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Synthesis of Unsymmetrical α,α-Diarylacetates

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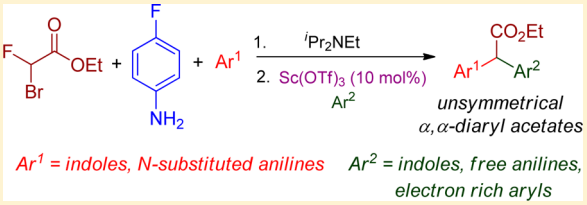
Supporting Information

ABSTRACT: Ethyl bromofluoroacetate has been developed as a precursor for the convenient synthesis of unsymmetrical α,α-diarylacetates featuring indoles, anilines, and other electron-rich aromatics. In conjunction with a mild Lewis acid catalyzed C−N → C−C exchange, intermediate arylglycines can be synthesized and transformed into α,α-diarylacetates in a one-pot protocol, resulting in a net diarylation reaction exhibiting a wide scope. In the context of diarylacetates, the synthetic equivalence of the fluorinated reagent with α-nitro-α-diazo carbonyls was established.

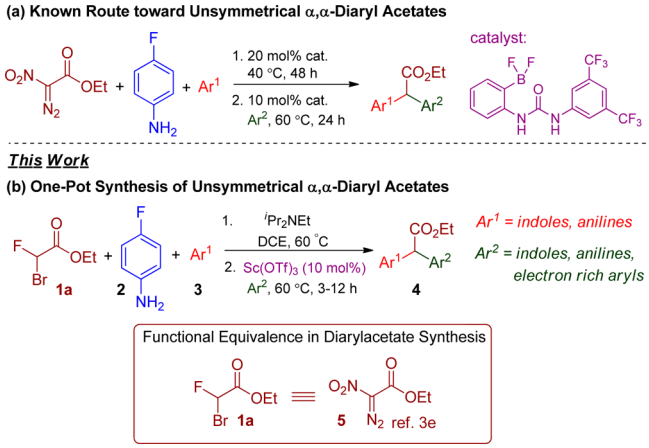


INTRODUCTION

The development of new methods to construct C−C bonds in an efficient manner is a fundamental tenet of modern chemistry research. Among the various kinds of reactions that can be envisaged, arylation of sp^3 carbon centers has attracted significant attention from the synthetic community. While many elegant processes are available for monoarylation,[1] the analogous bisarylation strategies are still in infancy, especially relating to the construction of unsymmetrical geminal diaryl motifs. Numerous biologically active compounds, including marketed drugs such as Femara, Etoposide, and Zoloft, feature the geminal diaryl moiety.[2] While a few literature reports provide innovative solutions to this problem, the reliance on the use of diazo derivatives and the lack of generality highlight the difficulties in this area.[3] Given the challenges associated with constructing this framework, we wanted to develop a simple protocol that would also offer versatility in the selection of the diaryl groups while maintaining simplicity such that no prefunctionalization of substrates would be required.

Our hypothesis was to employ ethyl bromofluoroacetate (**1a**) as a common progenitor for the convenient synthesis of aryl glycines (**18**, **19**), which would be viable precursors for generating α,α-diarylacetates featuring indoles, anilines, and other electron-rich aryls (Scheme 1b). The resulting approach would involve the generation of aryl glycines using a three-component reaction, which would preferably not require any catalysts/promoters while being generally applicable (Scheme 1b). This reaction would be a stepping stone toward our strategy to synthesize α,α-diarylacetates, which would entail the transformation of 4-fluoroanilinoyl-aryl glycines to bisarylated products, including those featuring a free aniline group. Overall, our plans attempt to address the synthesis of compounds containing unsymmetrical bisarylated sp^3 carbon centers. Central to our hypothesis is the electrophilic nature of the α-carbon in **1**, the leaving group property of the bromine and fluorine substituents, and the ability of 4-fluoroaniline to act as a placeholder for the second arylation until subjected to Lewis acid activation. We also envisaged that these reactions could be performed in a one-pot operation, resulting in diarylation, and offering access to a variety of unsymmetrical diarylacetates in a convenient manner without the use of traditional coupling reactions and explosive diazo precursors.

Scheme 1. Synthetic Approaches to Unsymmetrical Diarylacetates



RESULTS AND DISCUSSION

Mindful of the potential limitations of any direct method to synthesize unsymmetrical diarylacetates in high yield,[4] our studies began with attempts to evaluate the reactivity of ethyl bromofluoroacetate with indoles and anilines to ascertain if diarylacetate formation would be feasible, especially because it involves the cleavage of a C−F bond. Additionally, geminal dihaloacetates such as Br_2CHCO_2Et, $BrFCHCO_2Et$, and $ClFCHCO_2Et$ are not known to lend themselves to nucleophilic attack by arene nucleophiles.[5] We reasoned that, due to the fluorine substituent, the α-carbon in **1a** is more electrophilic

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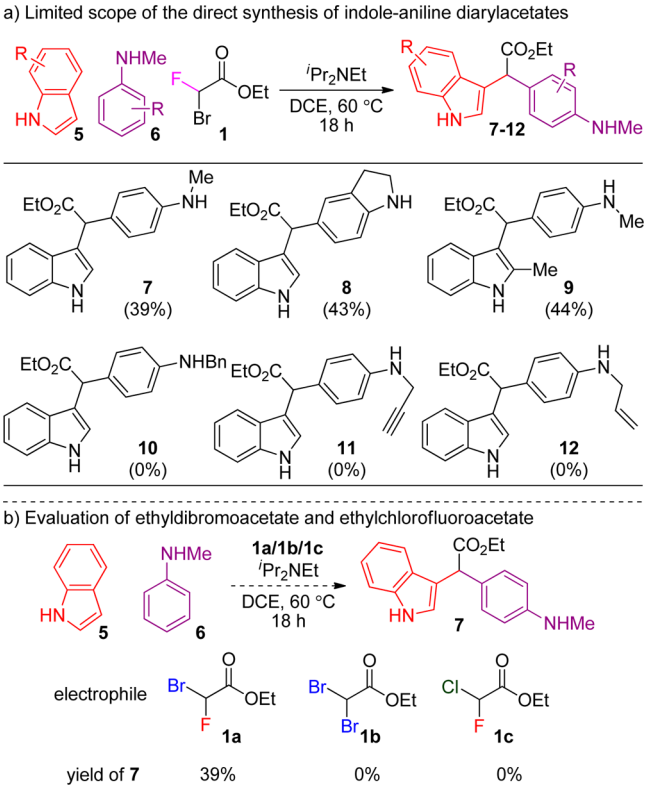
than other geminal dihaloacetates (as reflected in radical formations[6]) and, hence, may exhibit some reactivity. Indeed, it was observed that a reaction involving indole, *N*-methylaniline, and **1a** resulted in the unsymmetrical diaryl product **7**, albeit in low yield. We investigated a few additional precursors and found that, while *N*-methylaniline and indoline afforded diarylated products in low yields (compounds **7**, **8**, and **9**; Scheme 2a),

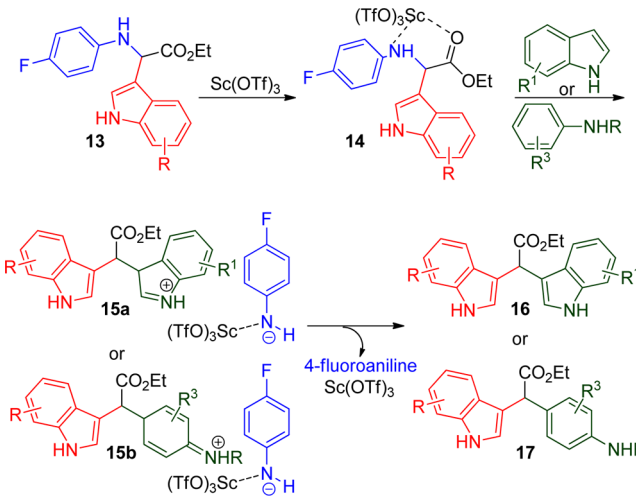
Scheme 2. Innate Reactivity of Indoles and Anilines with Geminal Dihaloacetates



N-Bn, *N*-propargyl, and *N*-allyl anilines provided no product (Scheme 2a). Employing pyrrole in place of indole also did not lead to the desired product, indicating another limitation of this protocol. Comparative reactions with ethyldibromoacetate and ethylchlorofluoroacetate failed to elicit any reactivity, thereby demonstrating that the fluorine substituent is necessary (Scheme 2b). It was clear from these results that, even if the direct reaction worked, its scope would be limited to synthesizing a few diarylacetates involving indoles and substituted anilines and it would not be of significant practical value. Hence, another strategy needed to be developed that could result in all classes of unsymmetrical diarylacetates (viz. indole-indole, indole-aniline, and aniline-aniline).

As per our hypothesis outlined in Scheme 1, we envisaged that indolyl glycines could be valuable precursors for generating a diverse selection of unsymmetrical α,α-diarylacetates if an efficient method could be developed for the exchange of the 4-fluoroanilinoyl moiety with a different aryl group. A simple strategy to realize this goal would be the development of a Lewis acid catalyzed C−N → C−C exchange in arylated 4-fluoroanilinoyl amino esters (Scheme 3). The application of the 4-fluoroaniline moiety as a leaving group (catalyzed by a boronate urea) was recently demonstrated by Mattson et al.[3e] in an elegant solution to the unsymmetrical diarylacetate synthesis

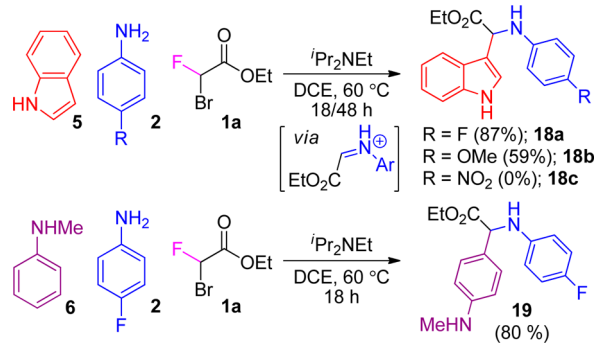
Scheme 3. Proposed Pathway for the Conversion of Arylglycines to α,α-Diarylacetates



problem, but that method relies on the use of α-nitro-α-diazo carbonyls whose explosive nature has been observed by synthetic chemists in the past.[3e,7] Our research efforts were aimed at providing an efficient and convenient synthetic alternative while maintaining a broad substrate scope.

The efficient assembly of the aryl glycines structure via a three-component reaction involving ethyl bromofluoroacetate, indole/anilines, and 4-fluoroaniline was critical for our subsequent plan to generate unsymmetrical α,α-diarylacetates. As shown in Scheme 4, the key indole-4-fluoroaniline adduct

Scheme 4. Synthesis of Intermediate Arylglycines 18 and 19



18 and the analogous *N*-methylaniline-4-fluoroanilne compound **19** were obtained in good yields. These reactions proceeded without any catalyst and required only mild heating, which increased the possibility of performing the subsequent step in the same reaction vessel. We also determined that 4-methoxyaniline affords analogous product **18b** in a lower yield (59%), while 4-nitroaniline does not react at all under the reaction conditions.

With a high yielding synthesis of the precursor **18** in hand, we explored the scope of the Lewis acid catalyzed installation of a second aryl group.[8] Under the reaction conditions outlined in Table 1, a test reaction employing **18a** and 2-methylindole revealed that many Lewis acid catalysts (10 mol %) afforded the product **24** efficiently (BF_3−OEt_2 (94%); Cu(OTf) (87%); $Cu(OTf)_2$ (93%); Ag(OTf) (96%); $Zn(OTf)_2$ (92%); $Sc(OTf)_3$ (98%)), and we selected $Sc(OTf)_3$ for further studies because it provided the highest yield. Using the same test

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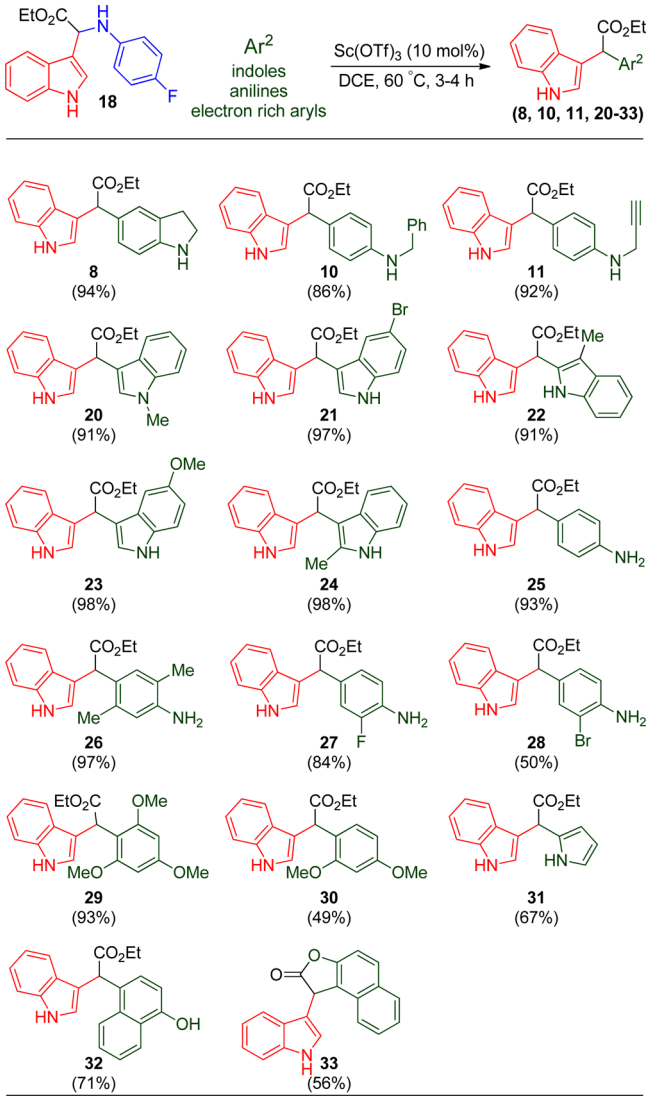
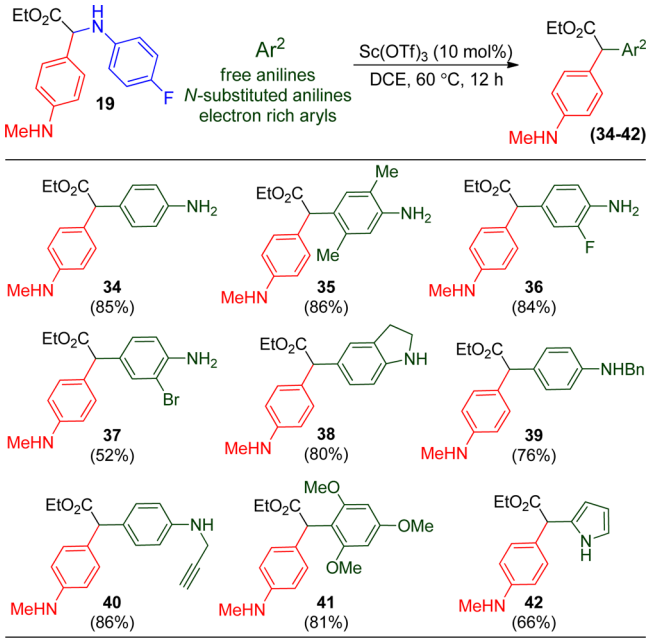
Table 1. Synthesis of Unsymmetrical Indole-Indole, Indole-Aniline, and Indole-Aryl Derivatives



reaction to evaluate arylglycines **18a** and **18b**, the 4-methoxy derivative was found to afford the product **24** in only 46% yield, while the 4-fluoro derivative resulted in 98% yield, and hence, **18a** was selected for further studies. As shown in Table 1, various substituted indoles (as Ar^2) were tolerated well, and indoline also provided the product (**8**) in 94% yield. Free anilines as well as *N*-substituted anilines reacted smoothly to afford the indole-aniline diarylacetates in high yields, as depicted in Table 1. Among other aryl moieties, 1,3,5-trimethoxybenzene provided the product (**29**) in high yield, while 1,3-dimethoxybenzene afforded regioisomers out of which compound **30** was the major product (49% yield). Pyrrole also resulted in the indole-pyrrole product **31** in 67% yield. 1-Naphthol provided the diaryl product in 71% yield, and 2-naphthol underwent an arylation−cyclization to afford the lactone **33** in 56% yield. Other heterocycles such as furan, thiophene, anisole, benzofuran, and benzothiophene did not react under these conditions. Key advantages of this protocol over the method in Scheme 2a includes the applicability of non-aniline electron-rich aryl moieties, the applicability of free anilines, improved scope with *N*-substituted anilines, and the high yields, particularly in the case of compound **8**, wherein an increase of 51% was observed compared to the direct method.

In order to access unsymmetrical aniline-aniline and other aniline-aryl derivatives, the 4-fluoroaniline derivative **19** was subjected to $Sc(OTf)_3$ under similar conditions outlined for the indole precursor **18**.[9] It was found that free anilines reacted via the *para* position to afford the unsymmetrical diarylacetates in generally high yields (52−86%).[10] Gratifyingly, *N*-benzylaniline provided the product in good yield, thereby overcoming the limitation of the direct protocol in Scheme 2. Various *N*-substituted anilines, including *N*-methylaniline, *N*-propargylaniline, and indoline, provided the corresponding products in high yields. 1,3,5-Trimethoxybenzene and pyrrole also exhibited good reactivity, as shown in Table 2. During our studies, it was

Table 2. Synthesis of Unsymmetrical Bisaniline and Aniline-Aryl Diarylacetates



discovered that *para*-substituted anilines did not participate (as Ar^2) in this reaction. It was observed that, while the reactions with indole derivative **18** were complete in 3−4 h, the reactions with *N*-methylaniline derivative **19** took longer (12 h) for completion. This difference can be attributed either to a possible competitive binding of $Sc(OTf)_3$ to **19** or to the greater electronic assistance provided by the indole ring in cleaving the C−N(aniline) bond compared to *N*-methylaniline.

With the development of efficient protocols for accessing various unsymmetrical α,α-diarylacetates, we proceeded to test whether the steps involved could be performed in a one-pot operation. Employing the above optimized conditions sequentially in the same reaction vessel smoothly afforded a variety of diarylacetates, as depicted in Table 3. While any indole or *N*-substituted aniline can be used in the first step, free anilines can only be employed as the second aryl group (Ar^2) because, if employed along with 4-F-aniline, they compete for C−N bond formation with **1a** and result in very low yields of the desired intermediate. The bisindole, indole-aniline, and the bisaniline products were synthesized efficiently (Table 3). Employing 1,3,5-trimethoxybenzene as the second nucleophile, the diaryl derivative **29** could also be accessed. Attempts to use 1,3,5-trimethoxybenzene as the first nucleophile in this one-pot protocol did not provide any product. Under these optimized

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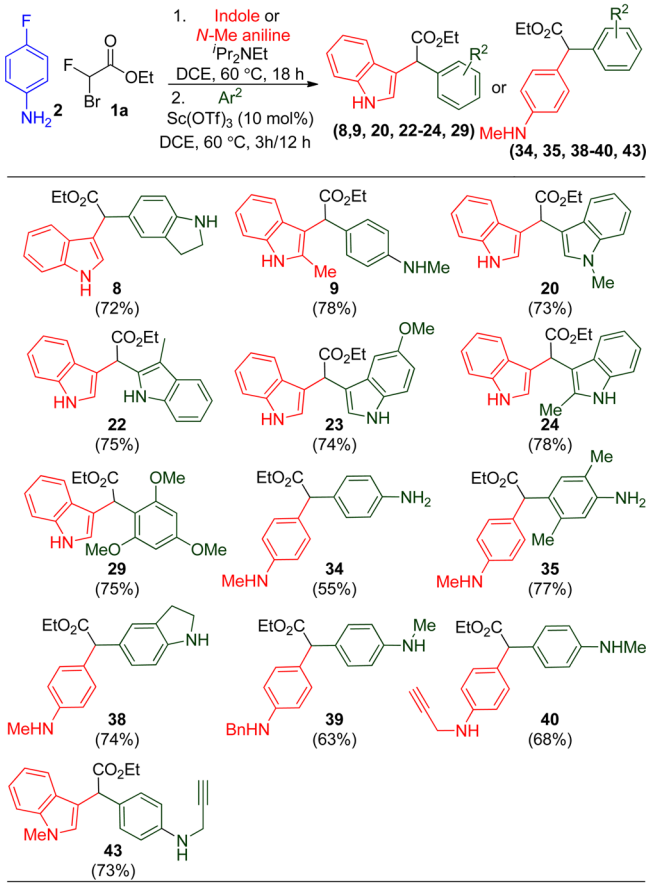
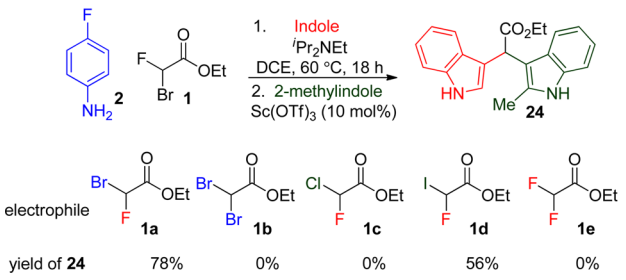
Table 3. One-Pot Synthesis of Unsymmetrical Diarylacetates

a) Scope of the one-pot diarylation reaction



b) Evaluation of various dihaloacetates as electrophiles



conditions, we again evaluated a series of dihaloacetates and found that only ethyl bromofluoroacetate and ethyl iodofluoroacetate reacted to provide the product (Table 3b). Since iodo-derivative **1d** has to be synthesized from the commercially available bromofluoroacetate **1a**, it offers no advantage over **1a**.[11] A comparison with the two-step methods outlined above revealed that the yields were slightly diminished (by 5−10%). A major advantage in terms of efficiency is that the intermediates analogous to **18** and **19** do not have to be isolated for every combination of Ar^1 and Ar^2. Additionally, the mild conditions, operational simplicity, and general applicability render this method very useful for populating the α,α-diarylacetate chemical space.

CONCLUSION

In summary, we have shown the application of ethyl bromofluoroacetate as a reagent for the convenient synthesis of unsymmetrical α,α-diarylacetates. The reactions developed rely on the propensity of a suitably placed C−F bond to cleave and the leaving group property of the 4-fluoroaniline moiety under Lewis acidic conditions. The synthetic method developed has a wide scope and is also amenable to be performed in a one-pot variant, effectively accomplishing a diarylation reaction that has been a challenging problem in the literature. The results also demonstrate the synthetic equivalence of ethyl bromofluoroacetate with α-nitro-α-diazo carbonyls with respect to the synthesis of diarylacetates. Further application of this reagent in the development of new reactions is currently being explored in our laboratory.

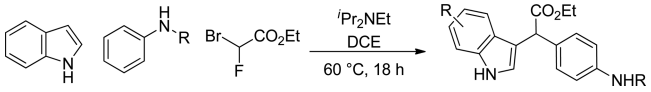
EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically pure material. Reaction were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualizing agent and *p*-anisaldehyde or $KMnO_4$ stain, and heat as developing agents. Merck silica gel (particle size 100−200 and 230−400 mesh) was used for flash column chromatography.

NMR spectra were recorded on 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) or 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) NMR spectrometers in $CDCl_3$ having TMS 0.03% as internal standard. Mass spectrometric data were obtained using Q-TOF ESI-MS.

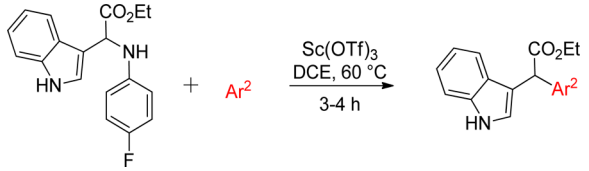
The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of a doublet of doublet.

General Procedure (I) for the Direct Synthesis of Unsymmetrical Indole-*N*-Substituted Aniline Diarylacetates 7−12.



A dried vial equipped with a magnetic bar was charged with indole (1 equiv), aniline (2 equiv), ethyl bromofluoroacetate (2 equiv), and diisopropylethylamine (2 equiv). The reaction was performed in a nitrogen atmosphere at 60 °C using DCE (2.3 mL per mmol of indole) as solvent. After completion of reaction (checked by TLC), the reaction mixture was poured into a separating funnel containing 50 mL of ethyl acetate/water (1:1). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). All organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography using ethyl acetate/petroleum ether as eluting solvent.

General Procedure (II) for the Preparation of Diarylacetates 8, 21−32 from Ethyl 2-(4-Fluorophenylamino)-2-(1*H*-indol-3-yl)acetate (18).



A dried vial equipped with a magnetic bar was charged with ethyl 2-(4-fluorophenylamino)-2-(1*H*-indol-3-yl) acetate **18** (1 equiv), aryl nucleophile (Ar^1) (1.5 equiv), scandium triflate (0.1 equiv), and 1,2 dichloroethane (DCE; 6.0 mL per mmol of **18**). The reaction was heated at 60 °C under a nitrogen atmosphere. After 3−4 h (monitored by TLC), the reaction mixture was poured into a separating funnel containing 50 mL of ethyl acetate/water (1:1). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). All organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography using ethyl acetate/petroleum ether as eluting solvent.

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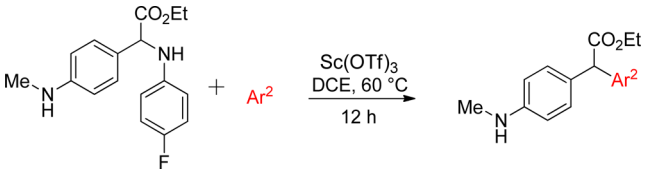
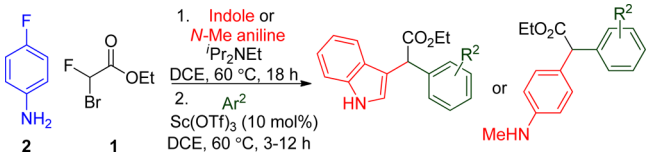
General Procedure (III) for the Synthesis of Diarylacetates 34–42 from Methyl 2-(4-Fluorophenylamino)-2-(4-(methylamino)-phenyl)acetate (19).



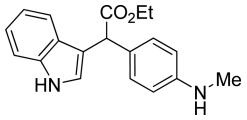
A dried vial equipped with a magnetic bar was charged with methyl 2-(4-fluorophenylamino)-2-(4-(methylamino)phenyl)acetate **19** (1 equiv), aryl nucleophiles (Ar^2) (1.5 equiv), scandium triflate (0.1 equiv), and DCE (6.0 mL per mmol of **19**) as solvent. The reaction was heated at 60 °C under a nitrogen atmosphere. After 12 h (monitored by TLC), the reaction mixture was poured into a separating funnel containing 50 mL of ethyl acetate/water (1:1). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). All organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography using ethyl acetate/pet ether as eluting solvent.

General Procedure (IV) for the One-Pot Synthesis of Unsymmetrical Diarylacetates.



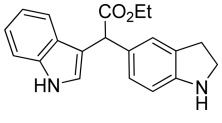
A dried vial equipped with a magnetic bar was charged with Ar^1 (indole/aniline) (1.0 equiv), 4-fluoroaniline (2.0/3.0 equiv), ethyl bromofluoroacetate (1.5 equiv), and diisopropylethylamine (1.5 equiv). The reaction was performed in a nitrogen atmosphere at 60 °C using DCE (2.3 mL per mmol of Ar^1) as solvent. After consumption of indole/aniline (as determined by TLC analysis), the reaction was cooled to room temperature and then aryl nucleophile Ar^2 (indoles/anilines; 2.0 equiv) was added, followed by scandium triflate (0.1 equiv), and DCE (1 mL). The reaction was again heated at 60 °C under a nitrogen atmosphere. After completion of reaction (monitored by TLC), the reaction mixture was poured into a separating funnel containing ethyl acetate/water (1:1). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). All organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography using ethyl acetate/petroleum ether as eluting solvent.

*Ethyl 2-(1H-Indol-3-yl)-2-(4-(methylamino)phenyl)acetate (**7**).*



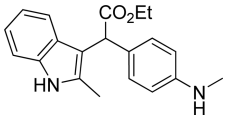
According to the general procedure **I**, indole (100 mg, 0.854 mmol) and *N*-methylaniline (183 mg, 1.71 mmol) provided **7** after flash chromatography (15–25% ethyl acetate in petroleum ether) as a cream colored solid (103 mg, 39%). R_f = 0.3 (20% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3411, 2979, 2926, 2813, 1720, 1601. mp = 140–142 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 7.51–7.44 (m, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.26 (s, 2H), 7.19–7.13 (m, 2H), 7.06 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 2H), 5.14 (s, 1H), 4.28–4.13 (m, 2H), 3.73 (s, 1H), 2.81 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (125 MHz, Chloroform-*d*) δ 173.6, 148.5, 136.4, 129.3, 127.4, 126.8, 123.2, 122.2, 119.7, 119.3, 114.6, 112.6, 111.2, 61.1, 48.3, 30.9, 14.4. Exact mass calculated for $C_{19}H_{21}N_2O_2^+$ $[M + H]^+$: 309.1598; found: 309.1600.

*Ethyl 2-(1H-Indol-3-yl)-2-(indolin-5-yl)acetate (**8**).*



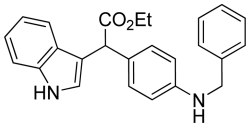
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and indoline (46 mg, 0.48 mmol) provided **8** after flash chromatography (15–25% ethyl acetate in petroleum ether) as a brown paste (96 mg, 94%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3403, 2978, 2902, 2857, 1723, 1616. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.17 (dd, *J* = 12.9, 7.3 Hz, 3H), 7.07 (q, *J* = 7.7 Hz, 2H), 6.62 (d, *J* = 7.9 Hz, 1H), 5.14 (s, 1H), 4.28–4.15 (m, 2H), 3.54 (t, *J* = 8.4 Hz, 2H), 2.98 (t, *J* = 7.9 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), (NH proton not observed). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.8, 150.9, 136.4, 129.9, 129.1, 127.5, 126.8, 124.8, 123.2, 122.2, 119.6, 119.2, 114.5, 111.3, 109.3, 61.1, 48.6, 47.6, 29.9, 14.3. Exact mass calculated for $C_{20}H_{21}N_2O_2^+$ $[M + H]^+$: 321.1598; found: 321.1602.

*Ethy-2-(2-methyl-1H-indol-3-yl)-2-(4-(methylamino)phenyl)-acetate (**9**).*



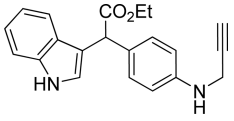
According to the general procedure **IV**, 2-methylindole (100 mg, 0.762 mmol) and *N*-methylaniline (164 mg, 1.52 mmol) provided **9** after flash chromatography (15–25% ethyl acetate in petroleum ether) as a dark yellow solid (192 mg, 78%). R_f = 0.4 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3400, 2662, 2929, 2905, 1719. mp = 97–99 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.53–7.46 (m, 1H), 7.28–7.24 (m, 2H), 7.14–7.06 (m, 3H), 7.01 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 2H), 5.17 (s, 1H), 4.24–4.14 (m, 2H), 2.81 (s, 3H), 2.34 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz Chloroform-*d*) δ 173.7, 146.2, 135.3, 132.9, 129.4(C-2), 128.0, 121.2, 119.7, 119.6, 114.0, 110.3, 109.1, 61.1, 47.6, 2.0, 14.4, 12.4. Exact mass calculated for $C_{20}H_{23}N_2O_2^+$ $[M + H]^+$: 323.1754; found: 323.1763.

*Ethyl 2-(4-(Benzylamino)phenyl)-2-(1H-indol-3-yl)acetate (**10**).*[4]



According to the general procedure **II**, **18** (100 mg, 0.33 mmol) and *N*-benzylaniline (91 mg, 0.5 mmol) provided **10** after flash chromatography (15–25% ethyl acetate in petroleum ether) as a yellowish paste (107 mg, 86%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3407, 3057, 2981, 2926, 1719, 1621. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.37–7.29 (m, 5H), 7.27 (dd, *J* = 6.0, 2.8 Hz, 1H), 7.23 (s, 2H), 7.18–7.11 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.61–6.54 (m, 2H), 5.12 (s, 1H), 4.31–4.26 (m, 2H), 4.24–4.14 (m, 2H), 4.02 (s, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz Chloroform-*d*) δ 173.6, 147.4, 139.5, 136.4, 129.4, 128.8, 127.7, 127.7, 127.4, 126.8, 123.2, 122.3, 119.7, 119.3, 114.6, 113.0, 111.2, 61.1, 48.6, 48.3, 14.4. Exact mass calculated for $C_{25}H_{24}N_2O_2^+$ $[M]^{\cdot+}$: 384.1832; found: 384.1834.

*Ethyl 2-(1H-Indol-3-yl)-2-(4-(prop-2-ynylamino)phenyl)acetate (**11**).*[4]



According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and *N*-propargylaniline (63 mg, 0.48 mmol) provided **11** after flash chromatography (15–25% ethyl acetate in petroleum ether) as a brown solid (98 mg, 92%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3410, 3286, 2980, 2925, 2853, 1721. mp = 109–111 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.18–7.13 (m, 2H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 2H), 5.14 (s, 1H), 4.27–4.13 (m, 2H), 3.89 (d, *J* = 2.5 Hz, 2H), 2.20 (t, *J* = 2.4 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.5, 146.1, 136.4, 129.4, 128.7, 126.8, 123.2, 122.2, 119.7, 119.2, 114.4, 113.6, 111.3, 81.1, 71.4, 61.1, 48.3,

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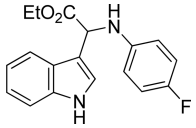
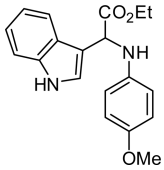
33.8, 14.3. Exact mass calculated for $C_{21}H_{20}N_2O_2^+$ $[M]^+$: 332.1519; found: 332.1520.

*Ethyl 2-(4-Fluorophenylamino)-2-(1H-indol-3-yl)acetate (**18a**).*[12]



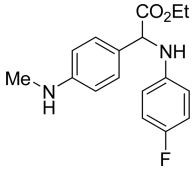
A dried vial equipped with a magnetic bar was charged with indole (100 mg, 0.854 mmol), 4-fluoroaniline (285 mg, 2.56 mmol), ethyl bromofluoroacetate (316 mg, 1.71 mmol), and diisopropylethylamine (221 mg, 1.71 mmol). The reaction was performed in a nitrogen atmosphere at 60 °C using DCE as solvent. After 18 h (reaction completion checked by TLC), the reaction mixture was poured into a separating funnel containing 50 mL of ethyl acetate/water (1:1). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). All organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. The residue provided pure **18** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a pale yellow solid (232 mg, 87%). R_f = 0.4 (20% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3408, 3058, 2982, 2846, 1729, 1614. mp = 128−130 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 7.14−7.08 (m, 1H), 7.08−7.02 (m, 1H), 7.00 (d, J = 2.6 Hz, 1H), 6.78−6.70 (m, 2H), 6.48−6.41 (m, 2H), 5.22 (s, 1H), 4.55 (s, 1H), 4.14 (dq, J = 10.9, 7.1 Hz, 1H), 4.01 (dq, J = 10.8, 7.1 Hz, 1H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 172.8, 156.23 (d, J = 235.8 Hz), 143.0, 136.5, 125.8, 123.3, 122.6, 120.1, 119.5, 115.77 (d, J = 22.4 Hz), 114.44 (d, J = 7.2 Hz), 112.2, 111.6, 61.8, 55.0, 14.2. Exact mass calculated for $C_{18}H_{16}FN_2O_2^-$ $[M - H]^-$: 311.1201; found: 311.1197.

*Ethyl 2-(1H-Indol-3-yl)-2-(4-methoxyphenylamino)acetate (**18b**).*



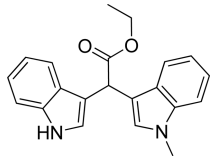
Employing the procedure outlined for **18a**, indole (100 mg, 0.854 mmol) and 4-methoxyaniline (474 mg, 2.56 mmol) provided **18b** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a yellow paste (164 mg, 59%). R_f = 0.3 (20% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3404, 3057, 2983, 2935, 2833, 1730. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.25−7.13 (m, 3H), 6.76 (d, J = 8.9 Hz, 2H), 6.63 (d, J = 9.0 Hz, 2H), 5.34 (s, 1H), 4.26 (dq, J = 10.7, 7.1 Hz, 1H), 4.14 (dq, J = 10.8, 7.1 Hz, 1H), 3.73 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{H}NMR (100 MHz, Chloroform-*d*) δ 173.0, 152.7, 140.9, 136.6, 126.0, 123.2, 122.6, 120.1, 119.7, 116.6, 115.0, 112.8, 111.5, 61.6, 55.8, 55.3, 14.3. Exact mass calculated for $C_{19}H_{19}N_2O_3^-$ $[M - H]^-$: 323.1401; found: 323.1391.

*Ethyl 2-(4-(Methylamino)phenyl)-2-(phenylamino)acetate (**19**).*[12]



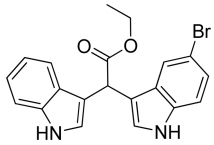
A dried vial equipped with a magnetic bar was charged with *N*-methylaniline (100 mg, 0.933 mmol), 4-fluoroaniline (415 mg, 3.73 mmol), ethyl bromofluoroacetate (345 mg, 1.87 mmol), and diisopropylethylamine (241 mg, 1.87 mmol). The reaction was performed in a nitrogen atmosphere at 60 °C using DCE as solvent. After 18 h (reaction completion checked by TLC), the reaction mixture was poured into a separating funnel containing 50 mL of ethyl acetate/water (1:1). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). All organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. The residue provided pure **19** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a brown solid (226 mg, 80%). R_f = 0.4 (20% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3414, 2982, 2901, 2816, 1731, 1614, 1512. mp = 74−76 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, J = 8.6 Hz, 2H), 6.84 (t, J = 8.7 Hz, 2H), 6.58 (d, J = 8.6 Hz, 2H), 6.51 (dd, J = 9.0, 4.4 Hz, 2H), 4.90 (s, 1H), 4.72 (s, 1H), 4.23 (dq, J = 10.8, 7.1 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 3.78 (s, 1H), 2.82 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 172.5, 156.11 (d, J = 235.5 Hz), 149.4, 142.80 (d, J = 1.7 Hz), 128.3, 125.7, 115.71 (d, J = 22.5 Hz), 114.37 (d, J = 7.2 Hz), 112.6, 61.6, 61.0, 30.7, 14.2. Exact mass calculated for $C_{17}H_{19}FN_2O_2^+$ $[M]^+$: 302.1425; found: 302.1444.

*Ethyl 2-(1H-Indol-3-yl)-2-(1-methyl-1H-indol-3-yl)acetate (**20**).*[3e]



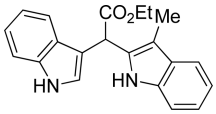
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and *N*-methylindole (63 mg, 0.48 mmol) provided **21** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a red paste (97 mg, 91%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3426, 3051, 2924, 2874, 1726. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.63 (dq, J = 7.8, 1.1 Hz, 2H), 7.30−7.25 (m, 2H), 7.24−7.19 (m, 1H), 7.16 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.08 (ddd, J = 8.1, 6.9, 1.3 Hz, 2H), 7.06−7.02 (m, 1H), 6.96 (s, 1H), 5.52−5.46 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.65 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.7, 137.3, 136.5, 128.1, 127.2, 126.8, 123.4, 122.2, 121.8, 119.6, 119.6, 119.4, 119.2, 113.9, 112.2, 111.4, 109.5, 61.2, 40.7, 32.9, 14.4. Exact mass calculated for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$: 333.1598; found: 333.1608.

*Ethyl 2-(5-Bromo-1H-indol-3-yl)-2-(1H-indol-3-yl)acetate (**21**).*[3e]



According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 5-bromoindole (94 mg, 0.48 mmol) provided **22** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a violet paste (146 mg, 97%). R_f = 0.2 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3409, 3054, 2978, 2927, 1718. ^{1}H NMR (396 MHz, Chloroform-*d*) δ = 8.10 (s, 1H), 8.05 (s, 1H), 7.78 (d, J = 1.4, 1H), 7.60 (d, J = 7.9, 1H), 7.31 (d, J = 8.1, 1H), 7.24 (dd, J = 8.6, 1.8, 1H), 7.20 (t, J = 7.5, 1H), 7.11 (d, J = 8.6, 2H), 7.00 (d, J = 2.3, 1H), 6.93 (d, J = 2.3, 1H), 5.43 (s, 1H), 4.23 (q, J = 7.1, 2H), 1.28 (t, J = 7.1, 4H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.5, 136.5, 135.0, 128.4, 126.6, 125.0, 124.8, 123.4, 122.3, 122.0, 119.7, 119.3, 113.3, 113.2, 112.9(C-2), 111.4, 61.5, 40.7, 14.3. Exact mass calculated for $C_{20}H_{21}BrN_3O_2^+$ $[M + NH_4]^+$: 414.0812; found: 414.0813.

*Ethyl 2-(1H-Indol-3-yl)-2-(3-methyl-1H-indol-2-yl)acetate (**22**).*[4]



According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 3-methylindole (63 mg, 0.48 mmol) provided **23** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a brown solid (103 mg, 91%). R_f = 0.2 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3408, 3056, 2922, 2855, 1721. mp = 107−109 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 7.96 (s, 1H), 7.52−7.43 (m, 2H), 7.25 (d, J = 8.1 Hz, 1H), 7.21−7.05 (m, 3H), 7.05−6.96 (m, 3H), 5.43 (s, 1H), 4.24−4.09 (m, 2H), 2.28 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*)δ 171.4, 135.2, 134.3, 129.1, 127.9, 125.2, 122.1, 121.5, 120.7, 119.0, 118.0, 117.8, 117.5, 111.6, 110.3, 109.8, 107.4, 60.6, 39.4, 13.2, 7.5. Exact mass calculated for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$: 333.1598; found: 333.1609.

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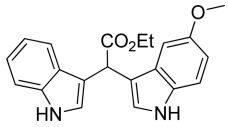
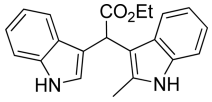
*Ethyl 2-(1H-Indol-3-yl)-2-(5-methoxy-1H-indol-3-yl)acetate (**23**).*[3e]



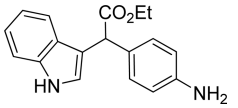
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 5-methoxyindole (71 mg, 0.48 mmol) provided **24** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a violet solid (109 mg, 98%). R_f = 0.2 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3408, 3057, 2982, 2937, 2831, 1721. mp = 54−57 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.94 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.20−7.13 (m, 2H), 7.12−7.06 (m, 2H), 6.94 (dd, *J* = 14.5, 2.4 Hz, 2H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.44 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.8, 154.1, 136.5, 131.6, 127.1, 126.8, 124.3, 123.6, 122.2, 119.6, 119.3, 113.5, 113.3, 112.4, 112.1, 111.4, 101.3, 61.3, 56.0, 40.8, 14.4. Exact mass calculated for $C_{21}H_{21}N_2O_3^+$ $[M + H]^+$: 349.1547; found: 349.1550.

*Ethyl 2,2-Di(1H-indol-3-yl)acetate (**24**).*



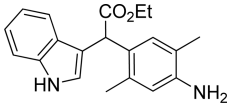
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 2-methylindole (63 mg, 0.48 mmol) provided **25** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a red paste (104 mg, 98%). R_f = 0.2 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3402, 3056, 2981, 2933, 1720. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.78 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.25−6.96 (m, 6H), 6.90 (d, *J* = 1.4 Hz, 1H), 5.40 (d, *J* = 1.3 Hz, 1H), 4.28−4.05 (m, 2H), 2.25 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*)δ 173.1, 136.1, 134.9, 132.6, 127.7, 126.7, 123.2, 121.7, 120.7, 119.5, 119.2, 119.1, 118.6, 113.2, 111.0, 110.1, 108.1, 60.8, 40.0, 14.0, 11.8.). Exact mass calculated for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$: 333.1598; found: 333.1607.

*Ethyl 2-(4-Aminophenyl)-2-(1H-indol-3-yl)acetate (**25**).*[3e]



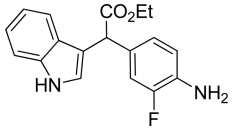
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and aniline (45 mg, 0.48 mmol) provided **26** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a brown solid (88 mg, 93%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3410, 3062, 2980, 2924, 1720. mp = 147−149 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.44 (dq, *J* = 7.9, 1.0 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.15−7.10 (m, 1H), 7.06−7.02 (m, 2H), 6.57 (d, *J* = 8.5 Hz, 2H), 5.14−5.08 (m, 1H), 4.25−4.10 (m, 2H), 3.56 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.5, 145.4, 136.3, 129.3, 128.6, 126.6, 123.1, 122.1, 119.5, 119.1, 115.2, 114.2, 111.2, 61.0, 48.2, 14.2. Exact mass calculated for $C_{18}H_{19}N_2O_2^+$ $[M + H]^+$: 295.1441; found: 295.1448.

*Ethyl 2-(4-Amino-2,5-dimethylphenyl)-2-(1H-indol-3-yl)acetate (**26**).*



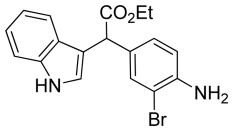
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 2,5-dimethylaniline (58 mg, 0.48 mmol) provided **27** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a gray paste (96 mg, 97%). R_f = 0.2 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3386, 2978, 2925, 1722, 1627, 1574. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.94 (s, 2H), 6.48 (s, 1H), 5.22 (s, 1H), 4.19−4.06 (m, 2H), 3.57 (br s, 2 H), 2.24 (s, 3H), 1.97 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 172.6, 141.6, 135.3, 133.7, 129.2, 126.4, 125.8, 122.5, 121.1, 119.5, 118.5, 117.9, 116.4, 113.3, 110.1, 59.9, 43.5, 18.3, 16.0, 13.2. Exact mass calculated for $C_{20}H_{23}N_2O_2^+$ $[M + H]^+$: 323.1754; found: 323.1765.

*Ethyl 2-(4-Amino-3-fluorophenyl)-2-(1H-indol-3-yl)acetate (**27**).*



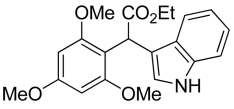
According to the general procedure **II**, **18** (100 mg, 0.33 mmol) and 2-fluoroaniline (53 mg, 0.5 mmol) provided **28** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a pink paste (84 mg, 84%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3384, 3057, 2981, 2926, 1721, 1636. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.22−7.16 (m, 2H), 7.11−7.03 (m, 2H), 7.00 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.73−6.66 (m, 1H), 5.13 (s, 1H), 4.22 (qd, *J* = 7.2, 3.1 Hz, 2H), 3.67 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.2, 151.65 (d, *J* = 239.0 Hz), 136.4,133.62 (d, *J* = 13.2 Hz), 129.50 (d, *J* = 6.2 Hz), 126.6, 124.5, 123.2, 122.4, 119.8, 119.1, 116.84 (d, *J* = 3.9 Hz), 115.47 (d, *J* = 19.6 Hz), 113.8, 111.4, 61.3, 48.1, 14.3. Exact mass calculated for $C_{18}H_{18}FN_2O_2^+$ $[M + H]^+$:313.1347; found: 313.1350.

*Ethyl 2-(4-Amino-3-bromophenyl)-2-(1H-indol-3-yl)acetate (**28**).*



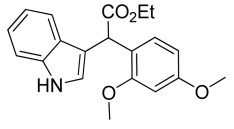
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 2-bromoaniline (83 mg, 0.48 mmol) provided **29** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a red paste (83 mg, 50%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3377, 3056, 2980, 2927, 1721, 1619. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (s, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.18 (s, 1H), 7.12−7.06 (m, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 5.02 (s, 1H), 4.13 (qd, *J* = 7.1, 4.1 Hz, 2H), 3.96 (s, 2H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 171.9, 142.1, 135.2, 131.2, 128.8, 127.4, 125.5, 122.0, 121.3, 118.7, 118.0, 114.6, 112.7, 110.2, 108.2, 60.1, 46.7, 13.2. Exact mass calculated for $C_{18}H_{18}BrN_2O_2^+$ $[M + H]^+$: 373.0546; found: 373.0554.

*Ethyl 2-(1H-Indol-3-yl)-2-(2,4,6-trimethoxyphenyl)acetate (**29**).*



According to the general procedure **II**, **18** (100 mg, 0.33 mmol) and 1,3,5-trimethoxybenzene (81 mg, 0.5 mmol) provided **30** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a light brown solid (110 mg, 93%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3402, 2938, 2840, 1730, 1609, 1595. mp = 119−122 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.01 (s, 1H), 7.72−7.67 (m, 1H), 7.29−7.24 (m, 1H), 7.14−7.08 (m, 2H), 7.00 (d, *J* = 2.0, 1H), 6.16 (s, 2H), 5.67 (s, 1H), 4.27 (dq, *J* = 10.8, 7.1, 1H), 4.14 (dq, *J* = 10.7, 7.1, 1H), 3.81−3.80 (m, 3H), 3.79 (s, 6H), 1.21 (t, *J* = 7.1, 3H). ^{13}C{1H}NMR (100 MHz, Chloroform-*d*) δ 173.9, 160.2, 158.3, 136.0, 127.8, 123.7, 121.5, 119.5, 119.2, 113.8, 111.1, 110.6, 91.0, 60.7, 55.8, 55.4, 37.1, 14.5. Exact mass calculated for $C_{21}H_{23}NO_5^+$ $[M]^+$: 369.1571; found: 369.1574.

*Ethyl 2-(2,4-Dimethoxyphenyl)-2-(1H-indol-3-yl)acetate (**30**).*



DOI: 10.1021/acs.joc.5b02383
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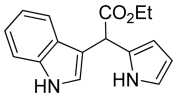
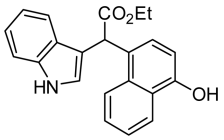
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 1,3-dimethoxybenzne (66 mg, 0.48 mmol) provided **31** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a yellowish paste (53 mg, 49%). R_f = 0.2 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3407, 3058, 2927, 2824, 1720. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.21−7.16 (m, 1H), 7.15 (s, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.35 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.48 (s, 1H), 4.26−4.14 (m, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 1.24 (t, *J* = 7.1, 3H). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.7, 160.0, 157.9, 136.4, 129.8, 127.0, 123.3, 122.3, 120.2, 119.7, 119.6, 113.3, 111.2, 104.1, 98.5, 60.9, 55.6, 55.4, 42.0, 14.4. Exact mass calculated for $C_{20}H_{22}NO_4^+$ $[M + H]^+$: 340.1543; found: 340.1544.

*Ethyl 2-(1H-Indol-3-yl)-2-(1H-pyrrol-2-yl)acetate (**31**).*



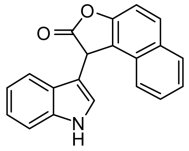
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and pyrrole (32 mg, 0.48 mmol) provided **32** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a dark red paste (57 mg, 67%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3405, 3057, 2980, 2923, 1721. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 8.09 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.22−7.17 (m, 1H), 7.13−7.07 (m, 2H), 6.75−6.69 (m, 1H), 6.16 (t, *J* = 2.6 Hz, 2H), 5.32 (s, 1H), 4.22 (qd, *J* = 7.1, 0.9 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 171.6, 135.2, 126.7, 125.3, 121.8, 121.4, 118.9, 118.1, 116.4, 112.4, 110.2, 107.2, 106.0, 60.4, 41.2, 13.1. Exact mass calculated for $C_{16}H_{17}N_2O_2^+$ $[M + H]^+$: 269.1285; found: 269.1298.

*Ethyl 2-(4-Hydroxynaphthalen-1-yl)-2-(1H-indol-3-yl)acetate (**32**).*



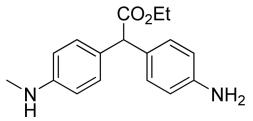
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 1-naphthol (70 mg, 480 μmol) provided **32** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a red paste (78 mg, 71%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3414, 3059, 2980, 2843, 1711. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.28−8.20 (m, 1H), 8.13 (dd, *J* = 7.9 Hz, 1.0, 1H), 8.10 (s, 1H), 7.57−7.38 (m, 3H), 7.36−7.29 (m, 1H), 7.22−7.11 (m, 2H), 7.09−6.99 (m, 2H), 6.48 (d, *J* = 7.9 Hz, 1H), 5.92 (s, 1H), 4.25 (qd, *J* = 7.1, 1.0 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 174.1, 151.3, 136.5, 132.8, 127.0, 126.9, 126.5, 126.5, 125.0, 125.0, 124.1, 123.3, 122.7, 122.4, 119.8, 119.2, 113.5, 111.4, 108.3, 61.5, 45.0, 14.3. Exact mass calculated for $C_{22}H_{20}NO_3^+$ $[M + H]^+$:346.1438; found: 346.1432.

*1-(1H-Indol-3-yl)naphtho[2,1-b]furan-2(1H)-one (**33**).*



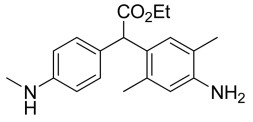
According to the general procedure **II**, **18** (100 mg, 0.32 mmol) and 2-naphthol (70 mg, 480 μmol) provided **33** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a yellowish paste (54 mg, 56%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3410, 2956, 2924, 2854, 1798. ^1H NMR (400 MHz, Chloroform-*d*) δ = 8.19 (s, 1H), 7.91 (dd, *J* = 18.2, 8.4 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.46 (t, *J* = 8.5 Hz, 2H), 7.41−7.30 (m, 3H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 5.49 (s, 1H). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 176.2, 151.8, 136.6, 131.1, 130.5, 129.7, 129.3, 127.5, 126.1, 124.9, 123.7, 123.4, 122.9, 120.4, 119.8, 119.1, 111.6, 111.6, 109.6, 42.1. Exact mass calculated for $C_{20}H_{13}NaNO_2^+$ $[M + Na]^+$:322.0838; found: 322.0845.

*Ethyl 2-(4-Aminophenyl)-2-(4-(methylamino)phenyl)acetate (**34**).*[3e]



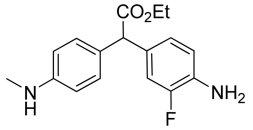
According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and aniline (46 mg, 0.5 mmol) provided **34** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a brown paste (80 mg, 85%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3413, 3375, 2980, 2927, 2813, 1723. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.09 (d, *J* = 19.9 Hz, 4H), 6.58 (dd, *J* = 25.1, 8.3 Hz, 4H), 4.79 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 1H), 2.80 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) (NH protons not observed). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.6, 148.4, 145.4, 129.6, 129.5, 129.4, 128.0, 115.2, 112.5, 60.9, 55.6, 30.9, 14.3. Exact mass calculated for $C_{17}H_{21}N_2O_2^+$ $[M + H]^+$: 285.1598; found: 285.1602.

*Ethyl 2-(4-Amino-2,5-dimethylphenyl)-2-(4-(methylamino)-phenyl)acetate (**35**).*



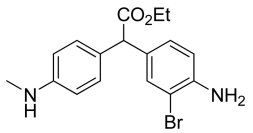
According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and 2,5-diethylaniline (60 mg, 0.5 mmol) provided **35** after flash chromatography (15−25% ethyl acetate in petroleum ether) as an orange solid (89 mg, 86%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3412, 3380, 2981, 2924, 1725. mp = 157−159 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.04 (d, *J* = 8.4 Hz, 2H), 6.91 (s, 1H), 6.54 (d, *J* = 8.6 Hz, 2H), 6.48 (s, 1H), 4.95 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.51 (s, 2H), 2.80 (s, 3H), 2.16 (s, 3H), 2.08 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), (NH proton not observed). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 174.0, 148.3, 143.4, 134.9, 130.2, 129.7, 127.9, 127.5, 120.0, 117.3, 112.5, 60.9, 52.4, 30.9, 19.5, 17.2, 14.3. Exact mass calculated for $C_{19}H_{25}N_2O_2^+$ $[M + H]^+$: 313.1911; found: 313.1916.

*Ethyl 2-(4-Amino-3-fluorophenyl)-2-(4-(methylamino)phenyl)-acetate (**36**).*



According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and 2-fluoroaniline (55 mg, 0.5 mmol) provided **36** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a yellow paste (84 mg, 84%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3379, 2981, 2922, 2851, 1726, 1636. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.14−7.10 (m, 2H), 6.96 (dd, *J* = 12.2, 2.0 Hz, 1H), 6.89−6.83 (m, 1H), 6.69 (dd, *J* = 9.2, 8.1 Hz, 1H), 6.58 (d, *J* = 8.6 Hz, 2H), 4.78 (s, 1H), 4.18 (qd, *J* = 7.1, 0.8 Hz, 2H), 2.82 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), (NH protons not observed). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.2, 151.61 (d, *J* = 239.0 Hz), 148.3, 133.42 (d, *J* = 13.0 Hz), 130.40 (d, *J* = 6.2 Hz), 129.4, 127.8, 124.55 (d, *J* = 3.0 Hz), 116.81 (d, *J* = 3.8 Hz), 115.60 (d, *J* = 19.7 Hz), 112.8, 61.1, 55.5, 31.0, 14.3. Exact mass calculated for $C_{17}H_{19}FN_2O_2^+$ $[M]^+$: 302.1425; found: 302.1435.

*Ethyl 2-(4-Amino-3-bromophenyl)-2-(4-(methylamino)phenyl)-acetate (**37**).*



According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and 2-bromoaniline (85 mg, 0.5 mmol) provided **37** after flash

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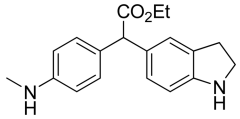
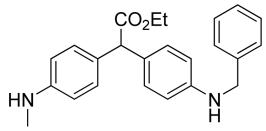
chromatography (15−25% ethyl acetate in petroleum ether) as a brown paste (63 mg, 52%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3376, 3413, 2980, 2928, 2901, 2813, 1725, 1615. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.04 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 8.6 Hz, 2H), 4.74 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 2.80 (s, 4H), 1.23 (t, *J* = 6.8 Hz, 3H). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.2, 148.6, 143.1, 132.5, 130.9, 129.4, 128.7, 127.4, 115.8, 112.6, 109.3, 61.2, 55.2, 30.9, 14.3. Exact mass calculated for $C_{17}H_{19}BrN_2O_2^+$ $[M]^+$: 362.0624; found: 362.0634.

*Ethyl 2-(Indolin-5-yl)-2-(4-(methylamino)phenyl)acetate (**38**).*



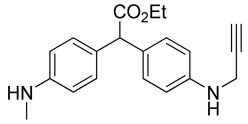
According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and indoline (59 mg, 0.5 mmol) provided **38** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a red paste (82 mg, 80%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3409, 3384, 2978, 2925, 2853, 1727. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.12 (d, *J* = 8.5 Hz, 2H), 7.05 (s, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.55 (dd, *J* = 8.3, 1.8 Hz, 3H), 4.79 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.51 (t, *J* = 8.3 Hz, 2H), 2.97 (t, *J* = 8.3 Hz, 2H), 2.80 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H) (NH proton not observed). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.8, 150.7, 148.4, 130.0, 129.9, 129.4, 128.3, 127.5, 124.9, 112.5, 109.3, 60.9, 55.9, 47.6, 30.9, 30.0, 14.3. Exact mass calculated for $C_{19}H_{23}N_2O_2^+$ $[M + H]^+$: 311.1754; found: 311.1764.

*Ethyl 2-(4-(Benzylamino)phenyl)-2-(4-(methylamino)phenyl)-acetate (**39**).*



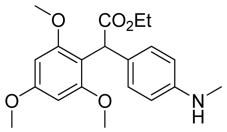
According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and *N*-benzylaniline (60 mg, 0.5 mmol) provided **39** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a brown paste (94 mg, 76%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3414, 3025, 2980, 2926, 2900, 2813, 1725, 1614, 1519. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37−7.27 (m, 5H), 7.12 (dd, *J* = 8.6, 7.0 Hz, 4H), 6.60−6.54 (m, 4H), 4.80 (s, 1H), 4.30 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.81 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H) (NH protons not observed). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.7, 148.4, 147.2, 139.6, 129.5, 129.4, 128.7, 128.6, 128.2, 127.6, 127.3, 112.9, 112.5, 60.9, 55.6, 48.5, 30.9, 14.3. Exact mass calculated for $C_{24}H_{26}N_2O_2^+$ $[M]^+$: 374.1989; found: 374.1985.

*Ethyl 2-(4-(Methylamino)phenyl)-2-(4-(prop-2-ynylamino)-phenyl)acetate (**40**).*



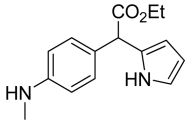
According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and *N*-propargylaniline (65 mg, 0.5 mmol) provided **40** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a yellow paste (92 mg, 86%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3409, 3283, 2923, 1725, 1614, 1519. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.17−7.11 (m, 4H), 6.63 (d, *J* = 8.5 Hz, 2H), 6.56 (d, *J* = 8.6 Hz, 2H), 4.81 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.91 (d, *J* = 2.4 Hz, 2H), 2.81 (s, 3H), 2.21 (t, *J* = 2.3 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H) (NH proton not observed. $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.6, 148.4, 145.9, 129.7, 129.5, 129.4, 128.1, 113.6, 112.5, 81.2, 71.4, 61.0, 55.7, 33.8, 30.9, 14.3. Exact mass calculated for $C_{20}H_{22}N_2O_2^+$ $[M]^+$: 322.1676; found: 322.1685.

*Ethyl 2-(4-(Methylamino)phenyl)-2-(2,4,6-trimethoxyphenyl)-acetate (**41**).*



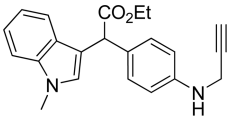
According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and *N*-methylaniline (83 mg, 0.5 mmol) provided **41** after flash chromatography (15−25% ethyl acetate in petroleum ether) as an orange solid (96 mg, 81%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3406, 2935, 2839, 1735. mp = 163−165 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.14 (d, *J* = 8.5 Hz, 2H), 6.56−6.48 (m, 2H), 6.14 (d, *J* = 0.7 Hz, 2H), 5.19 (s, 1H), 4.27−4.07 (m, 2H), 3.80 (s, 3H), 3.77 (s, 6H), 2.78 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H) (NH proton not observed). ^{13}C {1H}NMR (100 MHz, Chloroform-*d*) δ 174.4, 160.2, 158.2, 148.1, 130.1, 128.1, 112.3, 110.5, 91.0, 60.6, 55.8, 55.4, 45.2, 14.5. Exact mass calculated for $C_{20}H_{25}NO_5^+$ $[M]^+$: 359.1727; found: 359.1736.

*Ethyl 2-(4-(Methylamino)phenyl)-2-(1H-pyrrol-2-yl)acetate (**42**).*



According to the general procedure **III**, **19** (100 mg, 0.33 mmol) and pyrrole (33 mg, 0.5 mmol) provided **42** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a dark red paste (56 mg, 66%). R_f = 0.3 (30% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3408, 2981, 2923, 2896, 1723. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.74 (q, *J* = 2.6 Hz, 1H), 6.55 (d, *J* = 8.6 Hz, 2H), 6.15 (q, *J* = 2.8 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 4.94 (s, 1H), 4.19 (qd, *J* = 7.1, 2.5 Hz, 2H), 2.81 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H) (NH proton not observed). $^{13}C\{1H\}$NMR (100 MHz, Chloroform-*d*) δ 173.1, 148.7, 128.8, 128.5, 127.1, 117.6, 112.6, 108.4, 107.3, 61.4, 49.4, 30.9, 14.3. Exact mass calculated for $C_{15}H_{18}N_2O_2^+$ $[M]^+$: 258.1363; found: 258.1355.

*Ethyl 2-(1-Methyl-1H-indol-3-yl)-2-(4-(prop-2-ynylamino)-phenyl)acetate (**43**).*



According to the general procedure **IV**, *N*-methylindole (100 mg, 0.762 mmol) and *N*-propargylaniline (150 mg, 1.14 mmol) provided **43** after flash chromatography (15−25% ethyl acetate in petroleum ether) as a yellow paste (194 mg, 73%). R_f = 0.3 (20% ethyl acetate in petroleum ether). IR (neat): ν_{max}/cm^{-1} 3394, 3283, 3052, 2980, 2934, 1728, 1614. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.35−7.28 (m, 3H), 7.25 (d, *J* = 5.5 Hz, 1H), 7.15−7.05 (m, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 5.19 (s, 1H), 4.31−4.17 (m, 2H), 3.91 (d, *J* = 2.2 Hz, 2H), 3.74 (s, 3H), 2.24 (t, *J* = 1.78 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H) (NH proton not observed). $^{13}C\{1H\}$NMR (125 MHz, Chloroform-*d*) δ 173.5, 146.0, 137.1, 129.3, 128.8, 127.9, 127.2, 121.8, 119.2, 119.1, 113.5, 112.8, 109.3, 81.1, 71.4, 61.0, 48.2, 33.7, 32.7, 14.3. Exact mass calculated for $C_{22}H_{22}N_2O_2^+$ $[M]^+$: 346.1676; found: 346.1681.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02383.

^1H and ^{13}C spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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