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Palladium(II)-Catalyzed Enantioselective Arylation of α-Imino Esters

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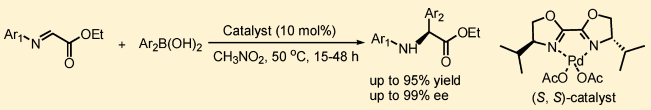
Supporting Information

ABSTRACT: A protocol for Pd(II)-catalyzed asymmetric arylation of *N*-aryl imino esters has been developed. The method affords a practical and direct access to chiral arylglycine derivatives in good yields and with high enantioselectivities.

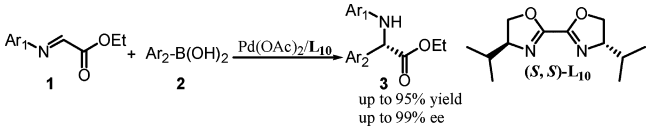


INTRODUCTION

Chiral arylglycines are fundamental building blocks of many pharmacologically active molecules[1] such as amoxicillins, nocardicins, cephalecins, and glycopeptide antibiotics. Optically active α-amino acids are also commonly utilized as auxiliaries and catalysts in modern organic synthesis.[2] Therefore, the exploration of a relatively straightforward methodology that can produce natural and unnatural α-amino acid derivatives with high levels of enantioselectivity is an important undertaking.[3]

The asymmetric addition of metallic or nonmetallic reagents to imines provides an efficient approach to various enantioenriched amines.[4] Among these extensive chiral amine-forming reactions, the addition of arylboronic acids to imines has attracted significant interest, because it capitalizes on the compatibility of diverse arylboronic acids with various functional groups. Although the transition-metal- or organo-catalyzed addition of arylboronic acids to *N*-acyl-*C*-arylimine such as *N*-sulfonyl, *N*-diphenylphosphinoyl, and *N*-sulfinyl imines has recently been well developed and produces α-chiral amines with excellent enantioselectivity,[5] this transformation could not provide chiral amino acids even through further reactions. Nevertheless, considering that α-imino esters have served as a cheap and easily available source of amino and carboxyl groups of amino acids,[6] Ellman,[7] Lu,[8] and Xu[9] successively realized the diastereoselective synthesis of α-amino acid derivatives via Rh-, Pd-, and In-catalyzed addition of aryl- or alkenylboronic acids to chiral starting material *N*-sulfinyl iminoacetates, respectively. Soon thereafter, Schaus and co-workers further developed a chiral biphenol-catalyzed asymmetric Petasis reaction of organoboronic acids, secondary amines, and glyoxylates to give chiral glycine derivatives,[10] but most of the optically active α-amino acid derivatives were only limited to those containing alkenyl groups at the α-position.[11] Herein we report an efficient asymmetric synthesis of arylglycines (up to 99% ee) based on palladium-catalyzed highly enantioselective addition of arylboronic acids (**1**) to *N*-aryl-*C*-acylimines (**2**) which are readily produced from primary arylamines and glyoxylates (see Scheme 1).

Scheme 1. Pd-Catalyzed Asymmetric Arylation of α-Imino Esters



RESULTS AND DISCUSSION

We initially conducted the Pd(II)-catalyzed addition of arylboronic acids to *N*-aryl-*C*-acylimines using (4-methoxyphenylimino)acetic acid ethyl ester (**1a**) and phenylboronic acid (**2a**) as the model substrates to screen the reaction conditions for the optimization of the catalyst, ligand, solvent, and temperature under an Ar atmosphere. As shown in Table 1, in the absence of any ligand, the Pd(II)-catalyzed arylation of *N*-aryl-*C*-acylimine **1a** afforded only trace amounts of the racemic (4-methoxyphenylamino)phenylacetic acid ethyl ester (**3a**) at 60 °C (<10% yield) (entries 1 and 2). In contrast, moderate to good yields occurred under Pd(II)/2,2′-bipyridine (bipy) conditions, possibly because bipy can enhance the nucleophility of arylpalladium species and accelerate the addition reaction (entries 3−6).[8] Among them, the $Pd(OAc)_2$ (5 mol %)/bipy (5 mol %) system (60 °C, 10 h) gave a good yield (78%) of the desired α-amino ester (**3a**) (entry 4) (see the Supporting Information for more details). Encouraged by these positive results, we further investigated the effect of chiral bidentate phosphine- or nitrogen-containing ligands on the enantioselectivity of this transformation. We quickly found that chiral pyridine-oxazoline ligands (PYOX; $\mathbf{L_6}$ and $\mathbf{L_7}$) and

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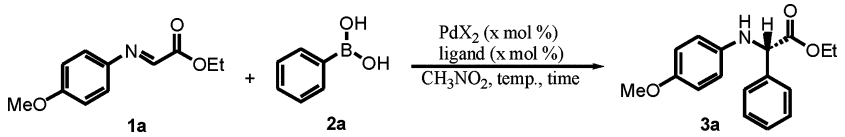
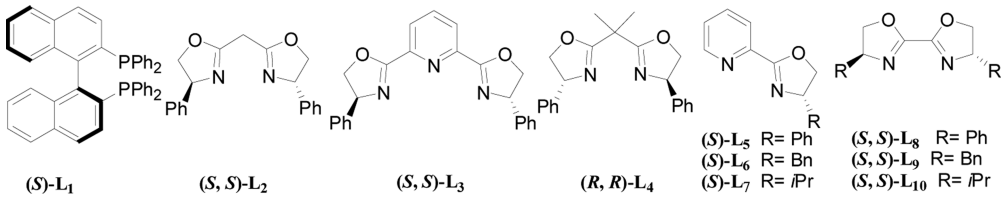
Table 1. Optimization Results for the Arylation of *C*-Acylimine (1a) and Boronic Acid (2a) with Pd(II)/Ligand as the Catalyst[a]



entry	PdX_2·ligand	*x*	time (h), temp (°C)	yield (%)[b]	ee (%)[c]
1	$Pd(TFA)_2$	5	10, 60	<5	
2	$Pd(OAc)_2$	5	10, 60	9	
3	$Pd(TFA)_2$·bipy	5	10, 60	33	
4	$Pd(OAc)_2$·bipy	5	10, 60	78	
5	$Pd(OAc)_2$·bipy	5	10, 90	64	
6	$Pd(OAc)_2$·bipy	5	10, 40	47	
7	$Pd(OAc)_2$·L_1	5	10, 60	trace	nd
8	$Pd(OAc)_2$·L_2	5	24, 60	<10	nd
9	$Pd(OAc)_2$·L_3	5	48, 60	0	nd
10	$Pd(OAc)_2$·L_4	5	48, 60	14	16
11	$Pd(OAc)_2$·L_5	5	16, 60	71	34
12	$Pd(OAc)_2$·L_6	5	16, 60	59	76
13	$Pd(OAc)_2$·L_7	5	16, 60	71	80
14	$Pd(OAc)_2$·L_8	5	48, 60	trace	nd
15	$Pd(OAc)_2$·L_9	5	24, 60	65	90
16	$Pd(OAc)_2$·L_{10}	5	24, 60	53	95
17	$Pd(OAc)_2$·L_{10}	10	24, 60	67 (13[d])	96
18	$Pd(OAc)_2$·L_{10}	10	24, 50	81	95

[a]Reactions were run with **1a** (0.1 mmol), **2a** (0.1 mmol), Pd(II) salt (5−10 mol %)/L (5−10 mol %), and CH_3NO_2 (3.0 mL) under Ar in a sealed pressure tube at the given temperature for the given time, followed by flash chromatography on SiO_2. Abbreviations: L = ligand, bipy = 2,2′-bipyridine, nd = not determined. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The yield of byproduct ethyl benzoate.



bis(oxazoline) ligands (BOX; L_9 and L_{10}) provided a significant improvement in enatioselectivity (entries 12, 13, 15, and 16). Among the tested PYOX and BOX ligands (L_4−L_{10}), L_{10} showed the best chiral induction ability (95% ee) in comparison to any other tested ligand (entries 10−16). Notably, evaluating phosphine-containing ligand L_1 and other oxazoline ligands (L_2, L_3, and L_8) did not enable the transformation to occur in the presence of $Pd(OAc)_2$ (entries 7−9 and 14). Diminished enantioselectivities were observed from the use of ligands (L_5 and L_8) that possess larger phenyl substitutents at the 4- and 4′-positions of the oxazoline ring (compared entries 11, 12, and 13; 14, 15, and 16). A catalyst loading of 10 mol % was found to be effective to achieve higher yield (compare entries 16 and 17). When the reaction temperature was lowered to 50 °C, a satisfying yield (81%) was obtained (compared entries 17 and 18). It is interesting that utilizing 10 mol % of $Pd(OAc)_2$ at 60 °C also provided a 13% yield of the byproduct ethyl benzoate (entry 17), which most likely resulted from the direct esterification of phenylboronic acids through the cleavage of carbonyl−imino σ bonds.

The optimal reaction conditions for the asymmetric arylation of *N*-aryl-*C*-acylimine required 10 mol % of $Pd(OAc)_2$, 10 mol % of L_{10}, and reaction temperature 50 °C. These catalytic systems proved to be general for a variety of *N*-aryl iminoacetates and arylboronic acids with excellent enantioselectivity (up to 99% ee) (Table 2). We initiated a study where we varied the *N*-aryl imino ester substrates. Aryl substitution on the imine nitrogen (Ar_1) shows no deleterious effects; both para-electron-donating (4-MeO, 4-Me) and para-electron-withdrawing (4-Cl, 4-Br, 4-NO_2) groups all afforded the corresponding α-amino esters (**3a**−**f**) in high yields (67−93%) with over 95% ee (entries 1−6). In addition, an *N*-(*m*-ethoxycarbonyl-substituted)aryl α-imino ester was also a suitable substrate for this transformation (entry 7).

We next evaluated the electronic and steric effect of substituents from arylboronic acids on the conversion and enantioselectivity of the reaction. Electron-rich arylboronic acids resulted in moderate to good yields (48−84%) with 84−96% ee (entries 8−12), except for 4-hydroxyphenylboronic acid (entry 13, 57% ee), and electron-deficient arylboronic acids resulted in poor yields, but their enantioselectivities still remained quite high (80−94%) (entries 14−17). The arylation of α-imino ester with arylboronic acids bearing larger steric bulkiness of ortho substituents or a naphthyl group also proceeded successfully to give the corresponding α-amino esters with high enantioselectivity (compare entries 10 and 11−12; 1 and 19). Boronic acids with heteroaromatic rings such as 3-thienyl, 2-thienyl, and 3-furyl are also good substrates to give the corresponding α-amino esters (**3u**−**w**) with 83−93% ee (entries 21−23). Unfortunately, no reaction occurred for 2-pyridylboronic acid,[12] and α-imino ester **1a** was completely recovered (entry 20).

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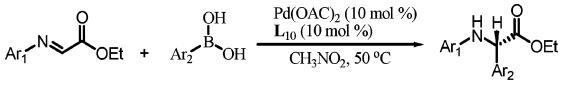
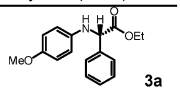
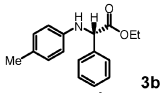
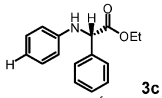
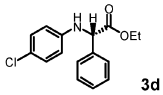
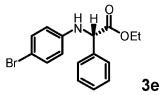
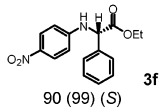
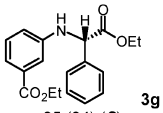
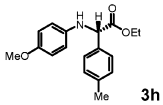
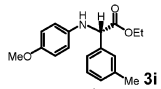
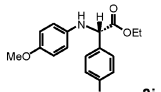
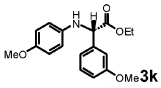
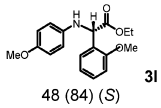
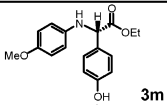
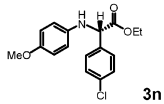
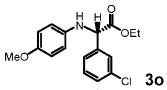
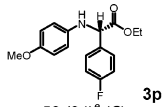
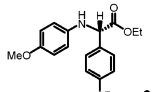
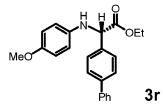
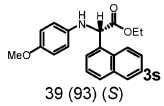
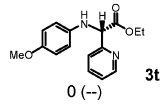
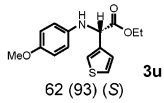
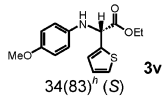
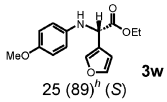
Table 2. Pd(II)-Catalyzed Asymmetric Addition of Arylboronic Acids 2 to *C*-Acylimine 1[a]



1 2 3

entry	Ar_1	Ar_2	product yield [b] (ee [c, d]) %
1	4-$MeOC_6H_4$	Ph	 **3a** 81 (95) (*S*)
2	4-MeC_6H_4	Ph	 **3b** 74 (97) [e] (*S*)
3	Ph	Ph	 **3c** 67 (96) [f] (*S*)
4	4-ClC_6H_4	Ph	 **3d** 93 (97) (*S*)
5	4-BrC_6H_4	Ph	 **3e** 90 (98) (*S*)
6	4-$NO_2C_6H_4$	Ph	 **3f** 90 (99) (*S*)
7	3-CO_2Et C_6H_4	Ph	 **3g** 95 (94) (*S*)
8	4-$MeOC_6H_4$	4-MeC_6H_4	 **3h** 67 (90)[e] (*S*)
9	4-$MeOC_6H_4$	3-MeC_6H_4	 **3i** 84 (96)[e] (*S*)
10	4-$MeOC_6H_4$	4-$MeOC_6H_4$	 **3j** 76 (93)[e] (*S*)
11	4-$MeOC_6H_4$	3-$MeOC_6H_4$	 **3k** 70 (95) (*S*)
12	4-$MeOC_6H_4$	2-$MeOC_6H_4$	 **3l** 48 (84) (*S*)
13	4-$MeOC_6H_4$	4-OHC_6H_4	 **3m** 47 (57)[e] (*S*)
14	4-$MeOC_6H_4$	4-ClC_6H_4	 **3n** 47 (94)[e] (*S*)
15	4-$MeOC_6H_4$	3-ClC_6H_4	 **3o** 38 (89)[e] (*S*)
16	4-$MeOC_6H_4$	4-FC_6H_4	 **3p** 59 (94)[e] (*S*)
17	4-$MeOC_6H_4$	4-$CF_3C_6H_4$	 **3q** 14 (80)[g] (*S*)
18	4-$MeOC_6H_4$	4-Biphenyl	 **3r** 83 (95) (*S*)
19	4-$MeOC_6H_4$	1-Naphthyl	 **3s** 39 (93) (*S*)
20	4-$MeOC_6H_4$	2-Pyridyl	 **3t** 0 (--)
21	4-$MeOC_6H_4$	3-Thienyl	 **3u** 62 (93) (*S*)
22	4-$MeOC_6H_4$	2-Thienyl	 **3v** 34(83)[h] (*S*)
23	4-$MeOC_6H_4$	3-Furyl	 **3w** 25 (89)[h] (*S*)

[a]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol, 0.10 equiv) and $\mathbf{L_{10}}$ (0.01 mmol, 0.10 equiv) were combined, dissolved in CH_3NO_2 (3.0 mL), and heated to 50 °C for 1 h. Then substrate **1** (0.1 mmol, 1.0 equiv) and **2** (0.1 mmol, 1.0 equiv) were added, and the reaction tube was sealed and heated at 50 °C for 24 h unless otherwise noted. Abbreviations: L = ligand, nd = not determined. [b]Yield refers to amount of isolated **3** after purification by flash chromatography on SiO_2. [c]Determined by chiral HPLC analysis. [d]The absolute configurations of **3a** were determined by comparing the optical rotation $[\alpha]_D$ with known data. Assuming an analogous reaction mechanism, the configurations of other α-amino acid derivatives are assigned as indicated in the table. [e]Reaction time 15 h. [f]1.20 equiv of phenylboronic acid was used. [g]Reaction time 36 h. [h]Reaction time 48 h.

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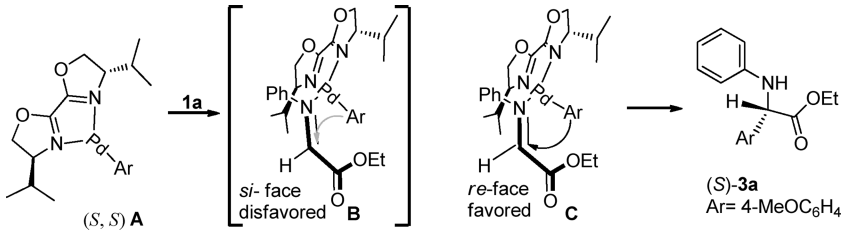
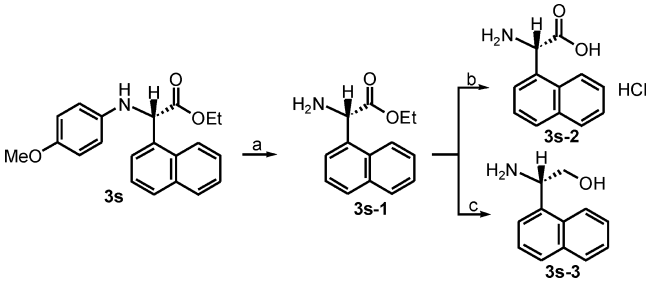
Scheme 2. Stereochemical Model



We determined the absolute stereochemistry of products **3a** via CAN deprotection of the PMP group and comparison with the optical rotation and ee value of the respective known amino ester (see the Experimental Section), and the absolute configuration is in good agreement with the proposed stereochemical model shown in Scheme 2. The imine nitrogen coordinates with the palladium active species A which resulted from palladium/$\mathbf{L_{10}}$ complexes and arylboronic acid **2a** via transmetalation.[8,13] The aryl group preferred to add to the *N*-arylimine carbon from the *re* face, avoiding the steric interaction between the aryl section of the imino ester and aryl group on Pd active species in a highly selective manner to produce (*S*)-**3a**, which is similar to the arylation of *N*-sulfonylimines that Nishimura, Zhou, and Lu previously reported.[5j,8,14]

An illustration of the utility of this reaction is shown in the concise asymmetric synthesis of 1-naphthyl-α-amino acid (**3s-2**) and β-(1-naphthyl)-β-amino alcohol (**3s-3**) (Scheme 3).[15]

Scheme 3. Application of the Protocol in the Synthesis of Enantiopure (1-Naphthyl)glycine and (1-Naphthyl)glycinol[a]



[a]Legend: (a) CAN, CH_3CN, room temperature, 12 h, 45% yield; (b) HCl/H_2O, reflux, 2.5 h, 96% yield; (c) $NaBH_4$, CH_3OH, room temperature, 24 h, 83% yield.

The CAN deprotection reaction of **3s**[16] provided 1-naphthyl-α-amino ester (**3s-1**) in 40% yield, and the following hydrolysis and reduction of **3s-1** provided α-(1-naphthyl)-α-amino acid (96% yield) and β-(1-naphthyl)-β-amino alcohol (83% yield), respectively. This procedure was accomplished in just two steps from readily available **3s** and is several steps shorter than the original route.[15]

In conclusion, we have developed a Pd(II)/chiral BOX system -catalyzed asymmetric addition of arylboronic acids to *N*-aryl-α-imino esters to yield the arylglycine derivatives with high enantioselectivity. Removal of the PMP group can further provide valuable chiral amino acids and chiral amino alcohols.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all other commercially available reagents and solvents were used without further purification. Purifications of reaction products were carried out by flash chromatography using silica gel (40−63 mm). Infrared spectra (IR) were recorded on a FT-IR spectrophotometer and are reported as wavelength numbers (cm^{-1}). Infrared spectra were recorded by preparing a KBr pellet containing the title compound. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) as internal standard at ambient temperature unless otherwise indicated on a standard spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm), and coupling constants are reported as hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), and triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Melting points were determined on a microscopic melting point apparatus and are uncorrected. Low-resolution mass spectra were taken on a LC-MS instrument. High-resolution mass spectra (HRMS) were recorded on a IF-TOF spectrometer (Micromass). Enantiomeric excess values of all compounds were obtained from chiral HPLC analyses, and the UV detection was monitored at 254 nm. (*S*)-2-(4-phenyl-4,5-dihydrooxazol-2-yl)pyridine[17] ($\mathbf{L_5}$), (*S*)-2-(4-benzyl-4,5-dihydrooxazol-2-yl)-pyridine[17] ($\mathbf{L_6}$), (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine[17] ($\mathbf{L_7}$), (*S*)-4-phenyl-2-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-4,5-dihydrooxazole[18,19] ($\mathbf{L_8}$), (*S*,*S*)-4,4′-diisopropyl-4,5,4′,5′-tetrahydro[2.2]-bioxazolyl[18,19] ($\mathbf{L_{10}}$) and (*R*,*R*)-$\mathbf{L_{10}}$[18,19] were prepared according to the reported methods.

General Procedures for the Synthesis of 3a−v. A mixture of the substituted aniline (0.1 mmol, 12.3 mg), ethyl glyoxalate (1 equiv, 0.1 mmol, 10.2 mg), and anhydrous sodium sulfate (5 equiv, 0.5 mmol, 71 mg) in 2 mL of CH_2Cl_2 was stirred at room temperature for 0.5−3 h or refluxed in 2 mL of toluene at 110 °C for 1 h. Then the corresponding mixture was cooled to room temperature and filtered, and the filtrate was concentrated in vacuo without further purification and used in the next step. $Pd(OAc)_2$ (0.01 mmol, 0.1 equiv), (*S*,*S*)-isopropyl bisoxazoline $\mathbf{L_{10}}$ (0.01 mmol, 0.1 equiv), and CH_3NO_2 (1.0 mL) were combined in a pressure tube equipped with a stir bar under Ar, and the mixture was stirred at 45−50 °C for 1 h in order to make the Pd(II) salt coordinate with the ligand completely. Then *N*-aryl α-imino ester (0.1 mmol, 1.0 equiv) and arylboronic acid (0.1 mmol, 1.0 equiv) was added to the solution, and the tube was refreshed with Ar for 5 min, sealed, and heated to 50 °C in an oil bath for the given time. After the starting material has disappeared (monitored by TLC), the reaction mixture was cooled to room temperature and then filtered, the filtrate was concentrated in vacuo, and the corresponding crude product was purified directly by silica gel column chromatography (eluent consisting of hexane/EtOAc, from 20/1 to 15/1) to give the pure product α-amino ester. The ee value of the product was determined by chiral HPLC analysis and compared with the racemate.

*(S)-Ethyl 2-(4-methoxyphenylamino)-2-phenylacetate (**3a**):*[3c] 23.1 mg, 81% yield; $[\alpha]^{20}_D$ = +66.0° (*c* = 0.1, $CHCl_3$); ee = 95%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.05 mL/min, hexane 0.5 mL/min, λ 254 nm, *t*(minor) = 15.14 min, *t*(major) = 16.34 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2 H), 7.36−7.30 (m, 3 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 6.53 (d, *J* = 8.7 Hz, 2 H), 5.00 (s, 1 H), 4.67 (s, 1 H), 4.25−4.11 (m, 2 H), 3.70 (s, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 152.5, 140.3, 137.9, 128.8, 128.2, 127.3, 114.8, 61.7, 61.6, 55.7, 14.1; MS (ESI) *m*/*z* 286.6 [M^+], 324.6 [M + K^+]; IR (KBr) 3399, 2927, 2854, 1734, 1513, 1457, 1370, 1305, 1239, 1178, 1029, 820, 732, 688, 523 cm^{-1}.

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*(S)-Ethyl 2-(p-toluidino)-2-phenylacetate (**3b**):*[20] 19.9 mg, 74% yield; $[\alpha]^{20}_{D}$ = +95.9° (*c* = 0.22, $CHCl_3$); ee = 97%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 9.24 min, *t*(major) = 12.75 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 2 H), 7.37−7.28 (m, 3 H), 6.94 (d, *J* = 8.1 Hz, 2 H), 6.50 (d, *J* = 8.2 Hz, 2 H), 5.05 (s, 1 H), 4.83 (s, 1 H), 4.26−4.12 (m, 2 H), 2.21(s, 3 H), 1.22 (t, *J* = 8.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.0, 143.7, 137.9, 129.7, 128.8, 128.2, 127.3, 127.2, 113.6, 61.8, 61.1, 20.4, 14.1; MS (ESI) *m*/*z* 270.6 [M^+], 292.5 [M + Na^+], 308.6 [M + K^+]; IR (KBr) 3408, 2959, 2925, 2862, 1736, 1618, 1521, 1456, 1371, 1307, 1259, 1179, 1097, 1023, 807, 731, 698, 509 cm^{-1}.

*(S)-Ethyl 2-phenyl-2-(phenylamino)acetate (**3c**):*[21] 17.1 mg. 67% yield; $[\alpha]^{20}_{D}$ = +107.7° (*c* = 0.22, $CHCl_3$); ee = 96%, determined by HPLC analysis (Chiralcel OD-H, IPA 0.01 mL/min, hexane 0.35 mL/min, λ 254 nm, *t*(minor) = 18.42 min, *t*(major) = 16.03 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 2 H), 7.37−7.26(m, 3 H), 7.11 (t, *J* = 7.7 Hz, 2 H), 6.73−6.70 (m, 1 H), 6.56 (d, *J* = 8.4 Hz, 2 H), 5.06 (d, J = 5.6 Hz, 1 H), 4.96 (s, 1H), 4.29−4.11 (m, 2 H), 1.23 (t, *J* = 12.0 Hz, 8.0 Hz, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.9, 146.0, 137.8, 129.3, 128.8, 128.2, 127.2, 118.1, 113.4, 61.8, 60.8, 14.1; MS (ESI) *m*/*z* 256.5 [M^+], 278.5 [M + Na^+], 294.5 [M + K^+]; IR (KBr) 3406, 3055, 3028, 2983, 2931, 1735, 1603, 1504, 1453, 1369, 1313, 1257, 1178, 1075, 1023, 872, 747, 695, 508 cm^{-1}.

*(S)-Ethyl 2-(4-chlorophenylamino)-2-phenylacetate (**3d**):*[20] 27.0 mg, 93% yield; $[\alpha]^{20}_{D}$ = +97.5° (*c* = 0.2, $CHCl_3$); ee = 97%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.1 mL/min, hexane 0.4 mL/min, λ 254 nm, *t*(minor) = 9.94 min, *t*(major) = 11.15 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.48 (m, 2 H), 7.37−7.30 (m, 3 H), 7.09−7.05 (m, 2 H), 6.51−6.47 (m, 2 H), 5.06−5.03 (m, 2 H), 4.29−4.11 (m, 2 H), 1.23 (t, *J* = 8.0, 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.6, 144.5, 137.3, 129.0, 128.4, 127.2, 122.7, 114.5, 62.0, 60.8, 14.1; MS (ESI) *m*/*z* 290.5 [M^+], 328.5 [M + K^+]; IR (KBr) 3404, 2926, 2856, 1736, 1600, 1500, 1458, 1371, 1315, 1256, 1177, 1094, 1022, 816, 734, 698, 503 cm^{-1}.

*(S)-Ethyl 2-(4-bromophenylamino)-2-phenylacetate (**3e**):*[20] 30.0 mg, 90% yield; $[\alpha]^{20}_{D}$ = +79.5° (*c* = 0.22, $CHCl_3$); ee = 98%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.1 mL/min, hexane 0.4 mL/min, λ 254 nm, *t*(minor) = 10.22 min, *t*(major) = 12.03 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.48 (m, 2 H), 7.39−7.30 (m, 3H), 7.22 − 7.18 (m, 2 H), 6.46−6.42 (m, 2 H), 5.07 (s, 1H), 5.03 (s, 1 H), 4.29−4.11 (m, 2 H), 1.22 (t, *J* = 8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.5, 144.9, 137.2, 132.0, 128.9, 128.4, 127.2, 115.0, 109.8, 62.0, 60.7, 14.1; MS (ESI) *m*/*z* 334.5 [M^+]; IR (KBr) 3400, 2926, 2855, 1735, 1652, 1595, 1457, 1369, 1309, 1240, 1021, 878, 772, 697, 502 cm^{-1}.

*(S)-Ethyl 2-(4-nitrophenylamino)-2-phenylacetate (**3f**):*[20] 27.0 mg, 90% yield; $[\alpha]^{20}_{D}$ = +244.5° (*c* = 0.22, $CHCl_3$); ee = 99%, determined by HPLC analysis (Chiralcel IC, IPA 10%, hexane 90%, 0.8 mL/min, λ 254 nm, *t*(minor) = 26.20 min, *t*(major) = 24.89 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.99 (m, 2 H), 7.47−7.44 (m, 2 H), 7.39−7.31 (m, 3 H), 6.52- 6.48 (m, 2 H), 5.87 (d, *J* = 5.3 Hz, 1 H), 5.12 (d, *J* = 5.7 Hz, 1 H), 4.31−4.11 (m, 2 H), 1.22 (t, *J* = 8.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7, 150.9, 138.8, 136.1, 129.1, 128.8, 127.0, 126.2, 112.1, 62.5, 60.0, 14.0; MS (ESI) *m*/*z* 301.6 [M^+], 339.5 [M + K^+]; IR (KBr) 3779, 3403, 2923, 2854, 1734, 1668, 1601, 1513, 1460, 1373, 1309, 1240, 1179, 1028, 821, 754, 700, 503 cm^{-1}.

*(S)-Ethyl 3-(2-ethoxy-2-oxo-1-phenylethylamino)benzoate (**3g**).* colorless solid; mp 74−75 °C; 31.1 mg, 95% yield; $[\alpha]^{20}_{D}$ = +120.0° (*c* = 0.22, $CHCl_3$); ee = 94%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 10.91 min, *t*(major) = 12.52 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2 H), 7.39−7.29 (m, 5 H), 7.16 (t, *J* = 7.9 Hz, 1 H), 6.73−6.71 (m, 1 H), 5.17 (d, *J* = 6.1 Hz, 1 H), 5.12 (dd, *J* = 19.3, 6.1 Hz, 1 H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.25- 4.10 (m, 2 H), 1.36 (t, J = 8.0 Hz, 3 H), 1.22 (t, *J* = 8.0, 4.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 171. 6, 166.8, 146.0, 137.3, 131.4, 129.2, 128.9, 128.4, 127.2, 119.1, 117.6, 114.3, 61.9, 60.7, 29.7, 14.3, 14.0; HRMS (EI) calcd for [M + Na]$^+$ $C_{19}H_{21}NO_4$ 350.1363, found 350.1350; IR (KBr) 3857, 3393, 2978, 2929, 1955, 1720, 1605, 1495, 1369, 1324, 1244, 1180, 1106, 1023, 867, 751, 696, 540 cm^{-1}.

*(S)-Ethyl 2-(4-methoxyphenylamino)-2-p-tolylacetate (**3h**):*[3d] 20.0 mg, 67% yield; $[\alpha]^{20}_{D}$ = +87.5° (*c* = 0.2, $CHCl_3$); ee = 90%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.01 mL/min, hexane 0.35 mL/min, λ 254 nm, *t*(minor) = 33.83 min, *t*(major) = 36.17 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 2 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 6.73 (d, *J* = 8.7 Hz, 2 H), 6.55 (d, *J* = 8.7 Hz, 2 H), 4.98 (s, 1 H), 4.65 (s, 1 H), 4.25−4.11 (m, 2 H), 3.71 (s, 3 H), 2.34 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 152.4, 140.4, 137.9, 134.9, 129.5, 127.1, 114.8, 114.7, 61.6, 61.4, 55.7, 21.2, 14.1; MS (ESI) *m*/*z* 300.6 [M^+], 322.6 [M + Na^+]; IR (KBr) 3400, 2925, 2855, 1735, 1615, 1514, 1462, 1371, 1307, 1240, 1179, 1097, 1023, 807, 731, 698, 509 cm^{-1}.

*(S)-Ethyl 2-(3-chlorophenyl)-2-(4-methoxyphenylamino)acetate (**3i**):*[22] 25.1 mg, 84% yield; $[\alpha]^{20}_{D}$ = +51.4° (*c* = 0.14, $CHCl_3$); ee = 96%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.01 mL/min, hexane 0.35 mL/min, λ 254 nm, *t*(minor) = 30.90 min, *t*(major) = 34.88 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.19 (m, 3 H), 7.12 (d, *J* = 7.3 Hz, 1 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 6.56 (d, *J* = 8.8 Hz, 2 H), 4.97 (s, 1 H), 4.65 (s, 1 H), 4.27−4.10 (m, 2 H), 3.71 (s, 3 H), 2.35 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 152.5, 140.4, 138.5, 137.8, 129.0, 128.7, 127.8, 124.4, 114.9, 114.8, 61.8, 61.7, 55.7, 21.5, 14.1; MS (ESI) *m*/*z* 300.4 [M^+], 322.4 [M + Na^+], 338.3 [M + K^+]; IR (KBr) 3400, 2956, 2924, 2855, 1735, 1608, 1514, 1461, 1374, 1301, 1241, 1189, 1160, 1030, 820, 739, 696, 515, 444 cm^{-1}.

*(S)-Ethyl 2-(4-methoxyphenyl)-2-(4-methoxyphenylamino)-acetate (**3j**):*[3c] 23.9 mg, 76% yield; $[\alpha]^{20}_{D}$ = +91.0° (*c* = 0.2, $CHCl_3$); ee = 93%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.20 mL/min, hexane 0.80 mL/min, λ 254 nm, *t*(minor) = 9.49 min, *t*(major) = 11.96 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.3 Hz, 2 H), 7.26 (s, 1H), 6.89 (d, *J* = 8.3 Hz, 2 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 6.55 (d, *J* = 8.6 Hz, 2 H), 4.97 (s, 1 H), 4.64 (s, 1 H), 4.23−4.12 (m, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.06 (s, 1H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 159.5, 152.5, 140.4, 129.9, 128.4, 114.9, 114.8, 114.2, 61.6, 61.1, 55.7, 55.3, 14.1; MS (ESI) *m*/*z* 316.6 [M^+], 338.6 [M + Na^+]; IR (KBr) 3399, 2924, 2849, 1734, 1679, 1610, 1512, 1462, 1371, 1305, 1241, 1176, 1031, 823, 739, 527 cm^{-1}.

*(S)-Ethyl 2-(3-methoxyphenyl)-2-(4-methoxyphenylamino)-acetate (**3k**):*[11b] 22.1 mg, 70% yield; $[\alpha]^{20}_{D}$ = +61.0° (*c* = 0.2, $CHCl_3$); ee = 95%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.20 mL/min, hexane 0.80 mL/min, λ 254 nm, *t*(minor) = 6.69 min, *t*(major) = 7.67 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.9 Hz, 1 H), 7.09−7.04 (m, 2 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 6.72 (d, *J* = 8.7 Hz, 2 H), 6.54 (d, *J* = 8.7 Hz, 2 H), 4.97 (s, 1H), 4.65 (s, 1 H), 4.25−4.09 (m, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.0, 160.0, 152.5, 140.3, 139.5, 129.8, 119.6, 114.9, 114.8, 113.7, 112.8, 61.7, 55.7, 55.3, 29.7, 14.1; MS (ESI) *m*/*z* 316.4 [M^+], 338.4 [M + Na^+]; IR (KBr) 3397, 2926, 2851, 2063, 1731, 1685, 1599, 1513, 1461, 1370, 1242, 1187, 1159, 1033, 822, 780, 739, 694, 522, 459 cm^{-1}.

*(S)-Ethyl 2-(2-methoxyphenyl)-2-(4-methoxyphenylamino)-acetate (**3l**):*[23] 15.1 mg, 48% yield; $[\alpha]^{20}_{D}$ = +41.4° (*c* = 0.14, $CHCl_3$); ee = 84%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.01 mL/min, hexane 0.35 mL/min, λ 254 nm, *t*(minor) = 52.99 min, *t*(major) = 57.90 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.33 (m, 1 H), 7.29−7.24 (m, 1 H), 6.93 (t, *J* = 7.6 Hz, 2 H), 6.74−6.71 (m, 2 H), 6.63−6.59 (m, 2 H), 5.42 (s, 1 H), 4.59 (s, 1 H), 4.17−4.11 (m, 2 H), 3.90 (s, 3 H), 3.71 (s, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.0, 157.2, 152.5, 140.8, 129.3, 128.1, 126.7, 121.0, 115.1, 114.8, 111.2, 61.3, 56.1, 55.7, 29.7, 14.1; MS (ESI) *m*/*z* 338.1 [M + Na^+]; IR (KBr) 3388, 2924, 2852, 1734, 1672, 1599, 1512, 1462, 1371, 1242, 1188, 1026, 821, 747, 523 cm^{-1}.

*(S)-Ethyl 2-(4-hydroxyphenyl)-2-((4-methoxyphenyl)amino)-acetate (**3m**):*[11b] 14.1 mg, 47% yield; $[\alpha]^{20}_{D}$ = +41.9° (*c* = 0.16, $CHCl_3$); ee = 57%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.20 mL/min, hexane 0.80 mL/min, λ 254 nm, *t*(minor) = 8.32

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min, *t*(major) = 16.23 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2 H), 6.75 (dd, *J* = 21.1, 8.7 Hz, 4 H), 6.54 (d, *J* = 8.8 Hz, 2 H), 4.93 (s, 1 H), 4.76 (d, *J* = 4.2 Hz, 0H), 4.63 (d, *J* = 4.0 Hz, 0.52 H) + 4.16 (ddt, *J* = 17.8, 14.2, 5.3 Hz, 0.4 H) = 1 H, 3.71 (s, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 155.7, 152.5, 140.3, 129.8, 128.6, 115.7, 114.8, 114.9, 61.7, 61.2, 55.8, 14.1; MS (ESI) *m*/*z* 302.1 [M^+]; IR (KBr) 3652, 3396, 2952, 1730, 1610, 1559, 1513, 1459, 1380, 1240, 1169, 1026, 951, 819, 517 cm^{-1}.

(S)-Ethyl 2-(4-chlorophenyl)-2-(4-methoxyphenylamino)acetate (**3n**):[22] 15.0 mg, 47% yield; $[\alpha]^{20}_D$ = +91.5° (*c* = 0.2, $CHCl_3$); ee = 94%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 12.34 min, *t*(major) = 13.73 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 6.73 (d, *J* = 8.7 Hz, 2 H), 6.51 (d, *J* = 8.7 Hz, 2 H), 4.98 (s, 1 H), 4.73 (s, 1 H), 4.25−4.12 (m, 2 H), 3.71 (s, 3 H),1.22 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.5, 152.6, 139.9, 136.6, 134.0, 129.0, 128.6, 114.9, 114.8, 62.0, 61.1, 55.7, 14.1; MS (ESI) *m*/*z* 320.5 [M^+], 342.5 [M + Na^+]; IR (KBr) 3399, 2926, 2855, 1736, 1593, 1514, 1463, 1371, 1241, 1179, 1092, 1020, 820, 739, 508 cm^{-1}.

(S)-Ethyl 2-(3-chlorophenyl)-2-(4-methoxyphenylamino)acetate (**3o**): yellow oil; 12.1 mg, 38% yield; $[\alpha]^{20}_D$ = +29.0° (*c* = 0.2, $CHCl_3$); ee = 89%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 13.16 min, *t*(major) = 15.32 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.39 (t, *J* = 3.6 Hz, 1 H), 7.33−7.21 (m, 2 H), 6.73 (d, *J* = 8.8 Hz, 2 H), 6.51 (d, *J* = 8.8 Hz, 2 H), 4.97 (s, 1 H), 4.73 (s, 1 H), 4.48−3.95 (m, 2 H), 3.71 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.4, 152.6, 140.12, 139.9, 134.7, 130.0, 128.4, 127.4, 125.4, 114.9, 114.8, 62.0, 61.3, 55.7, 14.0; HRMS (EI) calcd for [M + $Na]^+$ $C_{17}H_{18}ClNO_3$ 342.0867, found 342.0861; IR (KBr) 3395, 2924, 2854, 1737, 1671, 1593, 1514, 1463, 1373, 1240, 1183, 1094, 1025, 818, 751, 448 cm^{-1}.

(S)-Ethyl 2-(4-fluorophenyl)-2-(4-methoxyphenylamino)acetate (**3p**):[22] 17.9 mg, 59% yield; $[\alpha]^{20}_D$ = +57.5° (*c* = 0.2, $CHCl_3$); ee = 94%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 11.91 min, *t*(major) = 13.05 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.47 (m, 2 H), 7.04 (t, *J* = 8.5 Hz, 2 H), 6.73 (d, *J* = 8.7 Hz, 2 H), 6.53 (d, *J* = 8.7 Hz, 2 H), 5.00 (s, 1 H), 4.72 (s, 1 H), 4.25−4.13 (m, 2 H), 3.71 (s, 3 H), 2.05 (s, 1H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.8, 163.8, 161.4, 152.6, 140.0, 133.7, 133.7, 128.9, 128.8, 115.8, 115.6, 114.8, 114.7, 61.8, 61.0, 55.7, 14.0; MS (ESI) *m*/*z* 304.6 [M^+], 326.6 [M + Na^+]; IR (KBr) 3390, 2923, 2853, 1731, 1600, 1509, 1463, 1299, 1231, 1178, 1025, 816, 744, 514 cm^{-1}.

(S)-Ethyl 2-(4-methoxyphenylamino)-2-(4-(trifluoromethyl)-phenyl)acetate (**3q**):[3d] 4.9 mg, 14% yield; $[\alpha]^{20}_D$ = +52.5° (*c* = 0.04, $CHCl_3$); ee = 80%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 12. 95 min, *t*(major) = 15.31 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (q, J = 8.4 Hz, 4 H), 6.72 (d, *J* = 8.5 Hz, 2 H), 6.72 (d, *J* = 8.5 Hz, 2 H), 6.49 (d, *J* = 8.5 Hz, 2 H), 5.05 (s, 1 H), 4.80 (s, 1 H), 4.26−4.12 (m, 2 H), 3.70 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.2, 152.7, 142.2, 139.7, 130.6, 130.2, 127.6, 125.8, 125.7,125.4, 122.7, 117.4, 114.9, 114.8, 62.1, 61.3, 55.7, 14.0; MS (ESI) *m*/*z* 353.0 [M^+], 377.1 [M + Na^+]; IR (KBr) 2924, 2854, 1738, 1673, 1617, 1514, 1461, 1374, 1325, 1241, 1168, 1128, 1067, 1021, 823, 742, 462 cm^{-1}.

(S)-Ethyl 2-([1,1′-biphenyl]-4-yl)-2-((4-methoxyphenyl)amino)-acetate (**3r**): yellow oil; 30.0 mg, 83% yield; $[\alpha]^{20}_D$ = +63.0° (*c* = 0.2, $CHCl_3$); ee = 95%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 16.30 min, *t*(major) = 17.19 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.51 (m, 6 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 6.75 (d, *J* = 8.6 Hz, 2 H), 6.58 (d, *J* = 8.6 Hz, 2 H), 5.06 (s, 1 H), 4.73 (s, 1 H), 4.33−4.10 (m, 2 H), 3.72 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 152.5, 141.1, 140.6, 140.3, 136.9, 128.8, 127.7, 127.5, 127.4, 127.1, 114.9, 114.8, 61.8, 61.5, 55.7, 14.1; HRMS (EI) calcd for [M + $Na]^+$ $C_{23}H_{23}NO_3$ 384.1570, found 384.1574; 326.6 [M + $Na]^+$; IR (KBr) 3380, 2925, 2855, 1735, 1599, 1504, 1474, 1371, 1318, 1260, 1178, 1138, 1110, 1020, 834, 734, 697, 495 cm^{-1}.

(S)-Ethyl 2-(4-methoxyphenylamino)-2-(naphthalen-1-yl)acetate (**3s**): yellow oil; 13.1 mg, 39% yield; $[\alpha]^{20}_D$ = +17.0° (*c* = 0.2, $CHCl_3$); ee = 93%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(minor) = 14.46 min, *t*(major) = 17.55 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 7.64 (d, *J* = 7.2 Hz, 1 H), 7.61−7.51 (m, 2 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 6.72 (d, *J* = 8.7 Hz, 2 H), 6.56 (d, *J* = 8.7 Hz, 2 H), 5.77 (s, 1 H), 4.72 (s, 1 H), 4.30−3.99 (m, 2 H), 3.70 (s, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 152.6, 140.5, 134.1, 133.7, 131.4, 129.0, 128.9, 126.5, 125.9, 125.5, 124.9, 123.5, 114.9, 114.6, 61.8, 58.4, 55.7, 14.0; HRMS (EI) calcd for [M + $H]^+$ $C_{21}H_{21}NO$ 336.1594, found 336.1597; IR (KBr) 2955, 2924, 2855, 1736, 1513, 1461, 1375, 1263, 1193, 1024, 740 cm^{-1}.

(R)-Ethyl 2-(4-methoxyphenylamino)-2-(naphthalen-1-yl)acetate (**3s**). (*R*,*R*)-$\mathbf{L_{10}}$ used as a chiral ligand; yellow oil; 13.1 mg, 39% yield; $[\alpha]^{20}_D$ = −48.0° (*c* = 0.1, $CHCl_3$); ee = 96%, determined by HPLC analysis (Chiralcel Lux 5u Cellulose-1, IPA 0.10 mL/min, hexane 0.40 mL/min, λ 254 nm, *t*(major) = 15.24 min, *t*(minor) = 17.77 min).

We also increased the reaction scale to a gram scale in order to further synthesize the corresponding free amino acid (**3s-2**) and amino alcohol (**3s-3**). A mixture of 4-anisidine (5 mmol, 0.62 g), ethyl glyoxalate (5 mmol, 0.51 g), and anhydrous sodium sulfate (25 mmol, 3.55 g) in 100 mL of CH_2Cl_2 was stirred at room temperature for 3 h. Then the corresponding mixture was filtered, and the filtrate was concentrated in vacuo without further purification and used in the next step. $Pd(OAc)_2$ (0.5 mmol, 0.1 equiv, 0.11 g), (*S*,*S*)-isopropyl bisoxazoline $\mathbf{L_{10}}$ (0.5 mmol, 0.1 equiv, 0.11 g), and CH_3NO_2 (50 mL) were combined in a pressure tube equipped with a stir bar under Ar, and the mixture was stirred at 50 °C for 2 h in order to make the Pd(II) salt coordinate with the ligand completely. Then ethyl 2-((4-methoxyphenyl)imino)acetate (5 mmol, 1.0 equiv, 1.04 g) and naphthalen-1-ylboronic acid (5 mmol. 1.0 equiv, 0.86 g) were added to the solution, and the tube was refreshed with Ar for 5 min and then sealed and heated to 50 °C in an oil bath for 48 h. After the starting material disappeared (monitored by TLC), the reaction mixture was cooled to room temperature and then filtered, the filtrate was concentrated in vacuo, and the corresponding crude product was purified directly by silica gel column chromatography (eluent consisting of hexane/EtOAc, from 20/1) to give **3s** in 42% yield with 95% ee.

(S)-Ethyl 2-(4-methoxyphenylamino)-2-(thiophen-3-yl)acetate (**3u**): yellow oil; 18.0 mg, 62% yield; $[\alpha]^{20}_D$ = +23.5° (*c* = 0.2, $CHCl_3$); ee = 93%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.01 mL/min, hexane 0.35 mL/min, λ 254 nm, *t*(minor) = 46.28 min, *t*(major) = 53.32 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.30 (m, 2 H), 7.17 (d, *J* = 4.9 Hz, 1 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 6.59 (d, *J* = 8.8 Hz, 2 H), 5.13 (s, 1 H), 4.54 (s, 1 H), 4.32−4.10 (m, 2 H), 3.73 (s, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.8, 152.7, 140.4, 138.5, 126.5, 126.3, 122.8, 115.0, 114.9, 61.7, 58.1, 55.7, 14.1; HRMS (EI) calcd for [M + $H]^+$ $C_{15}H_{17}NO_3S$ 292.1002, found 292.1004; IR (KBr) 3394, 2924, 2855, 1736, 1674, 1513, 1461, 1374, 1240, 1184, 1096, 1028, 878, 741 cm^{-1}.

(S)-Ethyl 2-(4-methoxyphenylamino)-2-(thiophen-2-yl)acetate (**3v**):[24] 9.9 mg, 34% yield; $[\alpha]^{20}_D$ = +16.4° (*c* = 0.14, $CHCl_3$); ee = 83%, determined by HPLC analysis (Chiralcel AS-H,, IPA 5%, hexane 95%, 0.8 mL/min, λ 254 nm, *t*(minor) = 16.57 min, *t*(major) = 13.25 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.19 (m, 1 H), 7.13 (s, 1 H), 7.04−6.90 (m, 1 H), 6.76 (d, *J* = 8.7 Hz, 2 H), 6.63 (d, *J* = 8.5 Hz, 2 H), 5.26 (s, 1 H), 4.63 (s, 1 H), 4.35−4.08 (m, 2 H), 3.73 (s, 3 H), 1.27 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 153.0, 141.6, 140.0, 127.0, 125.5, 125.4, 115.3, 114.9, 62.0, 58.0, 55.7, 14.1; MS (ESI) *m*/*z* 314.3 [M + Na^+], 330.4 [M + K^+]; IR (KBr) 3383, 2925, 2855, 1738, 1671, 1513, 1462, 1373, 1240, 1183, 1023, 822, 741, 599, 541 cm^{-1}.

(S)-Ethyl 2-(furan-3-yl)-2-(4-methoxyphenylamino)acetate (**3w**): yellow oil; 6.9 mg, 25% yield; $[\alpha]^{20}_D$ = +4.6° (*c* = 0.26, $CHCl_3$); ee = 89%, determined by HPLC analysis (Chiralcel AD-H, IPA 0.05 mL/

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min, hexane 0.35 mL/min, λ 254 nm, *t*(minor) = 19.83 min, *t*(major) = 22.82 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ [7.47 (s, 0.3 H) + 6.47 (s, 0.3 H) + 6.35 (s, 1.4 H) + 7.39 (s, 1 H)] = 2 H, 6.76 (d, *J* = 8.3 Hz, 2 H), 6.63 (d, *J* = 8.3 Hz, 2 H), [5.13 (s, 0.7 H) + 4.98 (s, 0.3 H)] = 1 H, 4.53 (s, 1 H), 4.34−4.11 (m, 2 H), 3.73 (s, 3 H), 1.30−1.17 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 153.0, 150.4, 143.4, 142.7, 140.5, 140.0, 115.4, 115.2, 114.9, 110.6, 109.4, 108.0, 62.0, 56.3, 55.7, 29.7, 14.1; HRMS (EI) calcd for $[M + Na]^+$ $C_{15}H_{17}NO_4$ 298.1050, found 298.1055; IR (KBr) 3379, 2924, 2854, 1739, 1672, 1513, 1462, 1373, 1240, 1183, 1023, 822, 741, 599, 541 cm^{-1}.

*(S)-Ethyl 2-amino-2-(naphthalen-1-yl)acetate (**3s-1**).*[25] A CH_3CN (5.0 mL) solution of (*S*)-ethyl 2-(4-methoxyphenylamino)-2-(naphthalen-1-yl)acetate (**3s**; 67.0 mg, 0.2 mmol) was cooled to 0 °C, an aqueous solution of ammonium cerium nitrate (CAN, 484 mg, 0.88 mmol, 3.0 mL of H_2O) was added directly, and the corresponding mixture was stirred at ambient temperature for 12 h, and then its pH was adjusted to 1 using aqueous HCl solution (2 N). After the aqueous phase was washed with EtOAc (3 × 8 mL) and brought to basic by the addition of saturated $NaHCO_3$, the resulting suspension was extracted with CH_2Cl_2 (3 × 12 mL) and dried over anhydrous Na_2SO_4, and then the crude product was purified directly by silica gel column chromatography to afford 21 mg (45% yield) of **3s-1**: $[\alpha]^{20}_D$ = +29.6° (*c* = 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 7.82 (dd, *J* = 6.3, 3.0 Hz, 1 H), 7.61−7.41 (m, 4 H), 5.32 (s, 1 H), 4.34−4.05 (m, 2 H), 2.00 (s, 2 H), 1.16 (t, *J* = 7.1 Hz, 3 H); MS (ESI) *m*/*z* 231.0 $[M^+]$, 253.0 $[M + Na^+]$; IR (KBr) 3862, 3748, 3679, 3615, 3053, 2924, 2855, 1735, 1672, 1512, 1460, 1371, 1301, 1211, 1163, 1104, 1025, 954, 784, 729, 520, 470 cm^{-1}.

*(S)-2-Amino-2-(naphthalen-1-yl)acetic acid hydrochloride (**3s-2**).*[26] (*S*)-Ethyl 2-amino-2-(naphthalen-1-yl)acetate (**3s-1**; 22.9 mg, 0.10 mmol) was refluxed in hydrochloric acid (1.5 mL, 4.0 M) for 2.5 h. Then the mixture was washed with diethyl ether and concentrated under vacuum to yield 22.8 mg (96% yield) of **3s-2** as a colorless solid: $[\alpha]^{20}_D$ = +85.0° (*c* = 0.24, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 8.01 (d, *J* = 8.4 Hz, 1 H), 7.92 (dd, *J* = 12.4, 8.4 Hz, 2 H), 7.60−7.44 (m, 4H), 5.88 (s, 1 H); MS (ESI) *m*/*z* 224.7 $[M - HCl + Na^+]$; IR (KBr) 3462, 2922, 2852, 1636, 1411, 1266, 1211, 743, 531, 460 cm^{-1}.

*(S)-2-Amino-2-(naphthalen-1-yl)ethanol (**3s-3**).*[27] A MeOH (6 mL) solution of (*S*)-ethyl 2-amino-2-(naphthalen-1-yl)acetate (**3s-1**; 62 mg, 0.27 mmol) was cooled to 0 °C, and then $NaBH_4$ (55 mg, 1.62 mmol) was added in one portion. The resulting solution was stirred under ambient temperature for 24 h. After the reaction was complete (monitored by TLC), the organic solvents were evaporated under vacuum. Water (5 mL) was added, and after phase separation the corresponding aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated under high vacuum. The crude product was purified directly by silica gel column chromatography to give 42.0 mg (83% yield) of **3s-3**: $[\alpha]^{20}_D$ = +17.1° (*c* = 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.60 (d, *J* = 7.0 Hz, 1 H), 7.56−7.46 (m, 3 H), 4.93 (s, 1 H), 3.95 (s, 1 H), 3.77−3.59 (m, 1 H), 2.10 (s, 2 H); MS (ESI) *m*/*z* 188.9 $[M^+]$, 226.0 $[M + K^+]$; IR (KBr) 3657, 3347, 2976, 2925, 1665, 1597, 1509, 1461, 1383, 1251, 1155, 1072, 953, 801, 777, 486 cm^{-1}.

*(S)-Ethyl 2-amino-2-phenylacetate (**3a-1**).*[25] The absolute configuration of **3a** was determined by comparison with the known amino acid esters after removing the PMP protecting group.[22] A CH_3CN (5.0 mL) solution of (*S*)-ethyl 2-(4-methoxyphenylamino)-2-phenylacetate (**3a**; 57.0 mg, 0.2 mmol) was cooled to 0 °C and 3 mL of an aqueous solution of ammonium cerium nitrate (484 mg, 0.88 mmol) was added directly. The resulting solution was stirred under ambient temperature for 12 h and then treated with 2 N HCl to achieve an approximate pH 1. After the aqueous phase was washed with EtOAc (3× 8 mL) and brought to basic by the addition of saturated $NaHCO_3$, the resulting suspension was extracted with DCM (3 × 12 mL) and dried over anhydrous Na_2SO_4. The crude product was purified directly by silica gel column chromatography to give 22.2 mg (62% yield) of **3a-1**: $[\alpha]^{20}_D$ = +4.3° (*c* = 0.1, EtOH) (lit.[23] $[\alpha]^{20}_D$ = −120.5° (*c* = 0.44, EtOH)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.55 (m, 5 H), 4.95 (s, 1 H), 4.62−4.42 (m, 2 H), 2.37 (s, 2 H), 1.56 (t, *J* = 7.1 Hz, 3 H); MS (ESI) *m*/*z* 180.4 $[M^+]$, 202.4 $[M + Na^+]$, 218.5 $[M + K^+]$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables and figures giving details of the experimental conditions, ^{1}H and ^{13}C NMR spectra for all isolated compounds, and HPLC traces for determinations of the enantiomeric excess. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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