Asymmetric Strecker-Type Reaction of α-Aryl Ketones. Synthesis of (*S*)-αM4CPG, (*S*)-MPPG, (*S*)-AIDA, and (*S*)-APICA, the Antagonists of Metabotropic Glutamate Receptors

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Heating a mixture of α-aryl ketone with (*R*)-phenylglycinol produces a mixture of imine and 1,3-dioxazolidine. Treatment of this mixture with trimethylsilyl cyanide followed by transformation of nitrile to ester gives Strecker-type reaction products. The diastereoselectivity of the generated α-amino esters is from 2/1 to 7/1, and the (*R*,*S*)isomer is found as the major product. The (*R*,*S*) and (*R*,*R*)isomers can be separated by conversion to their *N*-Cbz or cyclization derivatives. Using this methodology, four antagonists of metabotropic glutamate receptors, (*S*)-αM4CPG, (*S*)-MPPG, (*S*)-AIDA, and (*S*)-APICA, are synthesized.

α,α-Disubstituted α-amino acids are now popular replacements for proteinogenic amino acids in peptides.[1] Because of the tetrasubstituted asymmetric carbon atom, incorporation of these compounds into peptides results in increased proteolytic stability and conformational restrictions. They can therefore be used as enzyme inhibitors for the investigation of enzymatic mechanisms.[1,2] In addition, many α,α-disubstituted α-amino acids also possess important biological activity.[3,4] For example, some α-alkylated phenylglycine derivatives have recently been found to be selective antagonists of metabotropic glutamate receptor.[4] Among these compounds, (*S*)-α-methyl-4-carboxyphenylglycine ((*S*)-αM4CPG)[4] and (*S*)-α-methyl-4-phosphonophenylglycine ((*S*)-MPPG)[5] showed poor selectivity for different mGluR isoforms (Figure 1). However, their racemic rigid analogues, 1-aminoindan-1,5-dicarboxylic acid (AIDA)[6] and 1-amino-5-phosphonoindan-1-carboxylic acid (APICA),[7] were found to have improved selectivity for mGluR isoforms. Because it has been found that (*R*)-αM4CPG had significant antagonist activity at NMDA and AMPA receptors while (*S*)-αM4CPG had only action at mGluRs,[4a] an efficient route for synthesizing these compounds enantioselectively is highly desirable to make them more useful as molecular tools in seeking the roles of mGluRs in physiological processes.[8]

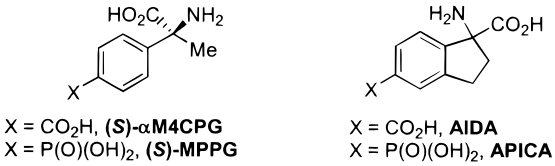

Figure 1. Structures of (*S*)-αM4CPG, (*S*)-MPPG, AIDA, and APICA.

In recent years, a number of methods for construction of chiral α,α-disubstituted α-amino acids have been reported.[1,9−11] In most cases the stereogenic center is established by alkylation of chiral, nonracemic enolates. This method needs many steps for the preparation of the target molecules. Moreover, synthesis of complex α,α-disubstituted α-amino acids is restricted due to the limited chiral pool.[1,9,10] On the other hand, the Strecker reaction is a well-known method for synthesizing α-amino acids because of its convenient procedure.[1b] Asymmetric Strecker reactions starting with chiral amines have been successfully used in synthesizing chiral α-monosubstitutedα-amino acids from aldehydes[12] and some specific chiral α,α-disubstituted α-amino acids such as phenylalanine, serine, and threonine derivatives from ke-

(1) For reviews, see the following. (a) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (b) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (c) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.

(2) (a) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Heterocycles* **1992**, *34*, 903. (b) Shrader, W. D.; Marlowe, C. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2207. (c) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2787. (d) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron* **1995**, *51*, 7321. (e) Gershonov, E.; Granoth, R.; Tzehoval, E.; Gaoni, Y.; Fridkin, M. *J. Med. Chem.* **1996**, *39*, 4833.

(3) (a) Knopfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1418. (b) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887.

(4) (a) Hayashi, Y.; Sekiyama, N.; Nakanishi, S.; Jane, D. E.; Sunter, D. C.; Bire, E. F.; Udvarhelyi, P. M.; Watkins, J. C. *J. Neurosci.* **1994**, *14*, 3370. (b) Sekiyama, N.; Hayashi, Y. Nakanishi, S.; Jane, D. E.; Tse, H.-W.; Birse, E. F.; Watkins, J. C. *Br. J. Pharmacol.* **1996**, *117*, 1493. (c) Ma, D.; Tian, H. *Tetrahedron: Asymmetry* **1996**, *6*, 1567.

(5) Jane, D. E.; Pittaway, K.; Sunter, D. C.; Thomas, N. K.; Watkins, J. C. *Neuropharmacology* **1995**, *34*, 851.

(6) Pellicciari, R.; Luneia, R.; Costantino, G.; Marinozzi, M.; Natalini, B.; Jakobsen, P.; Kanstrup, A.; Lombardi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1995**, *38*, 3717−3719.

(7) Ma, D.; Tian, H.; Sun, H.; Kozikowski, A. P.; Pshenichkin, S.; Wroblewski, J. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1195−1198.

(8) These compounds are now commercially available from the Tocris Cookson Ltd., the Alexis Biochemicals Corporation, and the Research Biochemicals International.

(9) (a) Schollkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. (b) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586. (c) Zhang, L.; Finn, J. M. *J. Org. Chem.* **1995**, *60*, 5719. (d) Smith, A. B.; Benowitz, A. B.; Favor, D. A.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1997**, *38*, 3809.

(10) (a) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233. (b) Ihara, M.; Takahashi, M.; Niitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Org. Chem.* **1989**, *54*, 5413.

(11) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1996**, *61*, 7398.

(12) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179.

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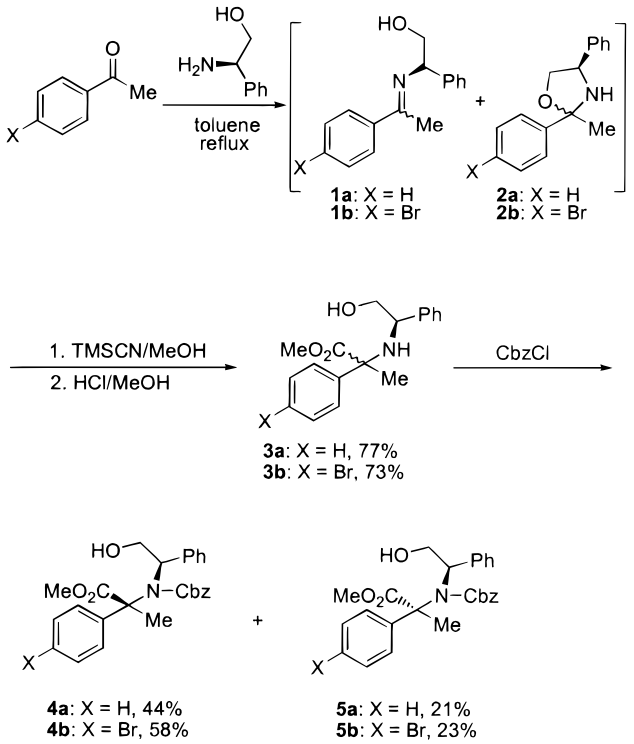
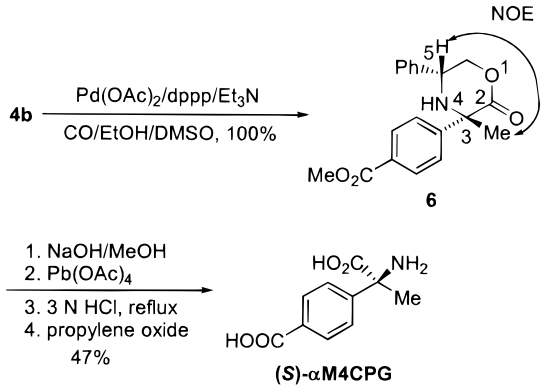
Scheme 1



tones.[13,14] However, to the best of our knowledge, there are no reports about asymmetric Strecker reaction of α-aryl ketone for preparing α-alkylated phenylglycine derivatives. In the course of studies of modulators for metabotropic glutamate receptors,[4c,7,15] we felt that it was necessary to investigate the asymmetric Strecker reaction of α-aryl ketone. The results of studies thus undertaken are detailed herein.

Initially, we used an asymmetric Strecker reaction of acetophenone as our model reaction. We tried all the reported procedures[12,13] using (*R*)-α-methylbenzylamine or (*R*)-phenylglycinol as the chiral source. It was found that under the conditions reported no desired aminonitriles were prepared and the ketone was recovered. After some experimentation, we realized that the problem might come from the difficult formation of the Schiff base in the first step. To promote the formation of the desired Schiff base, we refluxed the mixture of acetophenone and (*R*)-phenylglycinol in toluene with azeotropic removal of water (Scheme 1). After both starting materials disappeared, the resultant solution was concentrated under reduced pressure to give a mixture of the Schiff base **1a** and 1,3-oxazolidine **2a** determined by ^{1}H NMR. These intermediates might exist as an equilibrium mixture of the imine and 1,3-oxazolidine forms.[16] After these unstable intermediates were treated with trimethylsilyl cyanide in methylene chloride/methanol, we found that the corresponding aminonitrile could be isolated. The

Scheme 2



unstable aminonitrile was then transformed to ester **3a** by treatment with saturated methanolic HCl. The ^{1}H NMR spectrum of **3a** indicated the formation of two diastereoisomers in a ratio of about 2/1. These two isomers could not be separated by column chromatography. However, after protection with a Cbz group, we found that the two isomers **4a** and **5a** were separable by column chromatography. Thus, we could obtain pure diastereomers **4a** and **5a** through asymmetric Strecker reaction in 33.9% and 16.2% yields, respectively. Both compounds could be transformed into the corresponding (*S*)- or (*R*)-α-methylphenylglycine by carrying out a simple operation.

After we succeeded in the asymmetric Strecker reaction of acetophenone and separation of two diastereomers, the remaining problem was the assignment of the absolute configuration of a new stereogenic center. We planned to solve this problem by synthesizing (*S*)-αM4CPG using the developed method. Accordingly, starting with 4′-bromoacetophenone, we obtained two isomers **4b** and **5b** following the same procedure mentioned above. The ratio of the two isomers was about 2.5/1. When we submitted the major isomer to palladium-catalyzed carbonylation under standard conditions,[17] an unexpected product, lactone **6**, was isolated quantitatively. The formation of **6** implied that deprotection of the Cbz group and lactonization occurred simultaneously under these conditions. This cyclized product gave us a chance to determine the stereochemistry of the new stereogenic center by NMR techniques. In the NOESY spectrum of **6**, the marked NOE between 5-H and 3-Me was observed and we could therefore assign the configuration to be the (*R*,*S*)form. With **6** in hand, we finished the synthesis of (*S*)-αM4CPG by using the following steps (Scheme 2): (i) opening of the lactone ring with NaOH/MeOH; (ii) oxidation with $Pb(OAc)_2$ to remove the chiral auxiliary;[12] (iii) acidic hydrolysis to remove all the protecting groups; (iv) treatment of the generated amino acid hydrochloride salt with propylene oxide to release the free amino acid. This compound showed $[\alpha]^{25}_D$ = +91.9 (*c* 0.47, 6 N HCl), which was identical with that reported for (*S*)-αM4CPG.[4] Thus, the stereochemistry of the major Strecker reaction product of 4′-bromoacetophe-

(13) Cordi, A. A.; Lacoste, J.-M.; Borgne, F. L.; Herve, Y.; Vaysse-Ludot, L.; Descombes, J.-J. Courchay, C.; Laubie, M.; Verbeuren, T. J. *J. Med. Chem.* **1997**, *40*, 2931 and references therein.

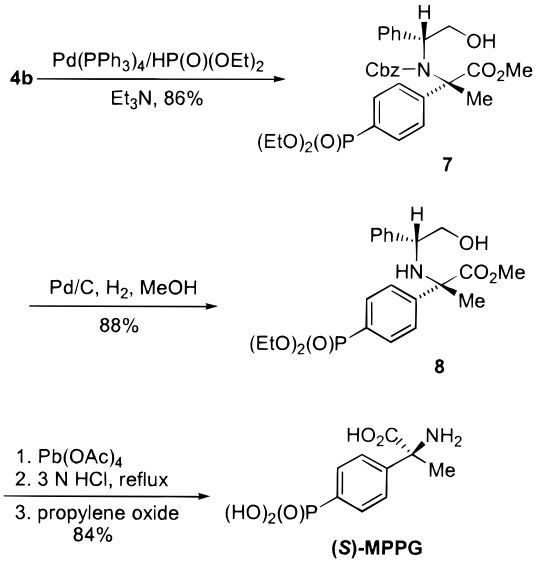
(14) (a) Ohfune, Y.; Horikawa, M. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 982. (b) Ohfune, Y.; Moon, S.-H.; Horikawa, M. *Pure Appl. Chem.* **1996**, *68*, 645.

(15) (a) Ma, D.; Tian, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3493. (b) Ma, D.; Ma, Z.; Jiang, J.; Yang, Z.; Zheng, C. *Tetrahedron: Asymmetry* **1997**, *8*, 889. (c) Ma, D.; Ma, J.; Dai, L. *Tetrahedron: Asymmetry* **1997**, *8*, 825. (d) Ma, D.; Ma, Z. *Tetrahedron Lett.* **1997**, *38*, 7599. (e) Ma, D.; Ma, Z.; Kozikowski, A. P.; Pshenichkin, S.; Wroblewski, J. T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2447.

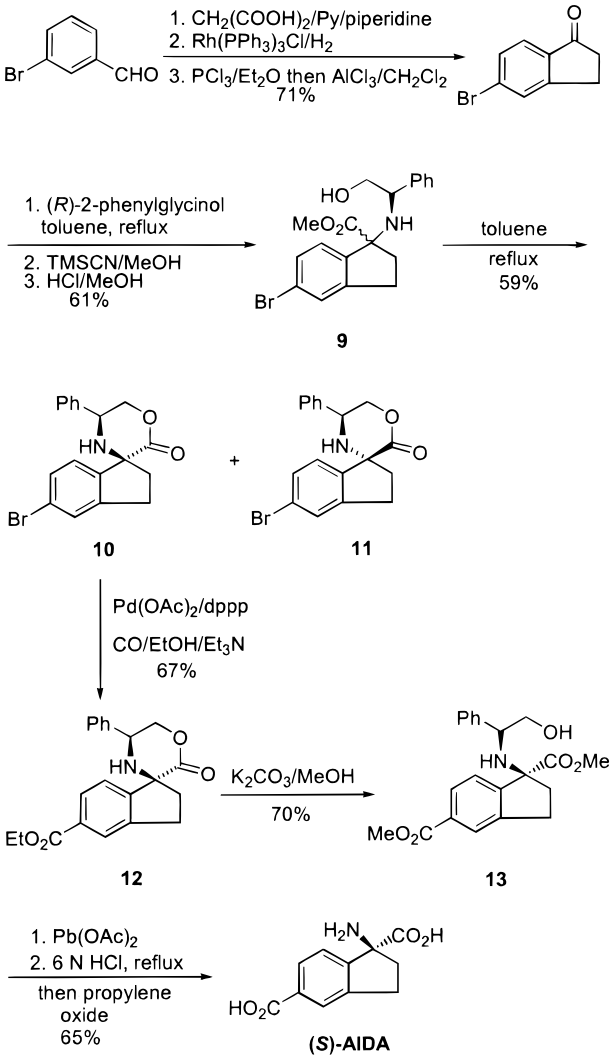
(16) A similar equilibrium mixture of the imine and 1,3-oxazolidine forms resulting from the reaction of phenylglycinol and aldehyde was reported. See: (a) Yamauchi, T.; Takahashi, H.; Higashiyama, K. *Chem. Pharm. Bull.* **1998**, *46*, 384. (b) Higashiyama, K.; Kyo, H.; Takahashi, H. *Synlett* **1998**, 489.

(17) (a) Schoenberg, A.; Bartolett, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Huth, A.; Beetz, I.; Schumann, I.; Thielert, T. *Tetrahedron* **1987**, *43*, 1071.

Scheme 3



Scheme 4



none was further confirmed to be in the (*R*,*S*)form. By comparing the ^{1}H NMR spectra of **4a** and **4b**, we could conclude that the stereochemistry of the major Strecker reaction product of acetophenone was also in the (*R*,*S*)-form.

The synthesis of (*S*)-MPPG was performed by employing the palladium-catalyzed phosphonation[18] as a key step (Scheme 3). Heating a mixture of **4b**, diethyl phosphite, and tetrakis(triphenylphosphine)palladium in triethylamine at 100 °C afforded the diethyl arylphosphonate **7** in 86% yield. Next, the Cbz protecting group of **7** was removed by hydrogenation under the Pd/C catalysis to provide **8**. The amino ester **8** was treated with lead tetraacetate to afford the corresponding Schiff base. Finally, (*S*)-MPPG was obtained in 84% overall yield by refluxing this Schiff base in 6 N HCl and subsequent reaction of the generated hydrochloride salt with propylene oxide. Thus, we have developed a new route for synthesis of (*S*)-αM4CPG and (*S*)-MPPG. The overall yields from 4′-bromoacetophenone were 20% and 27% for (*S*)-αM4CPG and (*S*)-MPPG, respectively. This new protocol is obviously more efficient than the old one.[15a]

To demonstrate the further applications of the present methodology, we undertook the synthesis of (*S*)-AIDA and (*S*)-APICA using the reaction sequence reported in Schemes 4 and 5. The starting material, 5-bromo-1-indanone,[19] was prepared from 3-bromobenzylaldehyde in 71% yield through Perkin reaction, hydrogenation of the olefin, and intramolecular acylation. Refluxing of this indanone with (*R*)-phenylglycinol in toluene with azeotropic removal of water afforded the corresponding mixture of the imine and 1,3-dioxazolidine forms, which was reacted with trimethylsilyl cyanide followed by treatment with saturated methanolic HCl to produce amino ester **9**. The overall yield of **9** (61% based on 30% ketone recovery) was lower due to the recovery of 5-bromo-1-indanone. However, the diastereoselectivity in this case was excellent and the ratio of the two diastereomers was about 7/1 as determined by ^{1}H NMR. Attempts to separate the two isomers by converting them to *N*-Cbz derivatives failed because the generated two isomers were found to be inseparable by column chromatography. Fortunately, refluxing **9** in toluene provided cyclized products **10** and **11** in 59% total yield, together with some decomposed products. The diastereomers **10** and **11** could easily be separated by column chromatography. The lactone **10** was a fine crystalline solid, which allowed us to determine its structure by X-ray crystallography. As shown in Figure 2, X-ray analysis of **10** clearly indicated the configuration of the new stereogenic center to be in the (*S*)form.

Starting from **10,** we could finish the synthesis of (*S*)-AIDA and (*S*)-APICA through two palladium-catalyzed reactions. Thus, palladium-catalyzed carbonylation and phosphonation of **10** were carried out to afford **12** and **14,** respectively. Both intermediates could be transformed into (*S*)-AIDA and (*S*)-APICA by following the procedure of preparing (*S*)-αM4CPG from **6**. To our best knowledge, this is the first asymmetric synthesis of these two biologically important compounds.

In conclusion, we have developed a successful procedure for the asymmetric Strecker reaction of an α-aryl ketone. The configuration of the new stereogenic center was always the (*S*)form when (*R*)-phenylglycinol was used as the chiral source in our tested cases. Although the diastereoselectivity and yield of the asymmetric Strecker reaction is not satisfactory, this synthetic

(18) Hirao, T. Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909.
(19) Quere, J. P.; Marechal, E. *Bull. Soc. Chim. Fr.* **1971**, 2983.

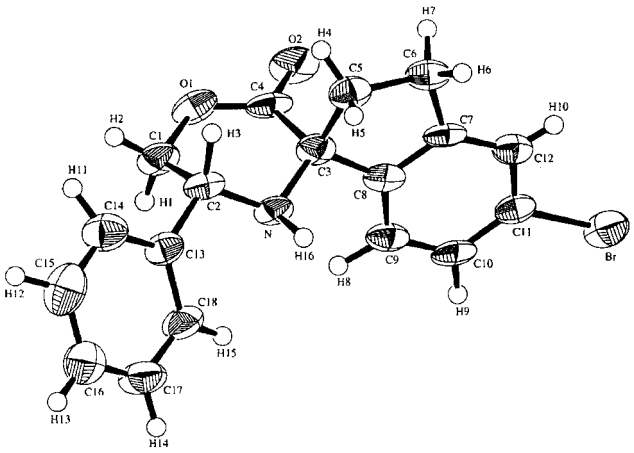
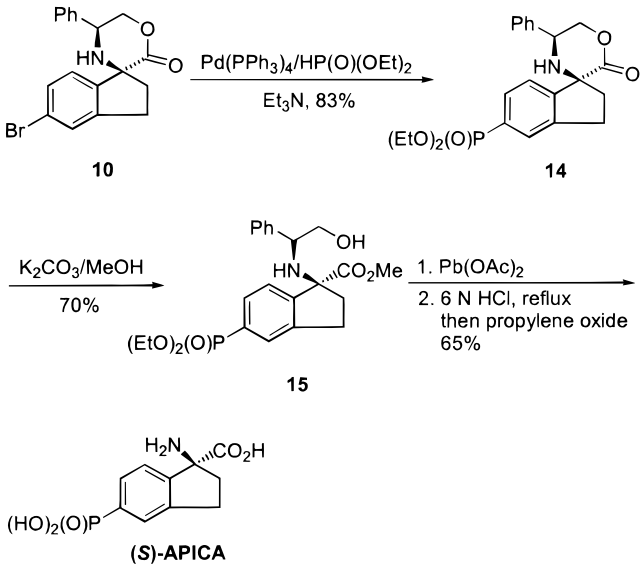


Figure 2. X-ray crystal structure of **10**.

Scheme 5



method is still useful due to its easy manipulation. The power of this new methodology has been demonstrated by the facile synthesis of (*S*)-αM4CPG, (*S*)-MPPG, (*S*)-AIDA, and (*S*)-APICA. Further optimization of the reaction conditions as well as application of this methodology to the synthesis of other biologically important α,α-disubstituted α-amino acids is being pursued in our laboratory and will be reported in due course.

Experimental Section

General Procedures. Analytically pure toluene and DMSO were used directly without further purification. CH_2Cl_2 was distilled from CaH_2, and THF was distilled from a deep blue ketyl prior to use. All other solvents were reagent grade quality and used as received. Na_2SO_4 was used as the drying agent in all workup procedures. All reactions were run in flame-dried glassware under a nitrogen atmosphere unless stated otherwise.

General Procedure for Asymmetric Strecker Reaction of α-Aryl Ketone. A mixture of α-aryl ketone (5 mmol) and (*R*)-phenylglycinol (5 mmol) in toluene (5 mL) was refluxed with azeotropic removal of water until the starting material disappeared (monitored by TLC). After removal of the solvent at reduced pressure, the residual oil was dissolved in 5 mL of dry methylene chloride. The resulting solution was cooled with ice−water, and then trimethylsilyl cyanide (7.5 mmol) and dry methanol (2 mL) were added. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 24 h. The solution was concentrated at reduced pressure, and the residue was dissolved in 10 mL of saturated methanolic HCl. After stirring for 12 h, the methanol was evaporated and the residue was diluted was 100 mL of ethyl acetate. The organic layer was washed with 10% aqueous $NaHCO_3$, water, and brine, respectively, and dried over Na_2SO_4. After removal of the solvent, the amino esters were obtained by column chromatography (silica gel, 1/3 ethyl acetate/petroleum ether as eluent) as a mixture of diastereomers.

***N*-[(*R*)-(2-Hydroxy-1-phenylethyl)]-(*S*)-2-amino-2-methylphenylacetic acid, methyl ester and *N*-[(*R*)-(2-hydroxy-1-phenylethyl)]-(*R*)-2-amino-2-methylphenylacetic acid, methyl ester (3a):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.18 (m, 10H), 3.80−3.72 (m, 1H), 3.69 (s, 3H, major isomer), 3.63−3.41 (m, 2H), 3.28 (s, 3H, minor isomer), 2.86 (br s, 2H), 1.55 (s, 3H, minor isomer), 1.42 (s, 3H, major isomer); MS *m*/*z* 300 ($M^+ + H^+$).

***N*-[(*R*)-(2-Hydroxy-1-phenylethyl)]-(*S*)-2-amino-2-methyl-(4′-bromophenyl)acetic acid, methyl ester and *N*-[(2-hydroxy-1-phenylethyl)]-(*R*)-2-amino-2-methyl-(4′-bromophenyl)acetic acid, methyl ester (3b):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.17 (m, 9H), 3.77−3.73 (m, 1H), 3.70 (s, 3H, major isomer), 3.65−3.42 (m, 2H), 3.32 (s, 3H, minor isomer), 2.63 (br s, 2H), 1.52 (s, 3H, minor isomer), 1.41 (s, 3H, major isomer); MS *m*/*z* 380 ($M^+ + H^+$, ^{81}Br), 378 ($M^+ + H^+$, ^{79}Br).

***N*-[(*R*)-(2-Hydroxy-1-phenylethyl)]-(*S*)-1-amino-1-carbmethoxy-5-bromoindan and *N*-[(*R*)-(2-hydroxy-1-phenylethyl)]-(*R*)-1-amino-1-carbmethoxy-5-bromoindan (9):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.26−7.10 (m, 6H), 7.00 (d, J = 7.9 Hz, 1H), 3.70−3.64 (m, 1H), 3.62 (s, 3H, major isomer), 3.53 (dd, J = 10.8, 4.7 Hz, 1H, major isomer), 3.38 (t, J = 10.8 Hz, 1H, major isomer), 3.29 (s, 3H, minor isomer), 2.82 (m, 3H), 2.49 (m, 2H), 1.86 (m, 1H); MS *m*/*z* 358 ($M^+ - CH_2OH$, ^{81}Br), 356 ($M^+ - CH_2OH$, ^{79}Br).

***N*-Carbobenzyloxy-*N*-[(*R*)-(2-hydroxy-1-phenylethyl)]-(*S*)-2-amino-2-methylphenylacetic Acid, Methyl Ester (4a) and *N*-Carbobenzyloxy-*N*-[(*R*)-(2-hydroxy-1-phenylethyl)]-(*R*)-2-amino-2-methylphenylacetic Acid, Methyl Ester (5a).** To a solution of **3a** (1.76 g, 5.8 mmol) in 50 mL of THF were added DMAP (0.86 g, 7.0 mmol), triethylamine (2 mL, 14.3 mmol), and benzyl chloroformate (1.20 g, 7.0 mmol), respectively. The resulting solution was stirred at room temperature for 12 h before it was partitioned between 100 mL of ethyl acetate and 50 mL of water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed, eluting with 1/3 ethyl acetate/petroleum ether to afford 1.1 g (44% yield) of **4a** and 0.42 g (17% yield) of **5a**. **4a**: yellow oil, $[\alpha]^{25}_D = +6.3$ (*c* 0.17, $CHCl_3$); IR (KBr) 3400, 3064, 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.23 (m, 15H), 5.16 (s, 2H), 4.24 (dd, J = 10.8, 4.0 Hz, 1H), 4.08 (t, J = 8.9 Hz,1H), 4.03 (dd, J = 8.8, 5.8 Hz, 1H), 3.63 (s, 3H), 1.29 (s, 3H); MS *m*/*z* 434 ($M^+ + H^+$); HRMS found *m*/*z* 374.1749 ($M^+ - CO_2Me$), $C_{24}H_{24}NO_3$ requires 374.1756. **5a**: yellow oil, $[\alpha]^{25}_D = -46$ (*c* 0.75, $CHCl_3$); IR (KBr) 3400, 3064, 1741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.23 (m, 15H), 5.13 (s, 2H), 4.16 (m, 2H), 3.83 (dd, J = 7.7, 5.8 Hz, 1H), 3.45 (s, 3H), 1.49 (s, 3H); MS *m*/*z* 342 ($M^+ - 91$); HRMS found *m*/*z* 374.1766 ($M^+ - CO_2Me$), $C_{24}H_{24}NO_3$ requires 374.1756.

***N*-Carbobenzyloxy-*N*-[(*R*)-(2-hydroxy-1-phenylethyl)]-(*S*)-2-amino-2-methyl-(4′-bromophenyl)acetic Acid, Methyl Ester (4b) and *N*-Carbobenzyloxy-*N*-[(*R*)-(2-hydroxy-1-phenylethyl)]-(*R*)-2-amino-2-methyl-(4′-bromophenyl)acetic Acid, Methyl Ester (5b).** Following the procedure for preparing **4a** and **5a** from **3a**, **4b** and **5b** were obtained from **3b** in 58% and 23% yields, respectively. **4b**: yellow oil, $[\alpha]^{25}_D = +73.4$ (*c* 0.25, $CHCl_3$); IR (KBr) 3348, 1743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.22 (m, 14H), 5.14 (s, 2H), 4.22 (dd, J = 11.0, 4.1 Hz, 1H), 4.05 (t, J = 11.0 Hz, 1H), 3.98 (dd, J = 9.0, 4.1 Hz, 1H), 3.60 (s, 3H), 1.26 (s, 3H); MS *m*/*z* 514 ($M^+ + H^+$, ^{81}Br), 512 ($M^+ + H^+$, ^{79}Br); HRMS found

m/*z* 452.0848 ($M^+ - CO_2Me$), $C_{24}H_{23}BrNO_3$ requires 452.0861. **5b**: yellow oil, $[\alpha]^{25}_D = -37.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.19 (m, 14H), 5.13 (s, 2H), 4.18 (m, 2H), 3.85 (dd, *J* = 7.7, 5.8 Hz, 1H), 3.46 (s, 3H), 1.50 (s, 3H); MS *m*/*z* 514 ($M^+ + H^+$, ^{81}Br), 512 ($M^+ + H^+$, ^{79}Br); HRMS found *m*/*z* 452.0871 ($M^+ - CO_2Me$), $C_{24}H_{23}BrNO_3$ requires 452.0861.

(3*S*,5*R*)-3-Methyl-3-(4′-carbethoxyphenyl)-5-phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (6). To a solution of **4b** (263 mg, 0.51 mmol), 1,3-bis(diphenylphosphino)propane (dppp, 43 mg, 0.13 mmol), anhydrous ethanol (5 mL), and triethylamine (0.72 mL, 5.1 mmol) in DMSO (5 mL) was added palladium acetate (24 mg, 0.10 mmol). The resultant solution was stirred under carbon monoxide (1 atm) at 70 °C for 3 h. After being cooled to room temperature, the reaction mixture was partitioned between 50 mL of ethyl acetate and 10 mL of water. The organic layer was separated, washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residual oil was chromatographed to give 183 mg (100%) of **6** as a pale yellow oil: $[\alpha]^{25}_D = +130.6$ (*c* 0.36, $CHCl_3$); IR (KBr) 3355, 1749, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.8 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.40−7.30 (m, 3H), 4.60 (dd, *J* = 11.3, 3.7 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.19 (dd, *J* = 11.3, 3.8 Hz, 1H), 4.00 (t, *J* = 11.3 Hz, 1H), 1.73 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); MS *m*/*z* 294 ($M^+ - 45$); HRMS found *m*/*z* 339.1449 (M^+), $C_{20}H_{21}NO_4$ requires 339.1471.

(*S*)-α-Methyl-4-carboxyphenylglycine ((*S*)-αM4CPG). A mixture of **6** (152 mg, 0.45 mmol) and 1 N NaOH (1 mL) in 3 mL of methanol was stirred at room temperature for 2 h. After the pH was adjusted to 4 by addition of 1 N HCl, the solution was concentrated at reduced pressure and the residue was dissolved in 2 mL of MeOH and 4 mL of methylene chloride. To the resulting solution was added lead tetraacetate (220 mg, 0.50 mmol) at 0 °C. After the suspension solution was stirred for 30 min, 10 mL of phosphate buffer (0.2 M, pH 7) was added to quench the reaction. The mixture was filtered through Celite, and the organic layer was separated, washed with water, and concentrated to dryness. The residual oil was mixed with 5 mL of 3 N HCl, and the resultant mixture was heated at reflux for 12 h. After being cooled to room temperature, the solution was extracted with methylene chloride and the aqueous layer was concentrated to dryness under reduced pressure. The residual solid was dissolved in 2 mL of anhydrous ethanol, and 0.2 mL of propylene oxide was added. After the mixture was heated at reflux for 15 min, the solvents were evaporated and the residue was chromatographed (C_{18} reverse-phase column, H_2O as eluent) to afford 28 mg (47%) of (*S*)-αM4CPG as a white solid: mp 340 °C (dec); $[\alpha]^{25}_D = +91.9$ (*c* 0.47, 6 N HCl); ^1H NMR (300 MHz, D_2O) δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 1.93 (s, 3H); MS *m*/*z* (FAB) 209 (M^+).

***N*-Carbobenzyloxy-*N*-[(*R*)-(2-hydroxy-1-phenylethyl)]-(*S*)-2-amino-2-methyl-(4′-diethylphosphonophenyl)acetic Acid, Methyl Ester (7).** Into a sealed tube were placed **4b** (1.51 g, 2.93 mmol), diethyl phosphite (0.61 g, 4.39 mmol), 20 mL of triethylamine, and $Pd(PPh_3)_4$ (678 mg, 0.58 mmol). The resulting suspension solution was heated at 100 °C for 4 h. After being cooled to room temperature, the solution was poured into 20 mL of water and then extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed to afford 1.43 g (86%) of **7**: $[\alpha]^{25}_D = -10.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 11.8, 8.4 Hz, 2H), 7.50 (dd, *J* = 6.4, 2.2 Hz, 2H), 7.35−7.15 (m, 10H), 5.06 (s, 2H), 4.18−3.92 (m, 6H), 3.51 (s, 3H), 1.22 (t, *J* = 6.5 Hz, 6H), 1.19 (s, 3H); MS *m*/*z* 570 ($M^+ + H^+$); HRMS found *m*/*z* 510.2061 (M^+), $C_{28}H_{33}NO_6P$ requires 510.2047.

***N*-[(*R*)-(2-Hydroxy-1-phenylethyl)]-(*S*)-2-amino-2-methyl-(4′-diethylphospphonophenyl)acetic Acid, Methyl Ester (8).** A suspension of **7** (1.20 g, 2.1 mmol) and Pd/C (10%, 150 mg) in 15 mL of methanol was stirred under hydrogen (1 atm) until the starting material disappeared (monitored by TLC). After the catalyst was filtered out, the filtrate was concentrated and then chromatographed to afford 918 mg (88% yield) of **8** as a colorless oil: $[\alpha]^{25}_D = +5.8$ (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 12.8, 8.4 Hz, 2H), 7.50 (dd, *J* = 6.0, 3.6 Hz, 2H), 7.31−7.17 (m, 5H), 4.06 (m, 4H), 3.77 (dd, *J* = 8.9, 4.2 Hz, 1H), 3.68 (s, 3H), 3.63 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.46 (dd, *J* = 10.8, 9.2 Hz, 1H), 3.01 (br s, 2H), 1.41 (s, 3H), 1.27 (t, *J* = 6.7 Hz, 6H); MS *m*/*z* 436 ($M^+ + H^+$); HRMS found *m*/*z* 404.1627 ($M^+ - OMe$), $C_{22}H_{30}NO_6P$ requires 404.1629.

(*S*)-α-Methyl-4-phosphonophenylglycine ((*S*)-MPPG). To a solution of **8** (672 mg, 1.54 mmol) in methylene chloride (7.4 mL) and methanol (3.7 mL) was added lead tetraacetate (687 mg, 1.54 mmol) at 0 °C. After the resultant mixture was stirred for 30 min, 20 mL of phosphate buffer (0.2 M, pH 7) was added to quench the reaction. The mixture was filtered through Celite, and the organic layer was separated, washed with water, and concentrated to dryness. The residual oil was mixed with 15 mL of 6 N HCl, and the resultant mixture was heated at reflux for 24 h. After being cooled to room temperature, the solution was extracted with methylene chloride and the aqueous layer was concentrated to dryness under reduced pressure. The residual solid was dissolved in 5 mL of anhydrous ethanol, and 0.2 mL of propylene oxide was added. After the mixture was heated at reflux for 15 min, the solvents were evaporated and the residue was chromatographed (C_{18} reverse-phase column, H_2O as eluent) to afford 375 mg (84%) of (*S*)-MPPG: mp 243 °C; $[\alpha]^{25}_D = +60.1$ (*c* 0.1, 6 N HCl); ^1H NMR (300 MHz, D_2O) δ 7.73 (dd, *J* = 12.4, 8.3 Hz, 2H), 7.55 (dd, *J* = 8.3, 2.8 Hz, 2H), 1.75 (s, 3H); MS *m*/*z* (FAB) 246 (M^+).

Cyclization of 9. A solution of **9** (378 mg, 1.0 mmol) in 50 mL of toluene was stirred at reflux for 24 h. After removal of the solvent, the residual oil was chromatographed (silica gel, 1/5 ethyl acetate/petroleum ether as eluent) to afford 185 mg (52% yield) of **10**: mp 197 °C; $[\alpha]^{25}_D = -42.7$ (*c* 0.66, $CHCl_3$); IR (KBr) 3400, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.32 (m, 9H), 4.52 (dd, *J* = 9.1, 4.8 Hz, 1H), 4.44 (m, 2H), 3.20 (m,1H), 3.05 (m, 2H), 2.17 (m, 1H), 1.97 (br s, 1H); MS *m*/*z* 360 ($M^+ + H^+$, ^{81}Br), 358 ($M^+ + H^+$, ^{79}Br). Anal. Calcd for $C_{18}H_{16}BrNO_2$: C, 60.34; H, 4.47. Found: C, 60.43; H, 4.61.

***N*-[(*R*)-(2-Hydroxy-1-phenylethyl)]-(*S*)-1-amino-1,5-dicarbmethoxyindan (13).** Following the similar procedure for preparing **6** from **4b**, ester **12** was obtained in 67% yield from **10**. To a solution of **12** (135 mg, 0.38 mmol) in 2 mL of absolute methanol was added anhydrous potassium carbonate (106 mg, 0.78 mmol). The resultant suspension solution was stirred at room temperature for 12 h before the solvent was evaporated via a rotoevaporator. Chromatography of the residue, eluting with 1/3 ethyl acetate/petroleum ether, afforded 122 mg (87%) of **13** as a yellow oil: $[\alpha]^{25}_D = +88.1$ (*c* 0.09, $CHCl_3$); IR (KBr) 3449, 3326, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.32−7.19 (m, 6H), 3.93 (s, 3H), 3.77 (dd, *J* = 8.4, 5.0 Hz, 1H), 3.70 (s, 3H), 3.60 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.47 (t, *J* = 10.6 Hz, 1H), 2.95 (m, 2H), 2.82 (br, s, 2H), 2.52 (m, 1H), 2.01 (m, 1H); MS *m*/*z* 370 ($M^+ + H^+$); HRMS found *m*/*z* 338.1392 ($M^+ - OMe$), $C_{20}H_{20}NO_4$ requires 338.1380.

(*S*)-1-Aminoindan-1,5-dicarboxylic Acid ((*S*)-AIDA). Following the procedure for preparing (*S*)-MPPG from **8**, (*S*)-AIDA was obtained from **13** in 65% yield: mp 287 °C; $[\alpha]^{25}_D = +86.3$ (*c* 0.8, 6 N HCl); ^1H NMR (300 MHz, D_2O) δ 8.01 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 3.26 (t, *J* = 7.3 Hz, 2H), 2.93 (dt, *J* = 14.3, 7.3 Hz, 1H), 2.47 (dt, *J* = 14.3, 7.3 Hz, 1H); MS *m*/*z* (FAB) 221 (M^+).

***N*-[(*R*)-(2-Hydroxy-1-phenylethyl)]-(*S*)-1-amino-1-carbmethoxy-5-diethylphosphonoindan (15).** Following the similar procedure for preparing **7** from **4b**, aryl phosphonate **14** was obtained in 83% yield from **10**. To a solution of **12** (47 mg, 0.11 mmol) in 2 mL of absolute methanol was added anhydrous potassium carbonate (32 mg, 0.22 mmol). The resultant suspension solution was stirred at room temperature for 12 h before the solvent was evaporated via rotevaporator. Chromatography of the residue, eluting with 1/3 ethyl acetate/petroleum ether, afforded 43 mg (85% yield) of **15** as a yellow oil: $[\alpha]^{25}_D = +5.6$ (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$)

δ 7.65 (d, J = 13.4 Hz, 1H), 7.54 (dd, J = 12.9, 7.7 Hz, 1H), 7.31−7.18 (m, 6H), 4.10 (m, 4H), 3.73 (dd, J = 9.4, 4.4 Hz, 1H), 3.67 (s, 3H), 3.60 (dd, J = 10.9, 4.4 Hz, 1H), 3.44 (t, J = 10.2 Hz, 1H), 2.92 (m, 2H), 2.53 (m, 1H), 1.94 (m, 1H), 1.30 (t, J = 7.1 Hz, 6H); MS m/z 447 (M^+); HRMS found m/z 447.1806, $C_{23}H_{30}NO_6P$ requires 447.1810.

(*S*)-1-Amino-5-phosphonoindan-1-carboxylic Acid ((*S*)-APICA). Following the procedure for preparing (*S*)-MPPG from **8**, (*S*)-APICA was obtained from **15** in 65% yield: mp 198 °C; $[\alpha]^{25}_D$ = +66.8 (*c* 1.7, 6 N HCl); ^{1}H NMR (300 MHz, D_2O) δ 7.69 (d, J = 12.9 Hz, 1H), 7.61 (dd, J = 12.3, 7.8 Hz, 1H), 7.39 (dd, J = 7.9, 2.7 Hz, 1H), 3.20 (t, J = 7.5 Hz, 2H), 2.78 (dt, J = 14.4, 7.7 Hz, 1H), 2.35 (dt, J = 14.4, 7.6 Hz, 1H); MS m/z (FAB) 258 (M^+).

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Supporting Information Available: ^{1}H NMR spectra of compounds **4a**, **4b**, **5a**, (*S*)-αM4CPG, **7**, **8**, (*S*)-MMPG, **10**, **13**, (*S*)-AIDA, **15**, and (*S*)-APICA (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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