$_2$PHAL]: mp 119−120 °C; $[\alpha]^{25}_D = +50.8°$ ($c = 0.5$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 6.82 (d, $J = 8.3$ Hz, 1H), 6.81 (d, $J = 1.8$ Hz, 1H), 6.73 (dd, $J = 8.3$, 1.8 Hz, 1H), 5.29 (br s, 1H), 5.1 (s, 1H), 4.7 (br s, 1H), 3.8 (s, 3H), 3.76 (br s, 2H), 2.6 (br s, 1H, OH), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 149.8, 147.6, 137.0, 132.6, 128.5, 127.8, 127.2, 118.5, 114.0, 110.5, 79.9, 71.0, 66.7, 56.6, 55.9, 28.3; HRMS calcd for $C_{21}H_{27}NO_5$ $(M + Cs)^+$ 506.0944, found 506.0931; HPLC BOC group was removed and replaced by a Cbz

protecting group, Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 40.5 min (*S*), 67.2 min (*R*).

(1*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-(3,5-dimethoxyphenyl)-2-hydroxyethylamine (21A) [(DHQ)$_2$PHAL]: mp 97−98 °C; $[\alpha]^{25}_D = +44.6°$ (*c* = 0.5, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 1.8 Hz, 2H), 6.35 (d, *J* = 1.8 Hz, 1H), 5.23 (br s, 1H), 4.7 (br s, 1H), 3.8−3.7 (br s, 8H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 156.0, 142.0, 104.6, 99.3, 79.9, 66.6, 56.9, 55.2, 28.3; HRMS calcd for $C_{15}H_{23}NO_5$ $(M + Na)^+$ 320.1414, found 320.1467; HPLC BOC group was removed and replaced by a Cbz protecting group, Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 24.1 min (*S*), 30.0 min (*R*).

(1*R*)-*N*-(*tert*-Butyloxycarbonyl)-1-(3,5-bis(benzyloxy)-4-methoxyphenyl)-2-hydroxyethylamine (*ent*-22A) [(DHQD)$_2$PHAL]: mp 134−135 °C; $[\alpha]^{25}_D = -33.6°$ (*c* = 0.5, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.25 (m, 10H), 6.53 (s, 2H), 5.1 (s, 5H), 4.6 (br s, 1H), 3.86 (s, 3H), 3.7 (br s, 2H), 2.03 (br s, 1H, OH), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.7, 138.9, 137.0, 134.9, 128.5, 127.9, 127.3, 106.3, 80.0, 71.2, 66.7, 60.9, 56.7, 28.3; HRMS calcd for $C_{28}H_{33}NO_6$ $(M + Cs)^+$ 612.1362, found 612.1342; HPLC BOC group was removed and replaced by a Cbz protecting group, Chiralcel AD, 15% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 34.8 min (*S*), 63.5 min (*R*).

(1*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-(2-naphthyl)-2-hydroxyethylamine (23A) [(DHQ)$_2$PHAL]: mp 153−154 °C; $[\alpha]^{25}_D = +55.0°$ (*c* = 0.5, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8−7.7 (m, 4H), 7.48 (m, 2H), 7.4 (d, *J* = 8.6 Hz, 1H), 5.4 (br s, 1H), 4.9 (br s, 1H), 3.9 (br s, 2H), 2.4 (br s, 1H, OH), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 133.3, 132.9, 128.6, 127.9, 127.8, 126.3, 126.0, 125.4, 124.6, 80.0, 66.7, 56.9, 28.3; HRMS calcd for $C_{17}H_{21}NO_3$ $(M + Cs)^+$ 420.0576, found 420.0562; HPLC BOC group was removed and replaced by a Cbz protecting group, Chiralcel AD, 30% *i*-PrOH/hexane, 0.5 mL min^{-1}, 254 nm, 7.8 min (*S*), 10.7 min (*R*).

General Procedure for the Oxidation of Protected Amino Alcohols to the Corresponding Protected Amino Acids Using Ruthenium Trichloride/Periodic Acid Described for (1*S*)-*N*-(benzyloxycarbonyl)-1-phenyl-2-hydroxyethylamine (1A, Table 1)). (1*S*)-(*N*-Benzyloxycarbonyl)phenylglycine (24): In a 250-mL round-bottomed flask equipped with a magnetic stirrer, (*S*)-*N*-Cbz-phenylglycinol (1.3 g, 5.0 mmol) was dissolved in CCl_4 (100 mL) and acetonitrile (100 mL). To this solution were added water (15 mL) and periodic acid (4.7 g, 20.1 mmol, 4.1 equiv). The reaction mixture was stirred until both phases became clear, and ruthenium trichloride hydrate (0.293 g, 3 mol %) was then added at 0 °C. The reaction mixture was stirred at room temperature for 2 h and diluted with $CHCl_3$ (50 mL). The two phases were separated, and the aqueous phase was extracted with chloroform (2 × 50 mL). The combined organic extracts were washed with saturated NaCl solution and then concentrated to one-third of the original volume. The resulting solution/emulsion was filtered through Celite, and the filtrate was treated with 10% $NaHCO_3$ solution. The two layers were separated, and the aqueous layer was washed with chloroform after acidification to pH = ca. 5 with 15% aqueous citric acid; the product was extracted into ethyl acetate (2 × 75 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated to afford the pure acid **24** (1.1 g, 80% yield); mp 133−134 °C; $[\alpha]^{25}_D = +116.4°$ (*c* = 1, 95% EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 8.2 Hz, 1H, NH), 7.52−7.33 (m, 10 H), 5.20 (d, *J* = 8.2 Hz, 1H), 5.18 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 155.9, 137.2, 136.9, 128.7, 128.4, 128.0, 127.9, 127.8 (2C), 65.7, 58.2; HRMS calcd for $C_{16}H_{15}NO_4$ $(M + H)^+$ 285.1079, found 285.1088.

General Procedure for the Oxidation of Protected Amino Alcohols to the Corresponding Amino Acids Using TEMPO/NaOCl. All of the TEMPO−NaOCl oxidations, producing amino acids **25**−**32** in Table 4, were performed on the crude mixture of amino alcohol regioisomers as described in detail below for the mixture of (1*S*)-*N*-(benzyloxycarbonyl)-1-(4-(benzyloxy)phenyl)-2-hydroxyethylamine (**3A**) and **3B**.

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-(benzyloxy)phenyl)glycine (25): The crude mixture of amino alcohols **3A** and **3B** (20 g, 4:1 regioisomeric ratio, 53 mmol) isolated from the AA step (vide supra) was dissolved in acetone (400 mL) and added to an aqueous 5% $NaHCO_3$ solution (140 mL). This magnetically stirred heterogeneous mixture was cooled to 0 °C and treated sequentially with KBr (0.64 g, 5.4 mmol) and TEMPO (8.7 g, 56 mmol). Sodium hypochlorite (4−6%, 130 mL, ca. 67 mmol) was then added dropwise over a period of 10−15 min, while the mixture was vigorously stirred and maintained at 0 °C. After 1 h, additional NaOCl (50 mL, 26 mmol) was added, and stirring was continued at 0 °C for another hour followed by addition of a 5% $NaHCO_3$ solution (200 mL). When the acetone was removed on a rotary evaporator, the sodium salt of the product precipitated and was isolated by filtration of the aqueous suspension.[28] This salt was washed with ether (1 L) to remove the TEMPO impurities and the ketone which is formed from regioisomer **3B** in the oxidation step. The washed salt was then suspended in EtOAc:H_2O (1:0.5 L), and the aqueous phase was acidified to pH = 6 with 10% aqueous citric acid. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (2 × 250 mL). The combined organic phases were washed with water (500 mL) and brine (500 mL), dried over anhydrous $MgSO_4$, and concentrated to afford the pure acid **25** (14.6 g, 86% yield); mp 125−126 °C; $[\alpha]^{25}_D = +106.0°$ (*c* = 1, 95% EtOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.75 (br, 1H, OH, D_2O exchangeable), 8.04 (d, *J* = 7.92 Hz, 1H, NH), 7.52−7.29 (m, 12H), 6.96 (d, *J* = 8.6 Hz, 2H), 5.08 (s, 2H), 5.07 (br, 1H), 5.03 (dd, *J* = 12.6, 1.8 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.4, 158.9, 156.7, 137.8, 137.7, 130.0, 129.8, 129.2, 129.1, 128.6, 128.5, 128.4, 115.3, 101.0, 69.6, 65.9, 57.8; HRMS calcd for $C_{23}H_{21}NO_5$ $(M + Na)^+$ 414.1317, found 414.1327.

[The above detailed oxidation procedure for preparing acid **25** on a 53 mmol scale was also followed for the other seven cases below (**26**−**32**). However, the scale in these examples was only 2 mmol, and the workups diverged from that in the parent example, as described in footnote 28. As for **25**, the source of amino acids **26**−**32** is the crude regioisomeric mixture of amino alcohols from the AA step.]

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-(benzyloxy)-3-methoxyphenyl)glycine (26): mp 174−175 °C; $[\alpha]^{25}_D = +100.0°$ (*c* = 1, 95% EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07

(27) The regioselectivity of the AA reaction may change somewhat in large-scale reactions as observed in this particular case (i.e., 2 mmol scale, **3A**/**3B** = 88:12 and 44 mmol scale, **3A**/**3B** = 80:20).

(28) For all of the other entries in Table 4 (i.e., **26**−**32**), the sodium salts are soluble in water. Following evaporation of the acetone, the aqueous layer was washed twice with ether (removes TEMPO impurities and ketone from the minor regioisomer), acidified to pH 6 with 10% citric acid, and extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated to afford the pure acids **26**−**31**. For **32**, the sodium salt was neutralized with potassium dihydrogen phosphate, and the usual extractive workup gave acid **32**, which was recrystallized from ethyl acetate.

(d, $J = 16$ Hz, 1H, NH), 7.57−7.33 (m, 10H), 7.07 (br s, 1H), 7.0 (d, $J = 8.3$ Hz, 1H), 6.92 (d, $J = 8.3$ Hz, 1H), 5.13 (d, $J = 8.2$ Hz, 1H), 5.10 (s, 2H), 5.07 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 155.9, 148.9, 147.4, 137.2, 137.0, 129.6, 128.5, 128.4, 127.9, 127.9, 127.8, 120.2, 113.3, 111.7, 69.9, 65.6, 57.9, 55.6; HRMS calcd for $C_{24}H_{23}NO_6$ $(M + Na)^+$ 444.1423, found 444.1434.

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(3,4,5-trimethoxyphenyl)-glycine (27): mp 146−147 °C; $[\alpha]^{25}_D = +97.6°$ ($c = 1$, 95% EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, $J = 8.4$ Hz, 1H, NH), 7.35 (m, 5H), 6.77 (s, 2H), 5.10 (d, $J = 8.4$ Hz, 1H), 5.08 (s, 2H), 3.78 (s, 6 H, $2OCH_3$), 3.70 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 155.9, 152.8, 137.1, 136.9, 132.4, 128.5, 127.9, 127.8, 105.3, 65.7, 60.0, 58.3, 56.0; HRMS calcd for $C_{19}H_{21}NO_7$ $(M + Na)^+$ 398.1216, found 398.1230.

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-methoxynaphthyl)glycine (28): mp 70−72 °C; $[\alpha]^{25}_D = +126.0°$ ($c = 1$, 95% EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, $J = 8.2$ Hz, 1H), 8.2 (d, $J = 8.2$ Hz, 1H, NH), 8.05 (d, $J = 8.6$ Hz, 1H), 7.63 (t, $J = 7.2$ Hz, 1H), 7.56 (t, $J = 8.1$ Hz, 1H), 7.43 (d, $J = 8.1$ Hz, 1H), 7.33 (m, 5H), 6.99 (d, $J = 8.1$ Hz, 1H), 5.84 (d, $J = 8.1$ Hz, 1H), 5.09 (dd, 2H), 3.99 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 155.9, 154.9, 137.0, 131.8, 128.4, 127.9, 127.7, 127.2, 126.3, 125.4, 125.2, 125.0, 123.4, 122.1, 103.8, 65.6, 55.8, 54.5; HRMS calcd for $C_{21}H_{19}NO_5$ $(M + Na)^+$ 388.1161, found 388.1174.

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(3-nitrophenyl)glycine (29): mp 110 °C; $[\alpha]^{25}_D = +85.6°$ ($c = 1$, 95% EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, $J = 8.4$ Hz, 1H, NH), 8.36 (d, $J = 1.5$ Hz, 1H), 8.21 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.91 (d, $J = 7.68$ Hz, 1H), 7.69 (t, $J = 7.68$ Hz, 1H), 7.39 (m, 5H), 5.47 (d, $J = 8.4$ Hz, 1H), 5.08 (dd, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 155.9, 147.8, 139.8, 136.8, 134.8, 130.0, 128.4, 127.9, 127.8, 122.9, 122.4, 65.9, 57.3; HRMS calcd for $C_{16}H_{14}N_2O_6$ $(M + Na)^+$ 353.0750, found 353.0757.

(1*S*)-*N*-(Benzyloxycarbonyl)-1-(4-(trifluoromethyl)phenyl)-glycine (30): mp 154−156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (br, 1H, NH), 7.71 (d, $J = 7.9$ Hz, 2H), 7.63 (d, $J = 7.9$ Hz, 2H), 7.35 (m, 5H), 5.17 (d, $J = 6.5$ Hz, 1H), 5.06 (dd, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.7, 154.6, 146.1, 136.7, 127.9, 127.4, 127.3, 127.1, 124.2, 124.1, 100.0, 64.7, 59.3; HRMS calcd for $C_{17}H_{14}F_3NO_4$ $(M + Na)^+$ 376.0773, found 376.0762.

(1*S*)-*N*-(Benzyloxycarbonyl-1-(4-bromophenyl)glycine (31): mp 139−141 °C; $[\alpha]^{25}_D = +94.6°$ ($c = 1$, 95% EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, $J = 8.2$ Hz, 1H, NH), 7.54 (d, $J = 8.5$ Hz, 2H), 7.38 (m, 7H), 5.22 (d, $J = 8.2$ Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.4, 155.9, 136.9, 136.7, 131.4, 129.9, 128.4, 127.9, 127.8, 121.3, 65.8, 57.5; HRMS calcd for $C_{16}H_{14}BrNO_4$ $(M + Na)^+$ 386.0004/388, found 386.0014/388.

(*1S*)-*N*-(Benzyloxycarbonyl)-1-(3-pyridyl)glycine (32): mp 154−155 °C; $[\alpha]^{25}_D = +98.6°$ ($c = 1$, 95% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 8.52 (d, $J = 4.64$ Hz, 1H), 8.19 (d, $J = 8.1$ Hz, 1H, NH), 7.82 (d, $J = 7.85$ Hz, 1H), 7.39 (m, 6H), 5.25 (d, $J = 8.1$ Hz, 1H), 5.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.9, 149.1, 149.0, 136.9, 135.3, 133.4, 128.5, 127.9, 127.8, 123.6, 65.8, 56.0; HRMS calcd for $C_{15}H_{14}N_2O_4$ $(M + Na)^+$ 287.1032, found 287.1040.

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