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Metal-Free Insertion of Sulfoxonium Ylides into Arylamines in Water

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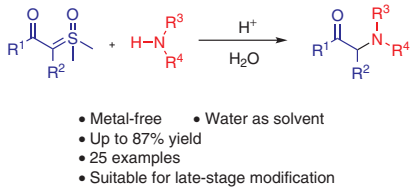

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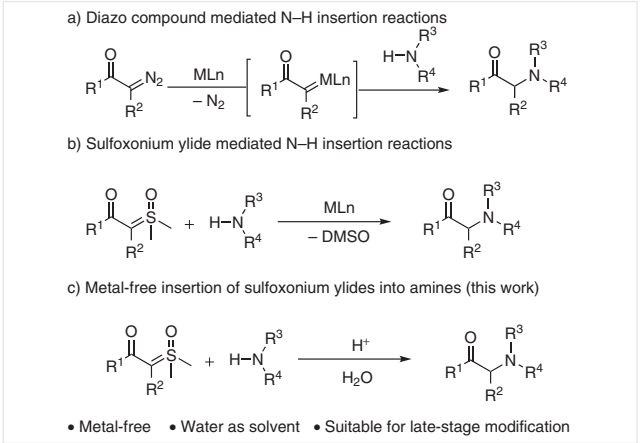
Abstract Carbenoid-based N–H insertions have undergone significant development with respect to C–N bond formation in recent years. However, the existing methods suffer from unstable starting materials, expensive metal catalysts and organic solvents. Herein, insertion of sulfoxonium ylides into arylamines under metal-free conditions has been developed. The method employs water as solvent at mild temperature and is amenable to the late-stage modification of structurally complex bioactive compounds.

Key words sulfoxonium ylides, metal-free, N–H insertion, C–N formation, α-amino acid ester

Nitrogen-containing compounds are extremely important because of their ubiquity in natural products and bioactive molecules.[1] For decades, organic chemists have studied in depth the construction of C–N bonds. Metal-catalyzed C–N cross-coupling reactions have been established as one of the most general protocols.[2] Carbenoid based N–H insertions, on the other hand, have undergone significant development with respect to C–N bond formation in recent years. In these insertion reactions, metal–carbenoids derived from diazo compounds are most widely used (Scheme 1a).[3] However, diazo compounds are toxic, unstable, and potentially explosive. It is thus highly desirable to develop more suitable carbene precursors.[4]

Sulfonium and sulfoxonium ylides have been investigated as synthetic precursors in organic transformations since they were first described in 1930.[5] In addition to their initial applications in epoxidation, cyclopropanation, aziridination reactions, and [2,3]-sigmatropic or Stevens rearrangements,[6] sulfoxonium ylides have recently gained prominence as potentially safer surrogates of diazo compounds in metal carbene reactions.[7] Baldwin first reported the rhodium-catalyzed N–H insertion reaction of sulfoxonium ylide derived carbenoids in 1993; Mangion then investigated a more general methodology in 2009 (Scheme 1b).[8] Although these methods offer generally better carbene precursors for N–H insertion reactions, they suffer from the need for expensive metal catalysts and organic solvents.[9] In 2016, Burtoloso described a catalyst-free insertion of sulfoxonium ylides into aryl thiols, but the authors did not assess amine reactivity.[10]

To expand the applications of sulfoxonium ylides, herein, we describe a simple and metal-free N–H insertion reaction of easily prepared sulfoxonium ylides and commercially available amines, through which α-amino acid esters can be obtained (Scheme 1c). Furthermore, because of the characteristics of water as solvent and ambient reaction temperature, this strategy is more suitable for chemical biology than the metal–carbenoid N–H insertions.[11] It is worth mentioning that König and Metzger reported the reaction of a similar α-sulfoxonium acetate derivative with aniline in



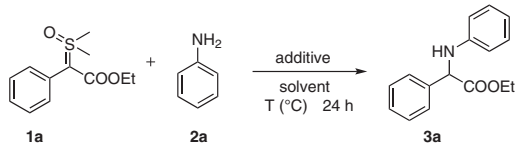
Scheme 1 Related N–H insertion reactions

the presence of HCl in 1965,[12] but the only example in this report required elevated temperature and gave a moderate yield.

We initially studied reactions of sulfoxonium ylide **1a** with aniline **2a** in dichloromethane (CH_2Cl_2) at 25 °C. Fortunately, the ideal α-amino acid ester **3a** was obtained in 60% yield (Table 1, entry 1). Subsequently, tetrahydrofuran (THF), dichloroethane (DCE) and other organic solvents were tested but their use failed to increase the yield (entries 2–5). However, the reaction proceeded well in water (entry 6). Considering that protonation of the ylide double bond is conducive to the nucleophilic displacement of dimethyl sulfoxide (DMSO),[10] we tried different acids as additives, and we found that nitric acid can effectively improve the conversion of sulfoxonium ylide **1a** (entries 7–11). We further explored the temperature, reaction time, and the number of equivalents of **2a** and nitric acid (for additional details see the Supporting Information), and finally established the optimal conditions (entry 12).

After finding the optimal conditions to synthesize α-amino acid ester **3**, we next evaluated the scope of the reaction by employing structurally different sulfoxonium ylides and amines. Anilines containing electron-donating or -withdrawing substituents at different positions proceeded smoothly (Scheme 2). Among them, methoxy-, methyl- and chloro-substituted anilines afforded the corresponding α-amino acid esters **3b–j** in moderate to good yields. We

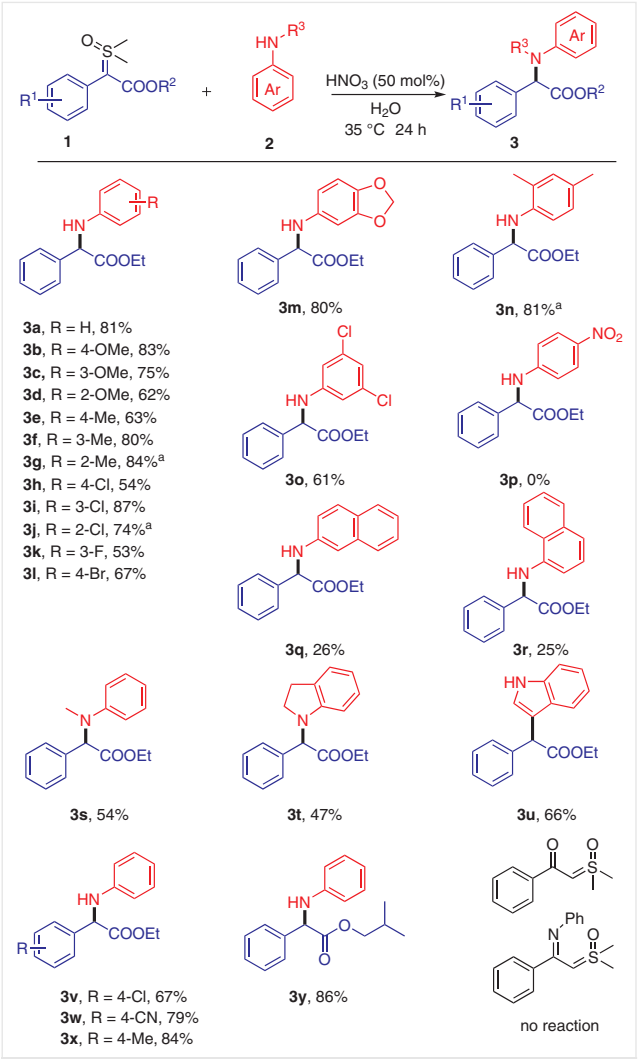
Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3a

Entry	Additive	Solvent	*T* (°C)	Yield (%)[b]
1	–	CH_2Cl_2	25	60
2	–	THF	25	51
3	–	DCE	25	32
4	–	DMF	25	trace
5	–	HOAc	25	26
6	–	H_2O	25	62
7	HCOOH	H_2O	25	65
8	1-AdCOOH	H_2O	25	41
9	HNO_3	H_2O	25	72
10	HCl	H_2O	25	63
11	H_2SO_4	H_2O	25	39
12[c]	HNO_3	H_2O	35	81

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), additive (20 mol%), solvent (2 mL) for 24 h at the specified temperature under air.
[b] Isolated yield.
[c] Additive (0.5 equiv).

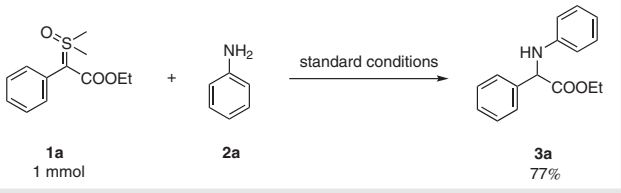


Scheme 2 Scope of sulfoxonium ylides and amines. *Reagents and conditions*: **1** (0.1 mmol), **2** (0.3 mmol), HNO_3 (50 mol%), H_2O (2 mL), 24 h, 35 °C under air. Isolated yields given. [a] Additive (2.0 equiv).

found that *ortho*-substituted substrates exhibited lower yields, possibly due to steric hindrance. Especially, **3g** and **3j** were only obtained in good yields with higher equivalent of HNO_3. Bromine- and fluorine- substituted anilines gave slightly lower yields when compared to chloro-substituted aniline (**3k–l**). Considering the ubiquity of poly-substituted aromatic amines, we further investigated some disubstituted aniline substrates and found that substrates with two electron-donating substituents had little effect on the yield (**3m**, **3n**), but the substrate with two electron-withdrawing substituents affected the yield of the reaction (**3o**). Surprisingly, nitro-substituted substrates were not suitable for this reaction (**3p**). When anilines were replaced with naphthylamines, the corresponding products **3q** and **3r** were only obtained in relatively low yields. In addition to aromatic

primary amines, aromatic secondary amines could also be amenable to the reaction (**3s**, **3t**). Interestingly, the indole substrate did not afford the desired α-amino acid ester under the optimal conditions; instead, it provided the 3-substituted product **3u**. Aliphatic amines were not good candidates for this reaction. Subsequently, sulfoxonium ylides possessing different substituents were also investigated (**3v**–**y**). Unfortunately, both α-carbonyl sulfoxonium ylides and imidoyl sulfoxonium ylide failed to undergo N–H insertion reaction under these conditions. We speculate that the electron-withdrawing group in the α-position of sulfoxonium ylide may increase its stability, but, on the other hand, it may also reduce its reactivity. Donor–acceptor sulfoxonium ylides have a suitable balance of stability and activity, but the α-carbonyl sulfoxonium ylide is too stable to react in this reaction.

To demonstrate the practical utility of the method as a synthetic tool, a 10-fold scale-up of the reaction was conducted and the yield was only slightly reduced (Scheme 3).



Scheme 3 10-fold scale-up reaction

Notably, this metal-free approach could be used for late-stage functionalization of structurally complex bioactive compounds. For example, cholesterol-derived sulfoxonium ylide **4** reacted with aniline **2a** to afford the desired α-amino acid ester **5** in 41% yield (Scheme 4).

In summary, we have developed a N–H insertion of sulfoxonium ylides under metal-free conditions that affords the corresponding α-amino acid esters through C–N formation. This strategy does not require unstable starting materials or metal catalysts and is amenable to the late-stage modification of structurally complex bioactive compounds. In contrast to the N–H insertions of metal–carbenoids that are commonly used, we believe this water-mediated insertion reaction, which proceeds at mild temperature, may open a new window to constructing C–N bonds in the field of biochemistry.

Unless noted, all reactions were carried out in flame-dried glassware with magnetic stirring under an atmosphere of air. Solvents used were of analytical purity. The product purification was done using silica gel column chromatography. NMR spectra were recorded with a Varian spectrometer (400 MHz for ^{1}H, 101 MHz for ^{13}C and 376 MHz for ^{19}F). Chemical shifts are reported in δ units (ppm) referenced to an internal $SiMe_4$ standard for ^{1}HNMR and chloroform-d (δ = 77.16 ppm) for ^{13}C NMR. HRMS spectra were recorded with a Waters Q-TOF Premier. Melting points were measured with YRT-3 melting point apparatus (Shantou Keyi Instrument & Equipment Co., Ltd., Shantou, China).

Compounds 3 and 5; General Procedure

To a flame-dried reaction tube equipped with a magnetic stir bar was added the sulfoxonium ylide **1** (0.1 mmol), aryl amine **2** (0.3 mmol) and 68% HNO_3 (0.05 mmol). Then H_2O (2 mL) was added and the mixture was stirred at 35 °C for 24 h. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/petroleum ether, 1:20) to give pure product.

Ethyl 2-Phenyl-2-(phenylamino)acetate (3a)

Yield: 81% (20.7 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dt, *J* = 8.4, 2.0 Hz, 2 H), 7.40–7.30 (m, 3 H), 7.17–7.10 (m, 2 H), 6.71 (tt, *J* = 7.4, 1.2 Hz, 1 H), 6.60–6.56 (m, 2 H), 5.08 (s, 1 H), 4.32–4.09 (m, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 146.1, 137.9, 129.4, 129.0, 128.4, 127.4, 118.2, 113.5, 62.0, 61.0, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NNaO_2$: 278.1151; found: 278.1158.

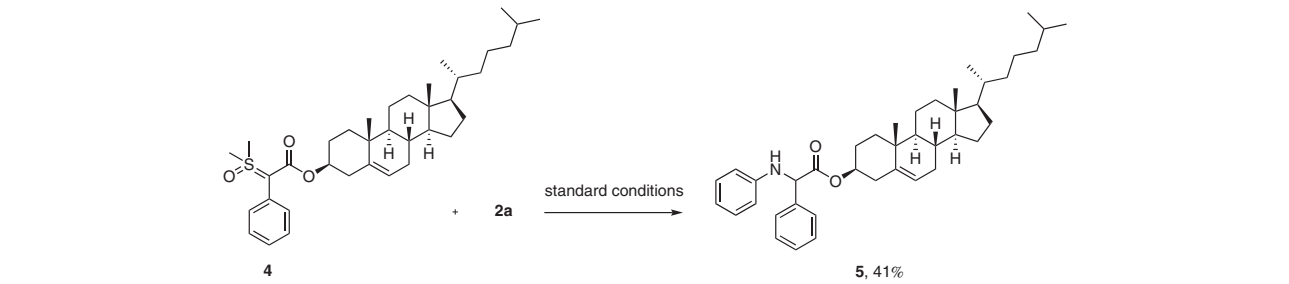
Ethyl 2-((4-Methoxyphenyl)amino)-2-phenylacetate (3b)

Yield: 83% (23.7 mg); light yellow solid; mp 84.9–86.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.2 Hz, 2 H), 7.34 (dt, *J* = 14.1, 7.2 Hz, 3 H), 6.73 (d, *J* = 8.9 Hz, 2 H), 6.54 (d, *J* = 8.9 Hz, 2 H), 5.01 (s, 1 H), 4.28–4.09 (m, 2 H), 3.71 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 152.6, 140.4, 138.0, 128.9, 128.3, 127.4, 115.0, 114.9, 61.8, 61.8, 55.8, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_3$: 308.1257; found: 308.1260



Scheme 4 Late-stage modification of bioactive compounds

Ethyl 2-((3-Methoxyphenyl)amino)-2-phenylacetate (3c)

Yield: 75% (21.4 mg); light-yellow solid; mp 98.2–100.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.0 Hz, 2 H), 7.34 (dt, *J* = 14.0, 7.0 Hz, 3 H), 7.03 (t, *J* = 8.2 Hz, 1 H), 6.27 (dd, *J* = 8.2, 2.4 Hz, 1 H), 6.19 (dd, *J* = 8.0, 2.4 Hz, 1 H), 6.12 (d, *J* = 2.4 Hz, 1 H), 5.06 (s, 1 H), 4.29–4.07 (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 = 171.9, 160.8, 147.5, 137.8, 130.1, 128.9, 128.3, 127.3, 106.5, 103.4, 99.6, 62.0, 60.9, 55.1, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_3$: 308.1257; found: 308.1261.

Ethyl 2-((2-Methoxyphenyl)amino)-2-phenylacetate (3d)

Yield: 62% (17.7 mg); light-yellow solid; mp 55.7–57.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.49 (m, 2 H), 7.37–7.27 (m, 3 H), 6.78 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.73 (td, *J* = 7.6, 1.6 Hz, 1 H), 6.66 (td, *J* = 7.6, 1.6 Hz, 1 H), 6.36 (dd, *J* = 7.6, 1.6 Hz, 1 H), 5.06 (s, 1 H), 4.30–4.07 (m, 2 H), 3.89 (s, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 147.2, 137.9, 136.1, 128.9, 128.3, 127.4, 121.2, 117.5, 110.8, 109.7, 61.8, 60.9, 55.6, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_3$: 308.1257; found: 308.1265.

Ethyl 2-Phenyl-2-(*p*-tolylamino)acetate (3e)

Yield: 63% (17.0 mg); light-yellow solid; mp 74.4–76.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, *J* = 8.4, 1.2 Hz, 2 H), 7.38–7.27 (m, 3 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.49 (d, *J* = 8.4 Hz, 2 H), 5.05 (s, 1 H), 4.28–4.09 (m, 2 H), 2.20 (s, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 143.8, 138.0, 130.0, 128.9, 128.28, 127.4, 127.3, 113.7, 61.9, 61.2, 20.5, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_2$: 292.1308; found: 292.1311.

Ethyl 2-Phenyl-2-(*m*-tolylamino)acetate (3f)

Yield: 80% (21.5 mg); light-yellow solid; mp 108.4–110.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 7.2 Hz, 2 H), 7.34 (dt, *J* = 14.0, 7.2 Hz, 3 H), 7.01 (t, *J* = 7.6 Hz, 1 H), 6.53 (d, *J* = 7.6 Hz, 1 H), 6.43 (s, 1 H), 6.37 (d, *J* = 8.0 Hz, 1 H), 5.07 (s, 1 H), 4.89 (s, 1 H), 4.30–4.08 (m, 2 H), 2.24 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 146.2, 139.1, 138.0, 129.2, 128.9, 128.3, 127.3, 119.2, 114.4, 110.5, 61.9, 60.9, 21.7, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_2$: 292.1308; found: 292.1317.

Ethyl 2-Phenyl-2-(*o*-tolylamino)acetate (3g)

Yield: 84% (22.6 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 7.2 Hz, 2 H), 7.33 (dt, *J* = 14.0, 7.2 Hz, 3 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 6.97 (t, *J* = 7.6 Hz, 1 H), 6.64 (t, *J* = 7.2 Hz, 1 H), 6.34 (d, *J* = 8.0 Hz, 1 H), 5.10 (s, 1 H), 4.29–4.10 (m, 2 H), 2.28 (s, 3 H), 1.21 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 144.2, 137.9, 130.3, 128.9, 128.3, 127.3, 127.1, 122.6, 117.8, 110.8, 62.0, 60.9, 17.7, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_2$: 292.1308; found: 292.1316.

Ethyl 2-((4-Chlorophenyl)amino)-2-phenylacetate (3h)

Yield: 54% (15.6 mg); yellow solid; mp 87.9–89.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 6.8 Hz, 2 H), 7.40–7.27 (m, 3 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 6.47 (d, *J* = 8.8 Hz, 2 H), 5.01 (s, 1 H), 4.31–4.07 (m, 2 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 171.6, 144.6, 137.4, 129.2, 129.0, 128.5, 127.3, 122.8, 114.6, 62.1, 60.9, 14.2.

HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}ClNNaO_2$: 312.0762; found: 312.0765.

Ethyl 2-((3-Chlorophenyl)amino)-2-phenylacetate (3i)

Yield: 87% (25.2 mg); light-yellow solid; mp 84.7–86.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.40–7.29 (m, 3 H), 7.01 (t, *J* = 8.0 Hz, 1 H), 6.69–6.39 (m, 3 H), 5.03 (s, 1 H), 4.29–4.08 (m, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 147.2, 137.3, 135.1, 130.3, 129.1, 128.5, 127.3, 118.1, 113.3, 111.7, 62.1, 60.6, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}ClNNaO_2$: 312.0767; found: 312.0770.

Ethyl 2-((2-Chlorophenyl)amino)-2-phenylacetate (3j)

Yield: 74% (21.4 mg); light-yellow solid; mp 59.5–62.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.47 (m, 2 H), 7.41–7.27 (m, 4 H), 6.99 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1 H), 6.62 (td, *J* = 7.6, 1.6 Hz, 1 H), 6.38 (dd, *J* = 8.0, 1.6 Hz, 1 H), 5.69 (s, 1 H), 5.09 (s, 1 H), 4.35–4.06 (m, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 142.1, 137.3, 129.4, 129.0, 128.5, 127.8, 127.2, 119.8, 118.1, 112.2, 62.1, 60.7, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}ClNNaO_2$: 312.0767; found: 312.0762.

Ethyl 2-((3-Fluorophenyl)amino)-2-phenylacetate (3k)

Yield: 53% (14.5 mg); light-yellow solid; mp 90.6–92.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dt, *J* = 8.4, 2.2 Hz, 2 H), 7.40–7.29 (m, 3 H), 7.05 (td, *J* = 8.1, 6.6 Hz, 1 H), 6.42–6.32 (m, 2 H), 6.22 (dt, *J* = 11.4, 2.3 Hz, 1 H), 5.12 (s, 1 H), 5.02 (s, 1 H), 4.32–4.08 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 164.0 (d, J_{C-F} = 243.1 Hz), 147.8 (d, J_{C-F} = 10.8 Hz), 137.3, 130.4 (d, J_{C-F} = 10.1 Hz), 129.0, 128.5, 127.3, 109.4 (d, J_{C-F} = 2.4 Hz), 104.6 (d, J_{C-F} = 21.5 Hz), 100.3 (d, J_{C-F} = 25.5 Hz), 62.1, 60.7, 14.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –112.72.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}FNNaO_2$: 296.1057; found: 296.1061.

Ethyl 2-((4-Bromophenyl)amino)-2-phenylacetate (3l)

Yield: 67% (22.4 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 2 H), 7.38–7.30 (m, 3 H), 7.19 (d, *J* = 8.8 Hz, 2 H), 6.43 (d, *J* = 8.8 Hz, 2 H), 5.01 (s, 1 H), 4.28–4.09 (m, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 145.0, 137.3, 132.1, 129.0, 128.5, 127.3, 115.1, 109.9, 62.1, 60.8, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}BrNNaO_2$: 356.0257; found: 356.0265.

Ethyl 2-(Benzo[*d*][1,3]dioxol-5-ylamino)-2-phenylacetate (3m)

Yield: 80% (23.9 mg); brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.2 Hz, 2 H), 7.34 (dt, *J* = 13.4, 7.2 Hz, 3 H), 6.59 (d, *J* = 8.3 Hz, 1 H), 6.21 (d, *J* = 2.2 Hz, 1 H), 5.99 (dd, *J* = 8.3, 2.2 Hz, 1 H), 5.85–5.77 (m, 2 H), 4.98 (s, 1 H), 4.28–4.08 (m, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 148.4, 141.8, 140.1, 137.8, 128.9, 128.4, 127.3, 108.7, 105.3, 100.7, 96.7, 61.9, 61.76, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_4$: 322.1050; found: 322.1051.

Ethyl 2-((2,4-Dimethylphenyl)amino)-2-phenylacetate (3n)

Yield: 81% (23.0 mg); light-yellow solid; mp 90.6–92.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 7.0 Hz, 2 H), 7.33 (dt, *J* = 14.4, 7.0 Hz, 3 H), 6.90 (s, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 6.26 (d, *J* = 8.1 Hz, 1 H), 5.08 (s, 1 H), 4.30–4.10 (m, 2 H), 2.26 (s, 3 H), 2.19 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 141.8, 138.1, 131.2, 128.9, 128.2, 127.3, 127.3, 126.9, 122.7, 111.0, 61.9, 61.1, 20.47, 17.6, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{21}NNaO_2$: 308.1465; found: 308.1466.

Ethyl 2-((3,5-Dichlorophenyl)amino)-2-phenylacetate (3o)

Yield: 61% (19.8 mg); light-yellow solid; mp 116.8–119.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 6.8 Hz, 2 H), 7.36 (dt, *J* = 10.5, 6.8 Hz, 3 H), 6.66 (s, 1 H), 6.41 (d, *J* = 1.8 Hz, 2 H), 5.20 (brs, 1 H), 4.99 (s, 1 H), 4.29–4.08 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 147.6, 136.7, 135.6, 129.2, 128.7, 127.2, 118.0, 111.7, 62.3, 60.4, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{15}Cl_2NNaO_2$: 346.0372; found: 346.0371.

Ethyl 2-(Naphthalen-2-ylamino)-2-phenylacetate (3q)

Yield: 26% (7.9 mg); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, *J* = 8.2 Hz, 2 H), 7.58–7.49 (m, 3 H), 7.41–7.28 (m, 4 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.66 (s, 1 H), 5.21 (s, 1 H), 4.33–4.11 (m, 2 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 143.7, 137.5, 135.0, 129.2, 129.0, 128.4, 127.8, 127.7, 127.3, 126.4, 126.1, 122.4, 118.1, 105.8, 62.0, 60.9, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NNaO_2$: 328.1308; found: 328.1312.

Ethyl 2-(Naphthalen-1-ylamino)-2-phenylacetate (3r)

Yield: 25% (7.6 mg); brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.00 (m, 1 H), 7.82–7.76 (m, 1 H), 7.58 (d, *J* = 6.7 Hz, 2 H), 7.57–7.43 (m, 2 H), 7.35 (dt, *J* = 12.3, 6.7 Hz, 3 H), 7.24–7.16 (m, 2 H), 6.34 (dd, *J* = 6.9, 1.6 Hz, 1 H), 5.24 (s, 1 H), 4.34–4.14 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 141.2, 137.6, 134.4, 129.0, 128.8, 128.4, 127.3, 126.5, 126.0, 125.1, 123.6, 120.2, 118.1, 105.7, 62.1, 61.0, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NNaO_2$: 328.1308; found: 328.1310.

Ethyl 2-(Methyl(phenyl)amino)-2-phenylacetate (3s)

Yield: 54% (14.5 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.34 (m, 3 H), 7.34–7.27 (m, 4 H), 6.89 (d, *J* = 8.2 Hz, 2 H), 6.82 (t, *J* = 7.3 Hz, 1 H), 5.65 (s, 1 H), 4.35–4.21 (m, 2 H), 2.81 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 150.0, 136.1, 129.4, 128.8, 128.6, 128.2, 118.1, 113.58, 65.9, 61.2, 34.7, 14.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_2$: 292.1308; found: 292.1315.

Ethyl 2-(Indolin-1-yl)-2-phenylacetate (3t)

Yield: 47% (13.2 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.32 (m, 5 H), 7.13–6.99 (m, 2 H), 6.69 (t, *J* = 7.6 Hz, 1 H), 6.47 (d, *J* = 7.6 Hz, 1 H), 5.27 (s, 1 H), 4.34–4.15 (m, 2 H), 3.66 (q, *J* = 8.9 Hz, 1 H), 3.21–3.09 (m, 1 H), 3.02–2.84 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 151.1, 135.4, 130.4, 128.80, 128.8, 128.4 127.2, 124.8, 118.4, 106.9, 64.0, 61.2, 50.0, 28.3, 14.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{19}NNaO_2$: 304.1308; found: 304.1310.

Ethyl 2-(1*H*-Indol-3-yl)-2-phenylacetate (3u)

Yield: 66% (18.4 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 7.49–7.40 (m, 3 H), 7.38–7.27 (m, 4 H), 7.22–7.15 (m, 2 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 5.25 (s, 1 H), 4.27–4.17 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 138.8, 136.4, 128.6, 128.5, 127.3, 126.8, 123.3, 122.4, 119.8, 119.2, 114.0, 111.3, 61.3, 49.1, 14.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{17}NNaO_2$: 302.1151; found: 302.1154.

Ethyl 2-(4-Chlorophenyl)-2-(phenylamino)acetate (3v)

Yield: 67% (19.4 mg); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.12 (t, *J* = 7.9 Hz, 2 H), 6.71 (t, *J* = 7.3 Hz, 1 H), 6.53 (d, *J* = 7.6 Hz, 2 H), 5.03 (s, 1 H), 4.27–4.11 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 145.8, 136.5, 134.2, 129.4, 129.1, 128.7, 118.4, 113.5, 62.2, 60.3, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}ClNNaO_2$: 312.0762; found: 312.0770.

Ethyl 2-(4-Cyanophenyl)-2-(phenylamino)acetate (3w)

Yield: 79% (22.9 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 3 H), 7.16–7.08 (m, 2 H), 6.80–6.65 (m, 2 H), 6.50 (d, *J* = 7.9 Hz, 2 H), 5.11 (s, 1 H), 4.29–4.12 (m, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 145.4, 143.5, 132.7, 129.5, 128.1, 118.6, 115.2, 113.5, 112.3, 62.6, 60.6, 14.11.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}N_2NaO_2$: 303.1104; found: 303.1102.

Ethyl 2-(Phenylamino)-2-(*p*-tolyl)acetate (3x)

Yield: 84% (22.6 mg); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.9 Hz, 2 H), 7.19–7.07 (m, 4 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 6.57 (d, *J* = 7.9 Hz, 2 H), 5.03 (s, 1 H), 4.29–4.08 (m, 2 H), 2.34 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 146.2, 138.1, 134.8, 129.6, 129.3, 127.2, 118.1, 113.5, 61.9, 60.6, 21.3, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_2$: 292.1308; found: 292.1311.

Isobutyl 2-Phenyl-2-(phenylamino)acetate (3y)

Yield: 86% (24.4 mg); white solid; mp 73.9–76.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 6.9 Hz, 2 H), 7.33 (dt, *J* = 15.0, 7.0 Hz, 3 H), 7.12 (t, *J* = 7.8 Hz, 2 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 6.57 (d, *J* = 7.9 Hz, 2 H), 5.08 (s, 1 H), 3.96–3.87 (m, 2 H), 1.86 (dq, *J* = 13.3, 6.8 Hz, 1 H), 0.81 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 146.1, 138.0, 129.3, 128.9, 128.3, 127.3, 118.1, 113.5, 71.8, 60.9, 27.8, 18.9, 18.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{21}NNaO_2$: 306.1465; found: 306.1463.

Cholesteryl 2-Phenyl-2-(phenylamino)acetate (5)

Yield: 41% (24.4 mg); light-yellow solid; mp 148.2–151.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.4 Hz, 2 H), 7.33 (dt, *J* = 14.5, 7.6 Hz, 3 H), 7.12 (t, *J* = 7.7 Hz, 2 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 6.56 (d, *J* = 7.9 Hz, 2 H), 5.33 (dd, *J* = 37.9, 5.1 Hz, 1 H), 5.04 (s, 1 H), 4.94 (s, 1 H), 4.64 (tt, *J* = 11.4, 5.1 Hz, 1 H), 2.36 (d, *J* = 8.1 Hz, 1 H), 2.18–1.78 (m, 6 H), 1.62–1.32 (m, 12 H), 1.25–1.01 (m, 9 H), 0.99 (s, 3 H), 0.91 (d, *J* = 6.1 Hz, 3 H), 0.89–0.84 (m, 6 H), 0.67 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.4, 146.2, 139.4, 139.3, 137.9, 137.9, 129.4, 128.9, 128.9, 128.3, 127.3, 123.2, 123.0, 118.1, 113.5, 75.6, 61.0, 56.8, 56.3, 50.1, 42.4, 39.8, 39.7, 38.2, 37.0, 36.7, 36.3, 35.9, 32.0, 32.0, 28.4, 28.2, 27.9, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{41}H_{57}NNaO_2$: 618.4282; found: 618.4284.

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