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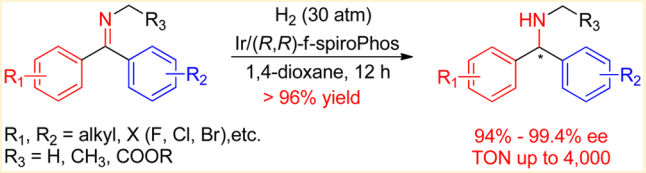
Enantioselective Hydrogenation of Diarylmethanimines for Synthesis of Chiral Diarylmethylamines

Duanyang Kong, Meina Li, Guofu Zi, Guohua Hou,* and Yong He*

Key Laboratory of Radiopharmaceuticals, College of Chemistry, Beijing Normal University, Beijing 100875, China

Supporting Information

ABSTRACT: An enantioselective hydrogenation of *N*-substituted diarylmethanimines under mild conditions has been first realized by using an iridium catalyst with a chiral f-spiroPhos ligand. This method provides an efficient access to the asymmetric synthesis of a variety of chiral diarylmethylamines and their derivatives with excellent enantioselectivities (up to 99.4% ee) and high turnover numbers (TON up to 4000).



INTRODUCTION

Chiral diarylmethylamines are extremely important building blocks and are widely present in a broad range of natural products, pharmaceuticals, and biologically active compounds (Figure 1).[1]

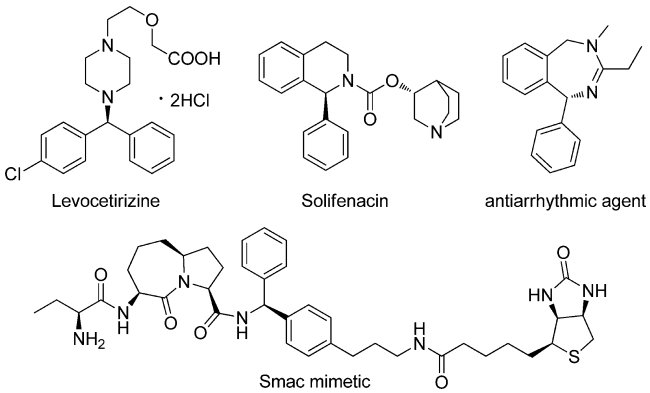


Figure 1. Structures of biologically active compounds containing diarylmethylamine moiety.

As a consequence, the synthesis of chiral diarylmethylamines has attracted considerable attention from chemists and several approaches including resolution of racemates, asymmetric additions of organometallic reagents to imines, and enantioselective transfer hydrogenation have been developed.[2−5]

Although a number of chiral transition-metal catalysts, organocatalysts, and biocatalysts have been developed and exhibited high enantioselectivties in asymmetric hydrogenation of aryl alkyl imines[6] and reductive amination of carbonyl compounds,[6c,7] surprisingly, up to now there is no efficient catalyst for asymmetric hydrogenation of diarylmethanimines. The following obstacles have possibly thwarted attempts involving their use as substrates in asymmetric hydrogenations: (1) The interconversion of *Z*/*E* isomers of imines results in a diminished enantioselectivity; (2) the instability and strong coordination of both substrates and products to the catalyst leads to deactivation and hindered hydrogenation; (3) for most chiral catalysts, it is very difficult to distinguish between two sterically similar aryl groups at a stereogenic center. Zhang and co-workers reported the asymmetric hydrogenation of benzophenone N−H iminium salts catalyzed by an iridium complex carrying a monodentate phosphoramidite ligand.[8] Despite benefits that include being protecting-group-free and high enantioselectivities, the hydrogenation of *ortho*-substituted substrates exhibited low efficiency and a very high catalyst loading (5 mol %, TON = 20) was required to achieve full conversions and good enantioselectivities. Furthermore, for the substrates without or with a smaller *ortho*-substituent (such as 2-F), this catalyst system was inefficient giving poor enantioselectivities. As one of the most efficient and straightforward approaches to chiral diarylmethylamines, the asymmetric hydrogenation of diarylmethanimines, with or without a N-protecting group, still remains a great challenge. Consequently, to develop novel high efficient catalysts for the asymmetric hydrogenation of this kind of substrates is highly desirable and of significant importance in asymmetric synthesis.

Recently, we demonstrated that the chiral ferrocenyl ligand, f-spiroPhos, containing a 1,1′-spirobiindane scaffold[9] was an efficient ligand for Rh/Ir-catalyzed asymmetric hydrogenation.[10] These encouraging results prompted us to investigate the asymmetric hydrogenation of this class of challenging diarylmethanimines. We herein report the asymmetric hydrogenation of these substrates catalyzed by an iridium/f-spiroPhos complex with excellent enantioselectivities (up to 99.4% ee) and high turnover numbers (TON of up to 4000), representing the best results for this kind of substrates to date (Scheme 1).

RESULTS AND DISCUSSION

Our initial investigation began with the hydrogenation of 2-methylbenzophenone imine **1a** as the model substrate under 80 atm of H_2 in CH_2Cl_2 at 40 °C with various iridium catalysts generated in situ from 0.5 mol % $[Ir(COD)Cl]_2$ and a series of 2.2 mol % phosphorus ligands. The evaluation of chiral ligands

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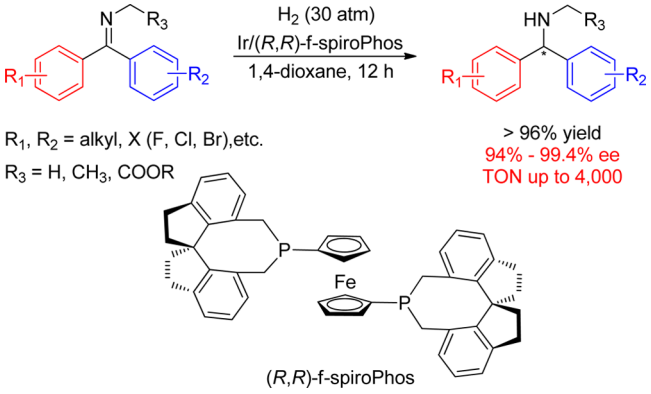
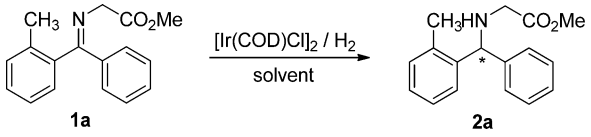
Scheme 1. Asymmetric Hydrogenation of Diarylmethanimines



indicated that f-spiroPhos was the most promising, achieving an enantioselectivity of 96% ee (Table 1, entry 7). Diphosphonite ligand **1** and (*S*,*S*)-f-Binaphane also gave moderate to good enantioselectivities (75% ee and 91% ee, respectively) with full conversions (entries 5−6), while (*S*,*R*)-DuanPhos and (*R*)-JosiPhos-1 only exhibited poor activities and enantioselectivities (entries 3−4). In addition to CH_2Cl_2, 1,4-dioxane was also suitable and afforded increased enantioselectivity (98% ee, entry 13). Although comparable enantioselectivities were achieved in THF and DME solvents, incomplete conversions were obtained (entries 10−11). A lower H_2 pressure (30 atm H_2) led to a slight decrease in conversion but with maintained enantioselectivity (entry 13). To our delight, increasing the reaction temperature to 60 °C resulted in complete conversion under 30 atm of H_2 pressure with a much shorter reaction time (12 h) without any erosion of enantioselectivity (entry 14).

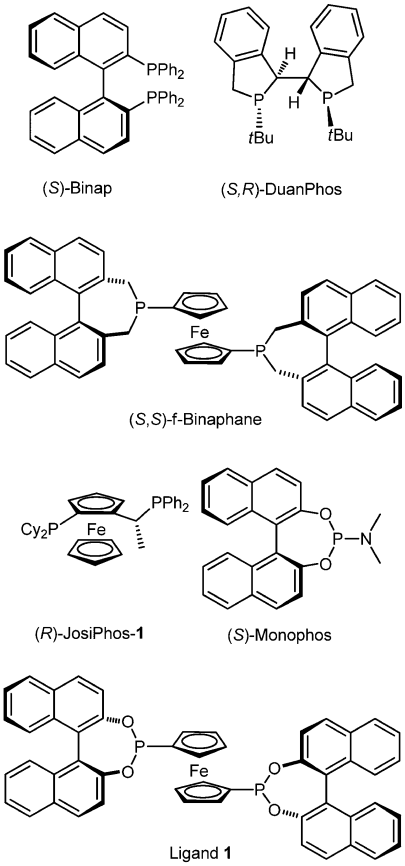
Encouraged by the promising result obtained in the hydrogenation of substrate **1a**, a variety of diarylmethanimines were prepared and hydrogenated using the Ir/f-spiroPhos catalyst under the optimized reaction conditions (Table 2, **1a**−**1x**). The hydrogenation appears to be sensitive to the steric difference of two aromatic rings. Substrates containing a methyl, fluoro, chloro, or bromo substituent at the *ortho* position of the aromatic ring gave excellent enantioselectivities (94%−98% ee), regardless of the steric and electronic properties of the substituents at the *meta* or *para* position of the second aromatic ring. Even for substrates with a coordinating 2-methoxy (**1e**) or smaller 2-F substituent (**1n**−**1o**), excellent enantioselectivities with full conversions were observed. 1-Naphthyl substituted imine (**1t**) was also smoothly hydrogenated furnishing the desired product in high enantioselectivity, 95% ee. Changing the ester moiety to CH_2CO_2Et and $CH_2CO_2{}^tBu$ had no obvious effect on the enantioselectivities and conversions providing the corresponding products **2u** and **2v** with similar ee values and full conversions. Notably, substrates without an *N*-ester group, **1w** and **1x**, were also successfully hydrogenated to the corresponding products **2w** and **2x** with even higher enantioselectivities, 99.4% ee and 99% ee, respectively, which means that the ester group is not required in order to achieve high reactivity and enantioselectivity in this hydrogenation. Considering the easy C−H imine activation by Ir complexes reported by Pfaltz and Xiao,[11] we envisioned that there was an effect of C−H imine activation in this hydrongenation, which was helpful for the discrimination between two aryl groups and the excellent enantioselectivities. But the results of deuteration reactions indicated that C−H imine activation by Ir complexes was not observed (see Experimental Section and Supporting Information (SI)).

Table 1. Ir-Catalyzed Asymmetric Hydrogenation of 1a, Optimizing Reaction Conditions[a]



entry	ligand	solvent	conv. (%)[b]	ee. (%)[c]
1	(*S*)-Monophos	CH_2Cl_2	<5	ND
2	(*S*)-Binap	CH_2Cl_2	60	85
3	(*S*,*R*)-DuanPhos	CH_2Cl_2	11	10
4	(*R*)-JosiPhos-1	CH_2Cl_2	<5	ND
5	(*S*,*S*)-f-Binaphane	CH_2Cl_2	<99	91
6	Ligand **1**	CH_2Cl_2	<99	75
7	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	<99	96
8	(*R*,*R*)-f-spiroPhos	toluene	25	42
9	(*R*,*R*)-f-spiroPhos	MeOH	31	65
10	(*R*,*R*)-f-spiroPhos	THF	58	97
11	(*R*,*R*)-f-spiroPhos	DME	72	97
12	(*R*,*R*)-f-spiroPhos	dioxane	<99	98
13[d]	(*R*,*R*)-f-spiroPhos	dioxane	97	98
14[e]	(*R*,*R*)-f-spiroPhos	dioxane	<99	98

[a]Unless otherwise mentioned, all reactions were carried out with a $[Ir(COD)Cl]_2$/ligand/substrate ratio of 0.5:1.1:100, 80 atm of H_2, 40 °C, 24 h. [b]Determined by ^1H NMR. [c]Determined by HPLC analysis using a chiral stationary phase. [d]30 atm of H_2, 40 °C, 24 h. [e]30 atm of H_2, 60 °C, 12 h.



Despite excellent results obtained in the hydrogenation of *ortho*-substituted imines, poor enantioselectivities were observed for substrates without an *ortho*-substituent,[12] which was possibly attributed to the persence of Z/*E* isomers of substrates. In the synthesis of the substrates bearing a *meta* or *para* substituent,

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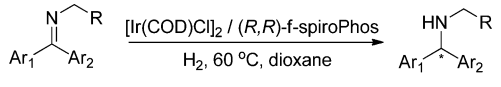
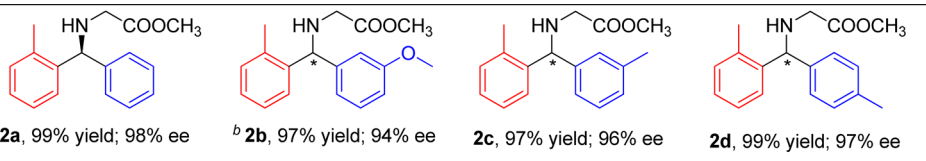
Table 2. Ir-Catalyzed Asymmetric Hydrogenation of Various Diarylmethanimines 1[a]



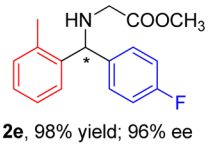
1 2

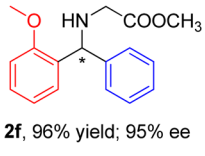

2a, 99% yield; 98% ee

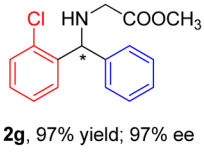
[b] **2b**, 97% yield; 94% ee

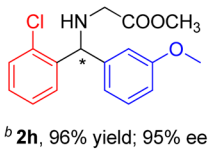
2c, 97% yield; 96% ee

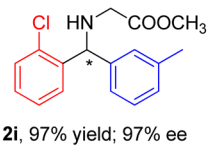
2d, 99% yield; 97% ee

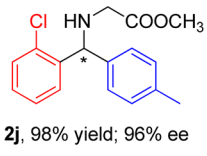

2e, 98% yield; 96% ee

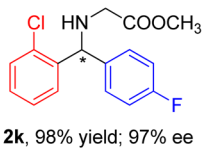

2f, 96% yield; 95% ee

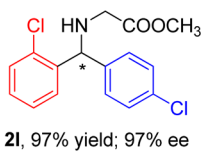

2g, 97% yield; 97% ee

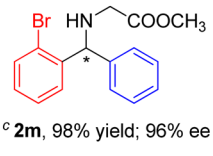

[b] **2h**, 96% yield; 95% ee

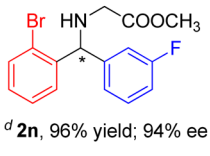

2i, 97% yield; 97% ee

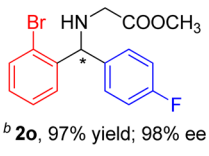

2j, 98% yield; 96% ee

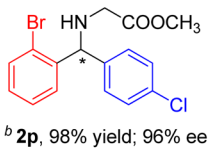

2k, 98% yield; 97% ee

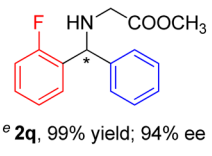

2l, 97% yield; 97% ee

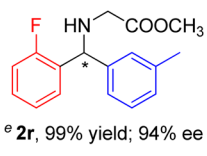

[c] **2m**, 98% yield; 96% ee

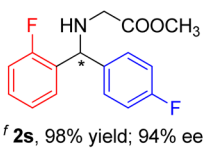

[d] **2n**, 96% yield; 94% ee

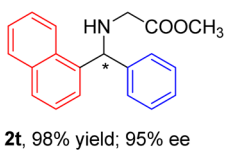

[b] **2o**, 97% yield; 98% ee

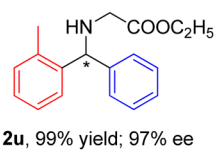

[b] **2p**, 98% yield; 96% ee

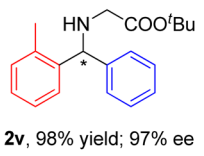

[e] **2q**, 99% yield; 94% ee

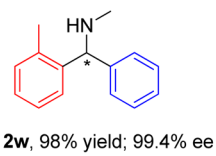

[e] **2r**, 99% yield; 94% ee

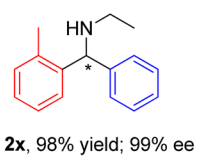

[f] **2s**, 98% yield; 94% ee

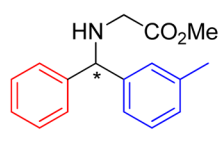

2t, 98% yield; 95% ee

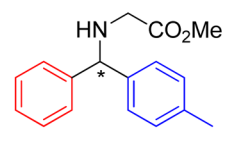

2u, 99% yield; 97% ee

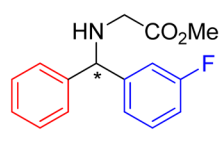

2v, 98% yield; 97% ee

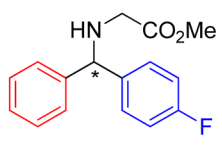

2w, 98% yield; 99.4% ee

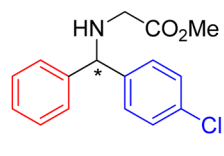

2x, 98% yield; 99% ee


3a, 95% yield; 97% ee


3b, 96% yield; 96% ee


3c, 94% yield; 94% ee


3d, 96% yield; 98% ee


3e, 96% yield; 96% ee

[a]Unless otherwise mentioned, all reactions were carried out with a $[Ir(COD)Cl]_2$/(*R*,*R*)-f-spiroPhos/substrate ratio of 0.5:1.1:100, dioxane, 30 atm of H_2, 60 °C, 12 h. The enantioselectivity was determined by HPLC analysis using a chiral stationary phase. [b]80 atm H_2, 60 °C, 12 h. [c]30 atm H_2, 60 °C, 24 h. [d]80 atm H_2, 80 °C, 36 h. [e]30 atm H_2, rt, 24 h. [f]30 atm H_2, rt, 36 h.

we found that these substrates were obtained as a mixture of Z/*E* isomers and the ratio was not changed during the hydrogenation. Although we attempted to isolate any isomer of them, we still got the mixture with a maintained ratio. These results revealed that the quick interconversion of Z/*E* imine isomers led to the difficulty of isolation. Fortunately, however, the introduction of

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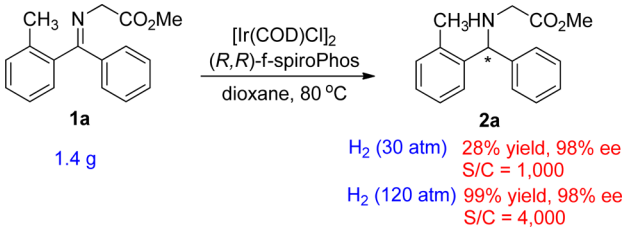
ortho substituents in imine substrates could prevent the isomerization and this class of *ortho* substituted imines could be prepared as a single isomer. Therefore, the desired products with excellent ee values could be obtained by the enantioselective hydrogenation of the corresponding 2-Cl or 2-Br substrates subsequently followed by dehalogenation of the hydrogenation products. For example, the substrate **1i** containing a 2-Cl substituent was hydrogenated to produce **2i** with 97% ee which was then dehalogenated catalyzed by Pd/C in the presence of K_2CO_3 affording the desired 3-Me product **3a** with the enantioselectivity maintained. In this way, *meta*- and *para*-substituted diarylmethylamines **3b**−**3e** could be readily provided with high yields and excellent enantioselectivities, up to 98% ee.

More remarkably, the hydrogenation could be accomplished on a gram scale with a much lower catalyst loading. Using 0.025 mol % of the Ir-(*R*,*R*)-f-spiroPhos catalyst, the hydrogenation of the substrates **1a** was successfully carried out affording the desired product quantitatively without any erosion of the enantioselectivity. These results indicated that this catalyst is exceptionally efficient for the asymmetric hydrogenation of these diarylmethanimines and shows very high turnover numbers (TON) approaching 4000, to the best of our knowledge, which represents the highest turnover numbers for this class of substrates so far (Scheme 2).

Scheme 2. Asymmetric Hydrogenation of 1a under Lower Catalyst Loading



Finally, this method could be used for the synthesis of chiral diarylmethylamines and some important pharmaceuticals (Scheme 3), such as the histamine H1-receptor antagonist Levocetirizine.[3a,13] The hydrogenation product **3e** was treated with $ICH_2COOC_2H_5$ affording compound **4** which could be readily converted to Levocetirizine.[14] The free chiral diarylmethylamines **5** could also be obtained with maintained enantioselectivities by removal of the *N*-substituted ester group.[15]

CONCLUSIONS

In conclusion, an enantioselective hydrogenation of *N*-substituted diarylmethanimines under mild conditions has been first realized by using an iridium catalyst with a chiral f-spiroPhos ligand. The reaction provides efficient access to the asymmetric synthesis of a variety of chiral diarylmethylamines with excellent enantioselectivities (up to 99.4% ee) and high turnover numbers (up to 4000).

EXPERIMENTAL SECTION

General Information. All the air- or moisture-sensitive reactions and manipulations were performed by using standard Schlenk techniques and in a nitrogen-filled glovebox. DME, THF, dioxane, and toluene were distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. Anhydrous MeOH was distilled from magnesium. ^{1}H NMR spectra were recorded on 400 MHz spectrometers. ^{13}C NMR (proton-decoupled) spectra were obtained at 100 MHz. $CDC1_3$ was the solvent used for the NMR analysis, with TMS as the internal standard. Chemical shifts were reported upfield to TMS (0.00 ppm) for ^{1}H NMR. Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double of doublets, t = triplet, q = quartet, m = multiplet) and coupling constants (*J*) in hertz (Hz). Optical rotation was determined using a polarimeter. HRMS data were recorded on a mass spectrometer with APCI or ESI.

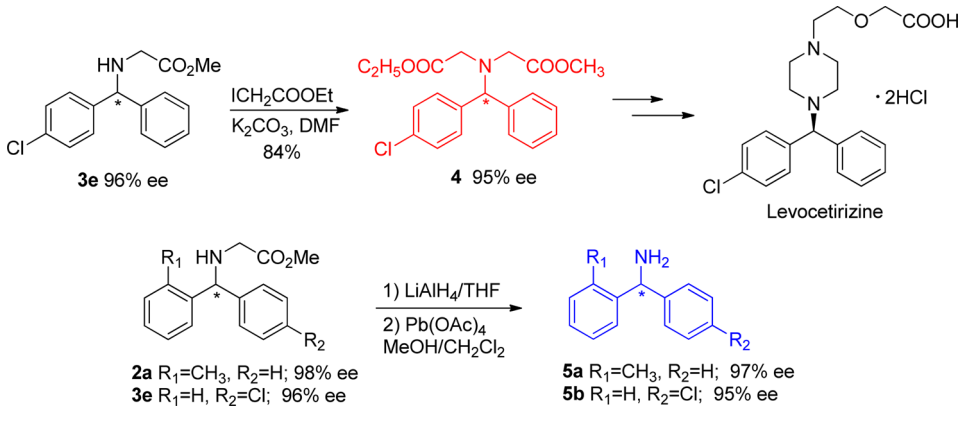
Preparation and Analytical Data of Substrates 1. A 50 mL round-bottom flask was charged with benzophenone imine (5.0 mmol), glycine ester hydrochloride (6.0 mmol), and CH_2Cl_2 (10.0 mL). The milky white mixture was stirred at rt−40 °C under an argon atmosphere until no starting material was detected by TLC. The white insoluble substance was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography (PE/EA/CH_2Cl_2 = 10/1/1 to 20/1/1) to afford **1** as a light yellow oil.[16]

*(E)-Methyl 2-((Phenyl(o-tolyl)methylene)amino)acetate (**1a**).* 1.24 g, yield 93%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (d, *J* = 7.7 Hz, 2H), 7.33−7.11 (m, 6H), 6.94 (d, *J* = 7.5 Hz, 1H), 4.00 (s, 2H), 3.62 (s, 3H), 1.97 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 172.6, 171.7, 138.9, 136.4, 135.5, 131.2, 131.1, 129.4, 128.9, 128.8, 127.7, 126.7, 55.9, 52.6, 19.8. TOF-HRMS calcd for $C_{17}H_{18}NO_2$ [M + H$^+$]: 268.1332, found 268.1333.

*(E)-Methyl 2-(((3-Methoxyphenyl)(o-tolyl)methylene)amino)-acetate (**1b**).* 1.37 g, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.21−7.19 (m, 2H), 7.17 (s, 1H), 7.15−7.07 (m, 2H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.83−6.80 (m, 1H), 3.94 (d, *J* = 2.0 Hz, 2H), 3.68 (s, 3H), 3.60 (s, 3H), 1.93 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 172.5, 171.7, 160.2, 140.5, 136.5, 135.5, 131.1, 129.8, 129.4, 127.8, 126.7, 121.8, 117.3, 113.3, 56.0, 55.9, 52.6, 19.8. TOF-HRMS calcd for $C_{18}H_{20}NO_3$ [M + H$^+$]: 298.1437, found 298.1439.

*(E)-Methyl 2-((m-Tolyl(o-tolyl)methylene)amino)acetate (**1c**).* 1.27 g, yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (s, 1H), 7.27−7.19 (m, 6H), 6.96 (d, *J* = 7.7 Hz, 1H), 4.06−3.97 (m, 2H), 3.67 (s, 3H), 2.27 (s, 3H), 2.00 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 172.8, 171.7, 138.9, 138.5, 136.6, 135.5, 132.0, 131.0, 129.3, 128.8, 128.7, 127.7, 126.7, 126.4, 55.9, 52.5, 21.9, 19.8. TOF-HRMS calcd for $C_{18}H_{20}NO_2$ [M + H$^+$]: 282.1488, found 282.1487.

Scheme 3. Asymmetric Synthesis of Levocetirizine and Diarylmethylamines



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*(E)-Methyl 2-((o-Tolyl(p-tolyl)methylene)amino)acetate (**1d**).* 1.23 g, yield 88%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (d, J = 7.8 Hz, 2H), 7.26−7.19 (m, 3H), 7.05 (d, J = 16.1 Hz, 2H), 6.94 (d, J = 7.2 Hz, 1H), 3.99 (s, 2H), 3.65 (s, 3H), 2.27 (s, 3H), 1.98 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.8, 171.2, 140.8, 136.0, 135.7, 134.9, 130.4, 129.0, 128.7, 128.1, 127.1, 126.1, 55.2, 51.9,21.4, 19.2. TOF-HRMS calcd for $C_{18}H_{20}NO_2$ [M + H$^+$]: 282.1488, found 282.1487.

*(E)-Methyl 2-(((4-Fluorophenyl)(o-tolyl)methylene)amino)acetate (**1e**).* 1.27 g, yield 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53−7.49 (m, 2H), 7.21−7.12 (m, 3H), 6.89−6.85 (m, 3H), 3.92 (s, 2H), 3.59 (s, 3H), 1.92 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4 (d, J = 26.0 Hz), 164.9 (d, $^1J_{C-F}$ = 249.0 Hz), 136.1, 135.4, 135.2 (d, J = 3.0 Hz), 131.1, 130.8 (d, J = 8.0 Hz), 129.5, 127.6, 126.8, 115.9, 115.6, 55.8, 52.5, 19.7. TOF-HRMS calcd for $C_{17}H_{17}NO_2F$ [M + H$^+$]: 286.1237, found 286.1238.

*(E)-Methyl 2-(((2-Methoxyphenyl)(phenyl)methylene)amino)-acetate (**1f**).* 1.30 g, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 (d, J = 7.4 Hz, 2H), 7.39−7.33 (m, 4H), 7.04−7.00 (m, 3H), 4.25−4.04 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 172.1, 169.4, 156.6, 139.6, 131.0, 130.9, 129.5, 128.9, 128.6, 125.2, 121.4, 111.5, 56.2, 56.0, 52.5. TOF-HRMS calcd for $C_{17}H_{18}NO_3$ [M + H$^+$]: 284.1281, found 284.1282.

*(E)-Methyl 2-(((2-Chlorophenyl)(phenyl)methylene)amino)-acetate (**1g**).* 1.32 g, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.5 Hz, 1H), 7.34−7.27 (m, 5H), 7.08 (d, J = 7.1 Hz, 1H), 4.21−3.92 (m, 2H), 3.68 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ:171.4, 169.0, 138.3, 135.6, 132.1, 131.2, 130.8, 130.4, 129.5, 128.8, 128.7, 127.7, 55.8, 52.5. TOF-HRMS calcd for $C_{16}H_{15}NO_2Cl$ [M + H$^+$]: 288.0785, found 288.0785.

*(E)-Methyl 2-(((2-Chlorophenyl)(3-methoxyphenyl)methylene)-amino)acetate (**1h**).* 1.41 g, yield 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43−7.41 (m, 1H), 7.35−7.27 (m, 3H), 7.19−7.15 (m, 1H), 7.09−7.07 (m, 1H), 7.03−7.01 (m, 1H), 6.91−6.88 (m, 1H), 4.21−3.90 (m, 2H), 3.75 (s, 3H), 3.67 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 168.9, 160.1, 139.8, 135.7, 132.2, 130.8, 130.4, 129.7, 129.5, 127.7, 121.7, 117.5, 113.2, 55.9, 52.6. TOF-HRMS calcd for $C_{17}H_{17}NO_3Cl$ [M + H$^+$]: 318.0891, found 318.0889.

*(E)-Methyl 2-(((2-Chlorophenyl)(m-tolyl)methylene)amino)-acetate (**1i**).* 1.31 g, yield 87%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (s, 1H), 7.44−7.41 (m, 1H), 7.33−7.29 (m, 2H), 7.22 (s, 1H), 7.16−7.14 (m, 2H), 7.08−7.06 (m, 1H), 4.20−3.90 (m, 2H), 3.68 (s, 3H), 2.28 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 169.3, 138.6, 138.3, 135.8, 132.2, 130.8, 130.4, 129.6, 128.9, 128.7, 127.7, 126.3, 55.9, 52.6, 21.9. TOF-HRMS calcd for $C_{17}H_{17}NO_2Cl$ [M + H$^+$]: 302.0942, found 302.0940.

*(E)-Methyl 2-(((2-Chlorophenyl)(p-tolyl)methylene)amino)-acetate (**1j**).* 1.33 g, yield 88%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48−7.41 (m, 3H), 7.33−7.29 (m, 2H), 7.09−7.06 (m, 3H), 4.19−3.89 (m, 2H), 3.67 (s, 3H), 3.29 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.6, 168.9, 141.7, 135.9, 135.7, 132.2, 130.7, 130.4, 129.6, 129.5, 128.7, 127.7, 55.8, 52.6, 22.0. TOF-HRMS calcd for $C_{17}H_{17}NO_2Cl$ [M + H$^+$]: 302.0942, found 302.0940.

*(E)-Methyl 2-(((2-Chlorophenyl)(4-fluorophenyl)methylene)-amino)acetate (**1k**).* 1.31 g, yield 86%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60−7.56 (m, 2H), 7.44−7.42 (m, 1H), 7.35−7.31 (m, 2H), 7.08−7.06 (m, 1H), 6.98−6.93 (m, 2H), 4.18−3.89 (m, 2H), 3.67 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 167.9, 165.1 (d, $^1J_{C-F}$ = 250.0 Hz), 135.4, 134.6 (d, J = 3.0 Hz), 132.1, 130.9 (d, J = 13.0 Hz), 130.7 (d, J = 24.0 Hz), 129.5, 127.9, 116.0, 115.8, 55.8, 52.7. TOF-HRMS calcd for $C_{16}H_{14}NO_2FCl$ [M + H$^+$]: 306.0691, found 306.0694.

*(E)-Methyl 2-(((2-Chlorophenyl)(4-chlorophenyl)methylene)-amino)acetate (**1l**).* 1.48 g, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53−7.50 (m, 2H), 7.45−7.42 (m, 1H), 7.37−7.29 (m, 2H), 7.26−7.23 (m, 2H), 7.08−7.05 (m, 1H), 4.18−3.90 (m, 2H), 3.68 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.2, 167.9, 137.5, 136.8, 135.2, 132.1, 131.0, 130.6, 130.0, 129.4, 129.1, 127.9, 55.9, 52.6. TOF-HRMS calcd for $C_{16}H_{14}NO_2Cl_2$ [M + H$^+$]: 322.0396, found 322.0394.

*(E)-Methyl 2-(((2-Bromophenyl)(phenyl)methylene)amino)-acetate (**1m**).* 1.41 g, yield 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62−7.57 (m, 3H), 7.38−7.33 (m, 2H), 7.30−7.23 (m, 3H), 7.08−7.05 (m, 1H), 4.20−3.90 (m, 2H), 3.68 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 170.1, 138.1, 137.9, 133.6, 131.3, 130.9, 129.6, 128.9, 128.8, 128.3, 121.4, 55.8, 52.6. TOF-HRMS calcd for $C_{16}H_{15}NO_2Br$ [M + H$^+$]: 332.0280, found 332.0280.

*(E)-Methyl 2-((((2-Bromophenyl)(3-fluorophenyl)methylene)-amino)acetate (**1n**).* 1.52 g, yield 87%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63−7.60 (m, 1H), 7.39−7.35 (m, 2H), 7.29−7.21 (m, 3H), 7.08−7.02 (m, 2H), 4.20−3.90 (m, 2H), 3.68 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.2, 169.0, 163.4 (d, $^1J_{C-F}$ = 243.0 Hz), 140.5 (d, J = 7.0 Hz), 137.4, 133.8, 131.2, 130.3 (d, J = 8.0 Hz), 129.6, 128.5, 124.7 (d, J = 3.0 Hz), 121.3, 118.3 (d, J = 22.0 Hz), 115.5 (d, J = 23.0 Hz), 55.9, 52.7. TOF-HRMS calcd for $C_{16}H_{14}NO_2FBr$ [M + H$^+$]: 350.0186, found 350.0185.

*(E)-Methyl 2-((((2-bromophenyl)(4-fluorophenyl)methylene)-amino)acetate (**1o**).* 1.45 g, yield 83%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62−7.56 (m, 3H), 7.38−7.34 (m, 1H), 7.28−7.25 (m, 1H), 7.07−7.05 (m, 1H), 6.98−6.94 (m, 2H), 4.18−3.88 (m, 2H), 3.68 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 167.5 (d, $^1J_{C-F}$ = 260.0 Hz), 163.8, 137.6, 134.3 (d, J = 3.0 Hz), 133.7, 131.1, 130.9 (d, J = 8.0 Hz), 129.5, 128.4, 121.3, 115.9 (d, J = 21.0 Hz), 55.8, 52.6. TOF-HRMS calcd for $C_{16}H_{14}NO_2FBr$ [M + H$^+$]: 350.0186, found 350.0185.

*(E)-Methyl 2-((((2-Bromophenyl)(4-chlorophenyl)methylene)-amino)acetate (**1p**).* 1.54 g, yield 84%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60−7.57 (m, 3H), 7.46−7.42 (m, 1H), 7.36−7.13 (m, 3H), 7.11−7.10 (m, 1H), 4.26−3.96 (m, 2H), 3.75 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.3, 168.9, 137.5, 137.3, 136.5, 133.7, 130.1, 129.5, 129.1, 128.4, 121.2, 55.8, 52.6. TOF-HRMS calcd for $C_{16}H_{14}NO_2ClBr$ [M + H$^+$]: 365.9890, found 365.9889.

*(E)-Methyl 2-(((2-fluorophenyl) (phenyl)methylene)amino)-acetate (**1q**).* 1.16 g, yield 86%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, J = 7.4 Hz, 2H), 7.33−7.20 (m, 4H), 7.13−7.00 (m, 3H), 4.13−4.00 (m, 2H), 3.61 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 166.8 (d, $^1J_{C-F}$ = 250.0 Hz), 139.0, 131.8, 131.3, 130.1, 128.9, 128.8, 125.1, 123.9, 123.7, 116.8 (d, J = 21.0 Hz), 56.3, 52.6. TOF-HRMS calcd for $C_{16}H_{15}NO_2F$ [M + H$^+$]: 272.1081, found 272.1082.

*(E)-Methyl 2-(((2-Fluorophenyl)(m-tolyl)methylene)amino)-acetate (**1r**).* 1.23 g, yield 86%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (s, 1H), 7.42−7.40 (m, 1H), 7.31−7.29 (m, 1H), 7.22−7.09 (m, 5H), 4.23−4.08 (m, 2H), 3.71 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 167.0, 159.3 (d, $^1J_{C-F}$ = 250.0 Hz), 138.8 (d, J = 44.0 Hz), 132.1, 131.7 (d, J = 7.0 Hz), 130.1 (d, J = 4.0 Hz), 129.0, 128.6, 126.4, 125.0 (d, J = 3.0 Hz), 123.9 (d, J = 18.0 Hz), 116.7, 116.5, 56.3, 52.6, 21.9. TOF-HRMS calcd for $C_{17}H_{17}NO_2F$ [M + H$^+$]: 286.1237, found 286.1238.

*(E)-Methyl 2-(((2-Fluorophenyl)(4-fluorophenyl)methylene)-amino)acetate (**1s**).* 1.18 g, yield 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62−7.56 (m, 2H), 7.42−7.37 (m, 1H), 7.21−7.04 (m, 3H), 6.96 (d, J = 8.7 Hz, 2H), 4.18−4.00 (m, 2H), 3.68 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.4, 165.9, 165.0 (d, $^1J_{C-F}$ = 247.0 Hz), 159.7 (d, $^1J_{C-F}$ = 247.0 Hz), 135.3 (d, J = 3.0 Hz), 131.9 (d, J = 8.0 Hz), 131.0 (d, J = 8.0 Hz), 130.1 (d, J = 4.0 Hz), 125.2 (d, J = 4.0 Hz), 123.5 (d, J = 19.0 Hz), 116.8 (d, J = 21.0 Hz), 115.8 (d, J = 22.0 Hz), 56.3, 52.7. TOF-HRMS calcd for $C_{16}H_{14}NO_2F_2$ [M + H$^+$]: 290.0987, found 290.0988.

*(E)-Methyl 2-((Naphthalen-1-yl(phenyl)methylene)amino)acetate (**1t**).* 1.35 g, yield 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.94 (t, J = 6.8 Hz, 2H), 7.69 (d, J = 7.9 Hz, 2H), 7.58−7.50 (m, 3H), 7.43−7.38 (m, 2H), 7.37−7.29 (m, 3H), 4.11−4.00 (m, 2H), 3.70 (s, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 171.2, 171.1, 139.0, 134.1, 133.4, 130.7, 130.1, 129.0, 128.6, 128.4, 128.2, 127.1, 126.6, 125.4, 125.3, 125.1, 55.5, 52.0. TOF-HRMS calcd for $C_{20}H_{18}NO_2$ [M + H$^+$]: 304.1332, found 304.1330.

*(E)-Ethyl 2-((Phenyl(o-tolyl)methylene)amino)acetate (**1u**).* 1.27 g, yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60−7.58 (m, 2H), 7.32−7.19 (m, 6H), 6.97 (d, J = 7.7 Hz, 1H), 4.15−4.10 (m, 2H), 4.01−4.00 (m, 2H), 2.00 (s, 3H), 1.19 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ: 172.4, 171.2, 139.0, 136.5, 135.5, 131.1, 131.0, 129.3, 128.8, 128.7, 127.8, 126.7, 61.4, 56.1, 19.8, 14.7. TOF-HRMS calcd for $C_{18}H_{20}NO_2$ [M + H$^+$]: 282.1488, found 282.1487.

*(E)-tert-Butyl 2-((Phenyl(o-tolyl)methylene)amino)acetate (**1v**).* 1.42 g, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59−7.57 (m, 2H),

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7.31−7.19 (m, 6H), 6.97 (d, J = 7.6 Hz, 1H), 3.97−3.87 (m, 2H), 2.00 (s, 3H), 1.38 (s, 9H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 172.0, 170.3, 139.1, 136.7, 135.5, 131.0, 130.9, 129.2, 128.8, 128.7, 127.9, 126.6, 81.6, 56.7, 28.6, 27.4, 19.8. TOF-HRMS calcd for $C_{20}H_{24}NO_2$ [M + H^+]: 310.1801, found 310.1803.

*(E)-N-(Phenyl(o-tolyl)methylene)methanamine (**1w**).* 0.91 g, yield 87%; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46−7.44 (m, 2H), 7.23−7.14 (m, 6H), 7.14−6.88 (m, 1H), 3.03 (s, 3H), 1.95 (s, 3H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 169.7, 138.9, 136.4, 134.9, 130.1, 129.8, 128.2, 128.1, 127.5, 127.1, 125.8, 40.9, 19.1. TOF-HRMS calcd for $C_{15}H_{16}N$ [M + H^+]: 210.1277, found 210.1280.

*(E)-N-(Phenyl(o-tolyl)methylene)ethanamine (**1x**).* 0.99 g, yield 89%; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.47−7.44 (m, 2H), 7.23−7.12 (m, 6H), 6.90−6.89 (m, 1H), 3.21−3.11 (m, 2H), 1.95 (s, 3H), 1.13−1.09 (m, 3H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 167.7, 139.2, 137.0, 135.0, 130.2, 129.9, 128.3, 128.2, 127.8, 127.4, 125.9, 48.2, 19.4, 16.0. TOF-HRMS calcd for $C_{16}H_{18}N$ [M + H^+]: 224.1433, found 224.1435.

General Procedure of Hydrogenation and Analytical Data of Products 2. A stock solution was made by mixing $[Ir(COD)Cl]_2$ with (*R*,*R*)-f-spiroPhos in a 1:1.1 molar ratio of Ir/(*R*,*R*)-f-spiroPhos in dioxane at room temperature for 20 min in a nitrogen-filled glovebox. An aliquot of the catalyst solution (1.0 mL, 0.001 mmol) was transferred by syringe into the vials charged with different substrates (0.1 mmol for each) in dioxane (2.0 mL). The vials were then placed into a steel autoclave. The inert atmosphere was replaced by H_2 and the reaction mixture was stirred under H_2 (30 atm) at 60 °C. The hydrogen gas was released slowly and carefully. The solution was concentrated and passed through a short column of silica gel to remove the metal complex affording the products as light yellow oil. The ee values of all products were determined by HPLC analysis on a chiral stationary phase.

*(S)-Methyl 2-((Phenyl(o-tolyl)methyl)amino)acetate (**2a**).* 26.6 mg, yield 99%; 98% ee; $[\alpha]_D^{20}$ = +20.6 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.8 min (major), t_B = 7.4 min (minor). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (d, J = 7.6 Hz, 1H), 7.27−7.01 (m, 8H), 5.00 (s, 1H), 3.63 (s, 3H), 3.32 (t, J = 18.2 Hz, 2H), 2.19 (s, 3H), 2.03 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.7, 142.9, 141.2, 136.5, 131.1, 129.0, 128.6, 127.7, 127.5, 127.2, 126.8, 62.8, 52.3, 49.5, 20.1. TOF-HRMS calcd for $C_{17}H_{20}NO_2$ [M + H^+]: 270.1488, found 270.1490.

*(+)-Methyl 2-(((3-Methoxyphenyl)(o-tolyl)methyl)amino)acetate (**2b**).* 29.0 mg, yield 97%; 94% ee; $[\alpha]_D^{20}$ = +19.6 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 8.7 min (minor), t_B = 9.8 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (d, J = 7.6 Hz, 1H), 7.25−7.11 (m, 4H), 6.95−6.92 (m, 2H), 6.77−6.75 (m, 1H), 5.06 (s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.45−3.35 (m, 2H), 2.30 (s, 3H), 2.13 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.6, 160.3, 144.6, 141.2, 136.5, 131.1, 130.0, 127.5, 127.2, 126.8, 121.0, 114.3, 113.0, 62.7, 55.7, 52.3, 49.5, 20.1. TOF-HRMS calcd for $C_{18}H_{22}NO_3$ [M + H^+]: 300.1594, found 300.1595.

*(+)-Methyl 2-((m-Tolyl(o-tolyl)methyl)amino)acetate (**2c**).* 27.5 mg, yield 98%; 96% ee; $[\alpha]_D^{20}$ = +23.5 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 5:95, 1.0 mL/min, 254 nm; t_A = 7.3 min (minor), t_B = 7.8 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (d, J = 7.7 Hz, 1H), 7.18−7.06 (m, 6H), 6.97 (d, J = 7.2 Hz, 1H), 5.00 (s, 1H), 3.66 (s, 3H), 3.34 (q, J = 17.6, 21.6 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 2.08 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.6, 142.8, 141.2, 138.6, 136.5, 131.1, 129.2, 128.8, 128.5, 127.4, 127.1, 126.7, 125.6, 62.7, 52.3, 49.5, 22.0, 20.1. TOF-HRMS calcd for $C_{18}H_{22}NO_2$ [M + H^+]: 284.1645, found 284.1644.

*(+)-Methyl 2-((o-Tolyl(p-tolyl)methyl)amino)acetate (**2d**).* 28.0 mg, yield 99%; 97% ee; $[\alpha]_D^{20}$ = +20.8 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 5.7 min (minor), t_B = 6.5 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (d, J = 7.7 Hz, 1H), 7.19−7.15 (m, 3H), 7.07−7.02 (m, 4H), 4.97 (s, 1H), 3.65 (s, 3H), 3.32 (q, J = 17.6, 22.1 Hz, 2H), 2.00 (s, 3H), 1.98 (m, 3H), 1.96 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.7, 141.4, 139.9, 137.3, 136.5, 131.1, 129.7, 128.5, 127.4, 127.0, 126.8, 62.5, 52.3, 49.5, 21.7, 20.1. TOF-HRMS calcd for $C_{18}H_{22}NO_2$ [M + H^+]: 284.1645, found 284.1644.

*(+)-Methyl 2-(((4-fluorophenyl)(o-tolyl)methyl)amino)acetate (**2e**).* 28.2 mg, yield 98%; 96% ee; $[\alpha]_D^{20}$ = +18.0 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.5 min (minor), t_B = 6.9 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (d, J = 8.6 Hz, 1H), 7.33−7.09 (m, 6H), 7.00−6.95 (m, 1H), 5.07 (s, 1H), 3.72 (s, 3H), 3.43−3.33 (m, 2H), 2.26 (s, 3H), 2.10 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.6, 162.5 (d, $^1J_{C-F}$ = 244.0 Hz), 141.2 (d, J = 41.0 Hz), 139.9, 138.7 (d, J = 3.0 Hz), 136.4 (d, J = 2.0 Hz), 131.2 (d, J = 13.0 Hz), 130.2 (d, J = 8.0 Hz), 127.5 (d, J = 24.0 Hz), 127.0 (d, J = 6.0 Hz), 126.8 (d, J = 12.0 Hz), 115.8 (d, J = 21.0 Hz), 62.3 (d, J = 45.0 Hz), 52.3 (d, J = 6.0 Hz), 49.5, (d, J = 11.0 Hz), 20.1 (d, J = 6.0 Hz). TOF-HRMS calcd for $C_{17}H_{19}NO_2F$ [M + H^+]: 288.1394, found 288.1396.

*(−)-Methyl 2-(((2-Methoxyphenyl)(phenyl)methyl)amino)acetate (**2f**).* 27.4 mg, yield 96%; 95% ee; $[\alpha]_D^{20}$ = −16.4 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 7.3 min (minor), t_B = 8.3 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.50−7.40 (m, 3H), 7.31−7.19 (m, 4H), 6.97−6.93 (m, 1H), 6.85−6.81 (m, 1H), 5.25 (s, 1H), 3.78 (m, 3H), 3.71(m, 3H), 3.40 (m, 2H), 2.23 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.5, 157.5, 143.5, 131.7, 128.8, 128.2, 127.4, 121.3, 111.1, 60.1, 55.9, 52.3, 49.7. TOF-HRMS calcd for $C_{17}H_{20}NO_3$ [M + H^+]: 286.1437, found 286.1440.

*(−)-Methyl 2-(((2-Chlorophenyl)(phenyl)methyl)amino)acetate (**2g**).* 28.1 mg, yield 97%; 97% ee; $[\alpha]_D^{20}$ = −25.8 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.3 min (minor), t_B = 7.1 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.68−7.66 (m, 1H), 7.40−7.38 (m, 2H), 7.29−7.12 (m, 6H), 5.32 (s, 1H), 3.68 (s, 3H), 3.34 (q, J = 17.4, 39.9 Hz, 2H), 2.17 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.3, 142.4, 140.7, 134.2, 129.1, 129.0, 128.9, 128.4, 128.0, 127.7, 62.7, 52.4, 49.5. TOF-HRMS calcd for $C_{16}H_{17}NO_2Cl$ [M + H^+]: 290.0942, found 290.0944.

*(−)-Methyl 2-(((2-Chlorophenyl)(3-methoxyphenyl)methyl)-amino)acetate (**2h**).* 30.7 mg, yield 96%; 95% ee; $[\alpha]_D^{20}$ = −22.4 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 8.3 min (minor), t_B = 9.2 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.69−7.67 (m, 1H), 7.32−7.14 (m, 4H), 7.03−6.99 (m, 2H), 6.78−6.75 (m, 1H), 5.34 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.38 (q, J = 17.4, 20.5 Hz, 2H), 2.20 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.3, 160.3, 144.0, 140.7, 134.2, 130.2, 130.0, 129.1, 128.9, 127.7, 120.7, 114.0, 113.2, 62.5, 55.7, 52.4, 49.5. TOF-HRMS calcd for $C_{17}H_{19}NO_3Cl$ [M + H^+]: 320.1047, found 320.1049.

*(−)-Methyl 2-(((2-Chlorophenyl)(m-tolyl)methyl)amino)acetate (**2i**).* 29.5 mg, yield 97%; 97% ee; $[\alpha]_D^{20}$ = −18.2 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 7.9 min (minor), t_B = 8.4 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.65−7.63 (m, 1H), 7.26−7.10 (m, 6H), 6.98 (t, J = 7.0 Hz, 1H), 5.26 (s, 1H), 3.66 (s, 3H), 3.31 (q, J = 17.4, 21.9 Hz, 2H), 2.25 (s, 3H), 2.13 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.4, 142.3, 140.8, 138.7, 134.2, 130.3, 129.2, 129.0, 128.9, 128.8, 128.7, 127.7, 125.4, 62.6, 52.4, 49.6, 22.1. TOF-HRMS calcd for $C_{17}H_{19}NO_2Cl$ [M + H^+]: 304.1098, found 304.1100.

*(−)-Methyl 2-(((2-Chlorophenyl)(p-tolyl)methyl)amino)acetate (**2j**).* 29.8 mg, yield 98%; 96% ee; $[\alpha]_D^{20}$ = −25.9 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 5.6 min (minor), t_B = 6.5 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.74−7.72 (m, 1H), 7.33−7.26 (m, 4H), 7.19−7.11 (m, 3H), 5.34 (s, 1H), 3.39 (q, J = 17.4, 22.6 Hz, 2H), 2.32 (s, 3H), 2.20 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.3, 140.9, 139.3, 137.6, 134.1, 130.2, 129.7, 129.0, 128.7, 128.2, 127.7, 62.4, 52.4, 49.5, 21.6. TOF-HRMS calcd for $C_{17}H_{19}NO_2Cl$ [M + H^+]: 304.1098, found 304.1100.

*(−)-Methyl 2-(((2-Chlorophenyl)(4-fluorophenyl)methyl)amino)-acetate (**2k**).* 30.1 mg, yield 98%; 97% ee; $[\alpha]_D^{20}$ = −19.6 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.2 min (minor), t_B = 7.3 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.70−7.68 (m, 1H), 7.40−7.15 (m, 5H), 7.00−6.95 (m, 2H), 5.33 (s, 1H), 3.72 (s, 3H),

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3.35 (q, J = 17.4, 23.8 Hz, 2H), 2.17 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.3, 162.6 (d, $^1J_{C-F}$ = 244.0 Hz), 140.5, 138.2, 138.1, 134.1, 130.4, 130.0 (d, J = 8.0 Hz), 129.0 (d, J = 15.0 Hz), 127.8, 115.9 (d, J = 22.0 Hz), 62.0, 52.5, 49.4. TOF-HRMS calcd for $C_{16}H_{16}NO_2FCl$ $[M + H^+]$: 308.0848, found 308.0848.

*(−)-Methyl 2-(((2-Chlorophenyl)(4-chlorophenyl)methyl)amino)-acetate (**2l**).* 31.4 mg, yield 97%; 97% ee; $[\alpha]_D^{20}$ = −28.2 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.7 min (minor), t_B = 8.2 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.67−7.65 (m, 1H), 7.37−7.25 (m, 6H), 7.20−7.17 (m, 1H), 5.32 (s, 1H), 3.72 (s, 3H), 3.35 (q, J = 17.4, 22.4 Hz, 2H), 2.13 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.2, 140.9, 140.3, 134.1, 133.7, 130.4, 129.8, 129.2, 129.1, 128.9, 127.8, 62.0, 52.5, 49.4. TOF-HRMS calcd for $C_{16}H_{16}NO_2Cl_2$ $[M + H^+]$: 324.0552, found 324.0551.

*(−)-Methyl 2-(((2-Bromophenyl)(phenyl)methyl)amino)acetate (**2m**).* 32.8 mg, yield 98%; 96% ee; $[\alpha]_D^{20}$ = −14.8 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.7 min (minor), t_B = 7.5 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.63−7.60 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.27−7.22 (m, 3H), 7.19−7.16 (m, 1H), 7.05−7.00 (m, 1H), 5.27 (s, 1H), 3.66 (s, 3H), 3.31 (q, J = 17.4, 22.4 Hz, 2H), 2.15 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.3, 142.3, 142.2, 133.6, 129.6, 129.2, 129.0, 128.4, 128.3, 128.0, 124.8, 65.0, 52.4, 49.5. TOF-HRMS calcd for $C_{16}H_{17}NO_2Br$ $[M + H^+]$: 334.0437, found 334.0437.

*(−)-Methyl 2-(((2-Bromophenyl)(3-fluorophenyl)methyl)amino)-acetate (**2n**).* 33.8 mg, yield 96%; 94% ee; $[\alpha]_D^{20}$ = −20.5 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.5 min (minor), t_B = 7.8 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.51−7.49 (m, 1H), 7.40−7.38 (m, 1H), 7.21−6.95 (m, 5H), 6.81−6.77 (m, 1H), 5.21 (s, 1H), 3.59 (s, 3H), 3.22 (q, J = 17.4, 21.6 Hz, 2H), 2.07 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.2, 163.5 (d, $^1J_{C-F}$ = 244.0 Hz), 145.1, 145.0, 141.6, 133.6, 130.5 (d, J = 8.0 Hz), 129.5, 128.5, 124.7, 124.0 (d, J = 3.0 Hz), 115.2 (d, J = 22.0 Hz), 114.9 (d, J = 21.0 Hz), 64.4 (d, J = 1.0 Hz), 52.5, 49.4. TOF-HRMS calcd for $C_{16}H_{16}NO_2FBr$ $[M + H^+]$: 352.0342, found 352.0342.

*(−)-Methyl 2-(((2-bromophenyl)(4-fluorophenyl)methyl)amino)-acetate (**2o**).* 34.2 mg, yield 97%; 98% ee; $[\alpha]_D^{20}$ = −22.4 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.1 min (minor), t_B = 7.0 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.68−7.65 (m, 1H), 7.52−7.30 (m, 4H), 7.12−7.08 (m, 1H), 7.00−6.96 (m, 2H), 5.30 (s, 1H), 3.72 (s, 3H), 3.35 (q, J = 17.4, 24.8 Hz, 2H), 2.13 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.2, 162.6 (d, $^1J_{C-F}$ = 244.0 Hz), 141.9, 138.1, 133.6, 130.1 (d, J = 8.0 Hz), 129.3 (d, J = 6.0 Hz), 128.4, 124.7, 116.0, 115.8 (d, J = 21.0 Hz), 64.4, 52.4, 49.4. TOF-HRMS calcd for $C_{16}H_{16}NO_2FBr$ $[M + H^+]$: 352.0342, found 352.0342.

*(−)-Methyl 2-(((2-Bromophenyl)(4-chlorophenyl)methyl)amino)-acetate (**2p**).* 36.1 mg, yield 98%; 96% ee; $[\alpha]_D^{20}$ = −21.9 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.7 min (minor), t_B = 7.9 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.67−7.65 (m, 1H), 7.52−7.50 (m, 1H), 7.40−7.25 (m, 5H), 7.12−7.07 (m, 1H), 5.32 (s, 1H), 3.72 (s, 3H), 3.37−3.35 (m, 2H), 2.19 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.1, 141.7, 140.8, 133.7, 133.6, 129.8, 129.4, 129.3, 129.2, 128.4, 124.6, 64.3, 52.4, 49.3. TOF-HRMS calcd for $C_{16}H_{16}NO_2ClBr$ $[M + H^+]$: 368.0047, found 368.0046.

*(+)-Methyl 2-(((2-Fluorophenyl)(phenyl)methyl)amino)acetate (**2q**).* 27.0 mg, yield 99%; 94% ee; $[\alpha]_D^{20}$ = +12.8 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 5:95, 1.0 mL/min, 254 nm; t_A = 8.0 min (minor), t_B = 8.5 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.59−7.55 (m, 1H), 7.39 (d, J = 7.4 Hz, 2H), 7.29−7.09 (m, 5H), 6.97−6.92 (m, 1H), 5.20 (s, 1H), 3.68 (m, 3H), 3.36 (s, 2H), 2.18 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.3, 161.1 (d, $^1J_{C-F}$ = 244.0 Hz), 142.7, 130.8, 130.6, 129.2, 129.1, 128.6 (d, J = 4.0 Hz), 128.0, 124.9 (d, J = 4.0 Hz), 116.0 (d, J = 22.0 Hz), 59.4 (d, J = 3.0 Hz), 52.4, 49.5. TOF-HRMS calcd for $C_{16}H_{17}NO_2F$ $[M + H^+]$: 274.1237, found 274.1238.

*(+)-Methyl 2-(((2-Fluorophenyl)(m-tolyl)methyl)amino)acetate (**2r**).* 28.4 mg, yield 99%; 94% ee; $[\alpha]_D^{20}$ = +10.4 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-3 (250 × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 8.4 min (minor), t_B = 9.0 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (t, J = 6.8 Hz, 1H), 7.24−6.96 (m, 7H), 5.20 (s, 1H), 3.72 (s, 3H), 3.40 (s, 2H), 2.32 (s, 3H), 2.19 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.3, 161.1 (d, $^1J_{C-F}$ = 244.0 Hz), 142.6, 138.7, 130.8 (d, J = 7.0 Hz), 129.1 (d, J = 8.0 Hz), 128.9, 128.7, 128.6 (d, J = 4.0 Hz), 125.0, 124.9 (d, J = 3.0 Hz), 116.1, 115.9, 59.3 (d, J = 2.0 Hz), 52.4, 49.4, 30.3, 22.0. TOF-HRMS calcd for $C_{17}H_{19}NO_2F$ $[M + H^+]$: 288.1394, found 288.1396.

*(+)-Methyl 2-(((2-Fluorophenyl)(4-fluorophenyl)methyl)amino)-acetate (**2s**).* 28.5 mg, yield 98%; 94% ee; $[\alpha]_D^{20}$ = +14.6 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 5.7 min (minor), t_B = 6.1 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.60−7.56 (m, 1H), 7.41−7.37 (m, 2H), 7.22−7.11 (m, 2H), 7.00−6.96 (m, 3H), 5.21 (s, 1H), 3.72 (s, 3H), 3.37 (s, 2H), 2.15 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.2, 162.6 (d, $^1J_{C-F}$ = 244.0 Hz), 161.0 (d, $^1J_{C-F}$ = 245.0 Hz), 138.4 (d, J = 3.0 Hz), 130.6 (d, J = 12.0 Hz), 129.6 (d, J = 8.0 Hz), 129.3, (d, J = 8.0 Hz), 128.4 (d, J = 4.0 Hz), 125.0 (d, J = 4.0 Hz), 115.9 (d, J = 14.0 Hz), 58.7 (d, J = 3.0 Hz), 52.4, 49.3, 30.2. TOF-HRMS calcd for $C_{16}H_{16}NO_2F_2$ $[M + H^+]$: 292.1143, found 292.1145.

*(−)-Methyl 2-((Naphthalen-1-yl(phenyl)methyl)amino)acetate (**2t**).* 29.9 mg, yield 98%; 95% ee; $[\alpha]_D^{20}$ = −23.5 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 9.1 min (major), t_B = 15.7 min (minor). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.17 (d, J = 7.7 Hz, 1H), 7.87−7.78 (m, 3H), 7.53−7.45 (m, 5H), 7.33−7.21 (m, 3H), 5.71 (s, 1H), 3.73 (s, 3H), 3.50 (q, J = 17.6, 27.8 Hz, 2H), 2.27 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.7, 143.1, 138.4, 134.5, 131.9, 129.4, 129.1, 128.5, 128.4, 127.9, 126.6, 126.1, 126.0, 125.2, 124.0, 62.6, 52.4, 49.6. TOF-HRMS calcd for $C_{20}H_{20}NO_2$ $[M + H^+]$: 306.1488, found 306.1487.

*(+)-Ethyl 2-((Phenyl(o-tolyl)methyl)amino)acetate (**2u**).* 28.0 mg, yield 98%; 97% ee; $[\alpha]_D^{20}$ = +23.8 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 6.4 min (minor), t_B = 6.8 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (d, J = 7.6 Hz, 1H), 7.37−7.11 (m, 8H), 5.10 (s, 1H), 4.19 (q, J = 7.1, 30.8 Hz, 2H), 3.39 (q, J = 17.5, 22.0 Hz, 2H), 2.28 (s, 3H), 2.11 (s, 1H), 1.27 (t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.2, 142.9, 141.2, 136.5, 131.1, 129.0, 128.6, 127.7, 127.4, 127.2, 126.7, 62.8, 61.3, 49.7, 20.1, 14.8. TOF-HRMS calcd for $C_{18}H_{22}NO_2$ $[M + H^+]$: 284.1645, found 284.1644.

*(+)-tert-Butyl 2-((Phenyl(o-tolyl)methyl)amino)acetate (**2v**).* 30.5 mg, yield 98%; 97% ee; $[\alpha]_D^{20}$ = +20.5 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-3 (250 mm × 4.60 mm), ipa/hex = 3:97, 1.0 mL/min, 254 nm; t_A = 5.3 min (minor), t_B = 5.9 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (d, J = 7.7 Hz, 1H), 7.37−7.10 (m, 8H), 5.08 (s, 1H), 3.28 (q, J = 17.4, 25.5 Hz, 2H), 2.28 (s, 3H), 2.14 (s, 1H), 1.47 (s, 9H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 172.5, 143.1, 141.4, 136.5, 131.1, 129.0, 128.6, 127.6, 127.4, 127.2, 126.8, 81.7, 62.8, 50.6, 28.7, 20.1. TOF-HRMS calcd for $C_{20}H_{26}NO_2$ $[M + H^+]$: 312.1958, found 312.1957.

*(+)-N-Methyl-1-phenyl-1-(o-tolyl)methanamine (**2w**).* 20.7 mg, yield 98%; 99.4% ee; $[\alpha]_D^{20}$ = +16.8 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-3 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; t_A = 9.0 min (major), t_B = 10.4 min (minor). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.60−7.58 (m, 1H), 7.34−7.11 (m, 8H), 4.88 (s, 1H), 2.43 (s, 3H), 2.30 (s, 3H), 1.56 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 143.0, 141.4, 135.8, 130.5, 128.4, 128.0, 127.0, 126.7, 126.3, 126.2, 65.3, 35.3, 19.6. TOF-HRMS calcd for $C_{15}H_{18}N$ $[M + H^+]$: 212.1433, found 212.1435. The analytical data are in accordance with those reported in the literature.[17]

*(+)-N-(Phenyl(o-tolyl)methyl)ethanamine (**2x**).* 22.1 mg, yield 98%; 99% ee; $[\alpha]_D^{20}$ = +14.0 (c = 0.5, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-3 (250 mm × 4.60 mm), ipa/hex = 5:95, 1.0 mL/min, 254 nm; t_A = 9.4 min (major), t_B = 13.6 min (minor). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.54−7.53 (m, 1H), 7.29−7.06 (m, 8H), 4.96 (s, 1H), 2.61−2.56 (m, 2H), 2.24 (s, 3H), 1.35 (s, 1H), 1.10−1.07 (m, 3H).

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$^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 143.9, 142.3, 136.3, 131.0, 128.9, 128.5, 127.4, 127.2, 127.0, 126.7, 63.9, 43.3, 20.2, 16.1. TOF-HRMS calcd for $C_{16}H_{20}N$ $[M + H^+]$: 226.1590, found 226.1589.

Procedure for the Synthesis of Compound 3. A 25 mL round-bottom flask was charged with compound **2** (0.5 mmol), MeOH (5 mL), K_2CO_3 (0.5 or 1.0 mmol), and 10% Pd/C (10 mg). The reaction vessel was purged with hydrogen three times, and then the mixture was stirred under atmospheric hydrogen (using a hydrogen balloon) at room temperature or 0 °C until no starting material was detected by TLC. The catalyst was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to afford **3** as a yellow oil.[18]

*(−)-Methyl 2-((Phenyl(m-tolyl)methyl)amino)acetate (**3a**).* 127 mg, yield 95%; 97% ee; $[\alpha]_D^{20} = -23.5$ ($c = 0.5$, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; $t_A = 6.4$ min (major), $t_B = 6.9$ min (minor). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.30−6.90 (m, 9H), 4.72 (s, 1H), 3.59 (s, 3H), 3.27 (s, 2H), 2.19 (s, 3H), 2.11 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.0, 143.3, 143.1, 138.2, 128.6, 128.5, 128.0, 127.4, 127.2, 124.4, 66.6, 51.8, 48.9, 21.5. TOF-HRMS calcd for $C_{17}H_{20}NO_2$ $[M + H^+]$: 270.1488, found 270.1490.

*(+)-Methyl 2-((Phenyl(p-tolyl)methyl)amino)acetate (**3b**).* 128 mg, yield 96%; 96% ee; $[\alpha]_D^{20} = -18.0$ ($c = 0.5$, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 3:97, 1.0 mL/min, 254 nm; $t_A = 8.0$ min (minor), $t_B = 9.2$ min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.28−6.97 (m, 9H), 4.71 (s, 1H), 3.58 (s, 3H), 3.25 (s, 2H), 2.17 (s, 3H), 2.07 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.1, 143.4, 140.3, 136.9, 129.3, 128.6, 127.3, 127.2, 127.1, 66.3, 51.8, 48.9, 21.1. TOF-HRMS calcd for $C_{17}H_{20}NO_2$ $[M + H^+]$: 270.1488, found 270.1490.

*(−)-Methyl 2-(((3-Fluorophenyl)(phenyl)methyl)amino)acetate (**3c**).* 128 mg, yield 94%; $[\alpha]_D^{20} = -15.2$ ($c = 0.5$, CH_2Cl_2); 94% ee; HPLC conditions: Lux 5u Amylose-2 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; $t_A = 6.5$ min (minor), $t_B = 6.7$ min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.26−7.01 (m, 8H), 6.79−6.74 (m, 1H), 4.74 (s, 1H), 3.58 (s, 3H), 3.25−3.21 (m, 2H), 2.07 (s, 1H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 172.9, 163.1 (d, $^1J_{C-F} = 244.0$ Hz), 145.9 (d, $J = 7.0$ Hz), 142.7, 130.0 (d, $J = 8.0$ Hz), 128.7, 127.5, 127.3, 123.0, 122.9, 114.1 (d, $J = 26.0$ Hz), 66.1, 51.9, 48.7. TOF-HRMS calcd for $C_{16}H_{17}NO_2F$ $[M + H^+]$: 274.1237, found 274.1238.

*(−)-Methyl 2-(((4-Fluorophenyl)(phenyl)methyl)amino)acetate (**3d**).* 131 mg, yield 96%; 98% ee; $[\alpha]_D^{20} = -18.7$ ($c = 0.5$, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; $t_A = 6.8$ min (minor), $t_B = 7.2$ min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.39−7.20 (m, 7H), 7.00−6.95 (m, 2H), 4.86 (s, 1H), 3.71 (s, 3H), 3.36 (s, 2H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.0, 161.9 (d, $^1J_{C-F} = 244.0$ Hz), 143.0, 139.0 (d, $J = 3.0$ Hz), 129.0 (d, $J = 8.0$ Hz), 128.7, 127.4 (d, $J = 15.0$ Hz), 115.5, 115.3, 65.8, 51.9, 48.8. TOF-HRMS calcd for $C_{16}H_{17}NO_2F$ $[M + H^+]$: 274.1237, found 274.1238.

*(−)-Methyl 2-(((4-Chlorophenyl)(phenyl)methyl)amino)acetate (**3e**).* 138 mg, yield 96%; 96% ee; $[\alpha]_D^{20} = -20.3$ ($c = 0.5$, CH_2Cl_2); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; $t_A = 6.9$ min (minor), $t_B = 8.2$ min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.26−7.10 (m, 9H), 4.74 (s, 1H), 3.58 (s, 3H), 3.24 (s, 2H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 173.5, 143.3, 142.3, 133.5, 129.3, 129.2, 129.1, 128.0, 127.8, 66.4, 52.4, 49.3. TOF-HRMS calcd for $C_{16}H_{15}NO_2Cl$ $[M + H^+]$: 288.0785, found 288.0785.

Procedure for the Synthesis of Compound 4. A mixture of **3e** (1.0 mmol), $ICH_2CO_2C_2H_5$ (1.1 mmol), and K_2CO_3 (1.0 mmol) in DMF (5.0 mL) was heated at 80−90 °C. The mixture was stirred until no starting material was detected by TLC and then concentrated in vacuo. The residue was extracted with EtOAc, washed with brine, dried over $NaSO_4$, and concentrated in vacuo. Purification by flash column chromatography on silica gel afforded **4** (316 mg) as a yellow oil.[14] Yield 84%; 95% ee; $[\alpha]_D^{20} = -17.8$ ($c = 0.5$, CH_2Cl_2); HPLC conditions: Lux 5u C-1 (250 mm × 4.60 mm), ipa/hex = 20:80, 1.0 mL/min, 254 nm; $t_A = 5.9$ min (minor), $t_B = 6.8$ min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.28−7.04 (m, 9H), 5.20 (s, 1H), 3.99−3.94 (m, 2H), 3.50 (s, 3H), 3.41−3.38 (m, 4H),1.09−1.05 (m, 3H). $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ: 172.4, 171.9, 142.1, 141.5, 133.5, 129.9, 129.4, 129.3, 128.6, 128.1, 60.9, 52.5, 52.4, 52.0, 14.7. TOF-HRMS calcd for $C_{20}H_{23}NO_4Cl$ $[M + H^+]$: 376.1310, found 376.1313.

Procedure for the Synthesis of Compound 5. A solution of **2a** or **3e** (0.18 mmol) in dry THF (5.0 mL) was added to a solution of $LiAlH_4$ (1.05 mmol) in dry THF (10 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C until complete formation of the corresponding amino-alcohol was observed by TLC. The reaction mixture was decomposed by the careful dropwise addition of water (2.0 mL), and the product was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography to give the corresponding aminoalcohol.[19] Lead acetate (0.148 mmol) was added to a solution of the corresponding aminoalcohol (0.124 mmol), CH_2Cl_2 (0.5 mL), and MeOH (0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. Hydroxylamine hydrochloride (1.24 mmol) was added, and the mixture was stirred at 0 °C for 30 min before concentration in vacuo. The residue was suspended in CH_2Cl_2 followed by filtration of the precipitate. The filtrate was extracted with 1 N HCl. The combined aqueous layers were washed with Et_2O, treated with 20% NaOH until pH 14, and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography to afford **5** as a yellow oil.[15a]

*(+)-Phenyl(o-tolyl)methanamine (**5a**).* 21 mg, yield 87%; 97% ee; $[\alpha]_D^{20} = +10.8$ ($c = 0.5$, $CHCl_3$); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; $t_A = 5.8$ min (minor), $t_B = 6.3$ min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.44−7.42 (m, 1H), 7.19−7.00 (m, 8H), 5.26 (s, 1H), 2.14 (s, 3H), 1.66 (s, 2H). The analytical data are in accordance with those reported in the literature.[20]

*(−)-(4-Chlorophenyl)(phenyl)methanamine (**5b**).* 24 mg, yield 89%; 95% ee; $[\alpha]_D^{20} = -6.9$ ($c = 0.5$, EtOH); HPLC conditions: Lux 5u Cellulose-1 (250 mm × 4.60 mm), ipa/hex = 10:90, 1.0 mL/min, 254 nm; $t_A = 6.6$ min (minor), $t_B = 7.8$ min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.37−7.21 (m, 9H), 5.17 (s, 1H), 1.76 (s, 2H). The analytical data are in accordance with those reported in the literature.[21]

Experiments of Deuteration Reactions. A 50 mL round-bottom flask was charged with benzophenone imine (5.0 mmol) which was synthesized by d_5-PhBr and 2-methylbenzonitrile, glycine ester hydrochloride (6.0 mmol), and CH_2Cl_2 (10.0 mL). The milky white mixture was stirred at rt−40 °C under an argon atmosphere until no starting material was detected by TLC. The white insoluble substance was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to provide the deuterium-labeling substrate. The procedure of hydrogenation of this deuterium-labeling substrate was carried out under the optimized reaction conditions according to the hydrogenation of substrates **1**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01273.

NMR and HPLC spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ghhou@bnu.edu.cn.

*E-mail: heyong@bnu.edu.cn.

Notes

The authors declare no competing financial interest.

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