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Exploration of Biaryl Carboxylic Acids as Proton Shuttles for the Selective Functionalization of Indole C–H Bonds

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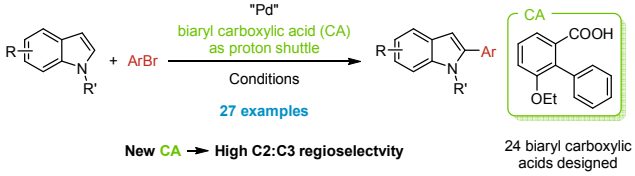
Supporting Information Placeholder



ABSTRACT: A survey of diversely substituted 2-arylbenzoic acid were synthesized and tested for use as proton shuttle in the direct arylation of indoles with bromobenzenes. It was found that 3-ethoxy-2-phenylbenzoic acid gives superior yield and selectivity for this class of substrates.

The direct functionalization of C–H bonds leading to value-added chemicals is a very intense line of research in transition metal catalysis.[1] The possibility to access a variety of functionalized substrates without the requirement for prefunctionalization can contribute to decrease step count, waste and the time necessary to prepare a given target. Over the past couple decades, it has been demonstrated in numerous catalytic systems, (with various metals) that carboxylic acids additives can have a dramatic impact on reactivity when it comes to C–H bond functionalization.[2] The rationale behind most cases is that the acid would bind to the transition metal and mediate the aryl deprotonation in the so-called concerted-metallation-deprotonation (CMD) event.[3] The protonated carboxylic acid is then released in the solution and transfers its proton to a stronger, typically inorganic, base. With regards to palladium, perhaps the most versatile carboxylic acid to perform this task so far is pivalic acid.[4] It is however not the only potent additive discovered for this purpose. In addition to Yu's new system using a modified pyridone[5] and some protected amino acids derivatives,[6] several reports found that the use of 2-substituted benzoic acids as well as bulky aliphatic carboxylic acids can also perform very well in some instances.[7]

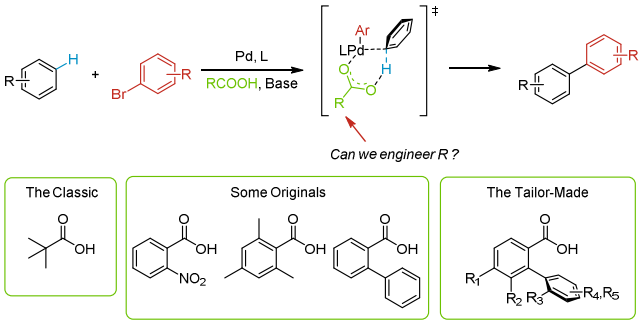
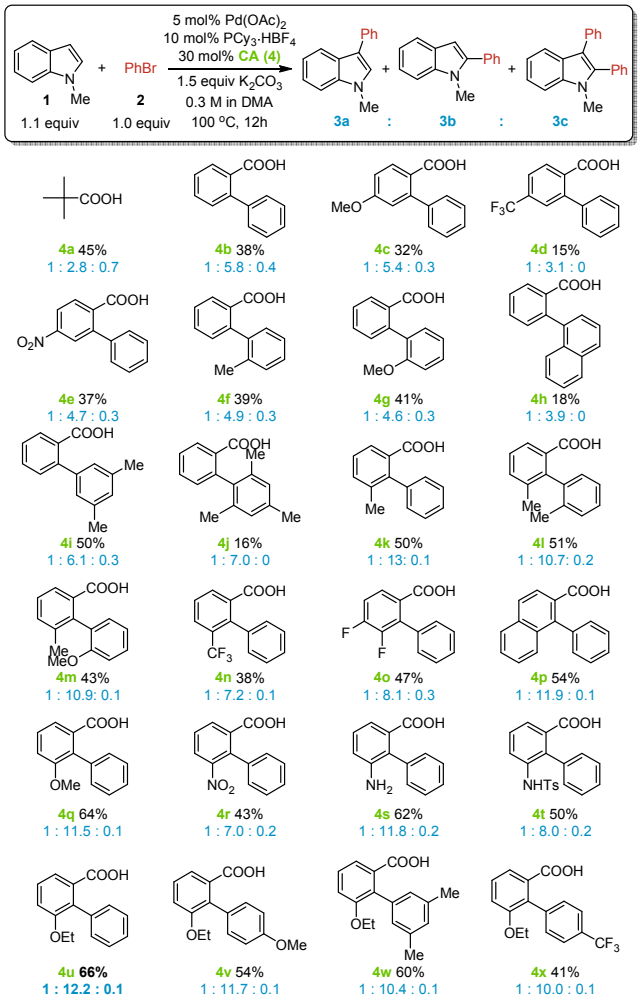


Figure 1. Role of carboxylic acids in C–H functionalization reactions

Given that most carboxylic acids that were employed for such purpose have been simple, commercially available structures, we were curious to see if one could possibly engineer a motif that would perform better, or differently than the ones most commonly employed (Figure 1).[8] With this mindset, we set out to focus our efforts on the biaryl carboxylic acid motif. As an analogy to the Buchwald ligands, which were presumably initially designed on the premise that they would be even bulkier than the very versatile P(t-Bu)3 ligand while being electronically tunable, we were curious to explore this motif for similar reasons. Herein, we report the synthesis and finding of a biaryl carboxylate proton shuttle that allows higher yield and selectivity for the direct arylation of indoles using aryl bromide electrophiles.[9]

In order to find a carboxylic acid that could be more efficient than pivalic acid, a system where the reaction with pivalic acid could be improved upon was necessary. For this purpose, our choice landed on the reaction of N-methylindoles with bromobenzene.[10] Given that the use of pivalic acid for this coupling gives a modest 45% yield and a 2.8:1 C2:C3 arylation regioselectivity, we thought it would be a good starting point to evaluate the performance of various biaryl carboxylic acids. Scheme 1 shows a selection of carboxylic acid we designed, synthesized and tested. We first started our investigation probing the electronic properties of the aromatic ring bearing the carboxylic acid. From this survey, it was impossible to observe any consistent trend relating to the electronic nature of the benzoic acid ring itself. It seems like both electron- rich (**4c**) and electron poor (**4d**, **4e**) carboxylic acids performed worse than the naked 2-phenylbenzoic acid (**4b**). While trying successively various different set of substitution, we noticed that a substituent at the 3-position of the benzoic acid had a pronounced positive impact on both the regioselectivity of arylation as well as the yield. Perhaps this substitution twists the second aromatic ring out of conjugation, so that it sits perpendicular to the benzoic acid. Interestingly, placing an *ortho*-substituent on this 2-aryl moiety to force this same type of conformation only resulted in diminished reactivity and regioselectivity.

Scheme 1. Evaluation of Biarylcarboxylic Acids[a]



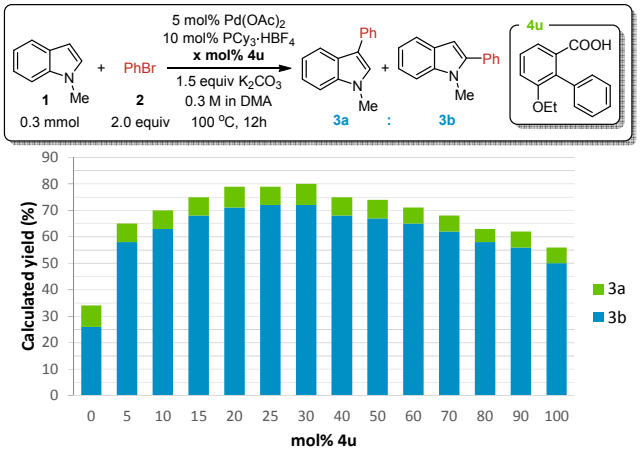
[a]Conditions: Aryl halide (0.3 mmol), *N*-methylindole (1.1 eq.), $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), carboxylic acid (0.3 eq.), K_2CO_3 (1.5 eq.) in DMA (0.3 M), 100 °C, 12 h. Calculated yields by GC-MS using benzophenone as internal standard.

Among the substituents tested at the 3-position, both the methoxy and the free amine gave significantly higher yields and regioselectivities than what we obtained with the pivalic acid system. In this case, a substituent with an electron donating group is beneficial. We also observed that an ethoxy group (**4u**) performed slightly better than the corresponding methoxy (**4q**). Thus, **4u** gave us a yield of 66%, and a 12.2:1 regioselectivity. This carboxylic acid performing significantly better than pivalic acid for this cross-coupling, we revisited some reaction parameters to improve the yield of the direct arylation. We thus established that increasing the amount of aryl bromide equivalents to 2 allowed the calculated yield to go from 66% to 81%.

The impact of the carboxylic acid loading on the reaction outcome was also studied. Scheme 2 shows the results obtained for the reaction of *N*-methylindole with bromobenzene. It is interesting to note that going from no carboxylic acid to 5 mol%, the calculated yield almost doubles. Adding more **4u** helps improving the yield of the

major regioisomer up to 72%. Amounts ranging from 20 mol% to 30 mol% provided the best results. Of note, regardless of the amount of the carboxylic acid used, roughly 7% of the regioisomer **3a** was obtained in all cases. This is perhaps due to a background reaction occurring either with the 10 mol% acetate contained in the reaction due to the presence of Pd(OAc)2 or with the carbonate base in solution.

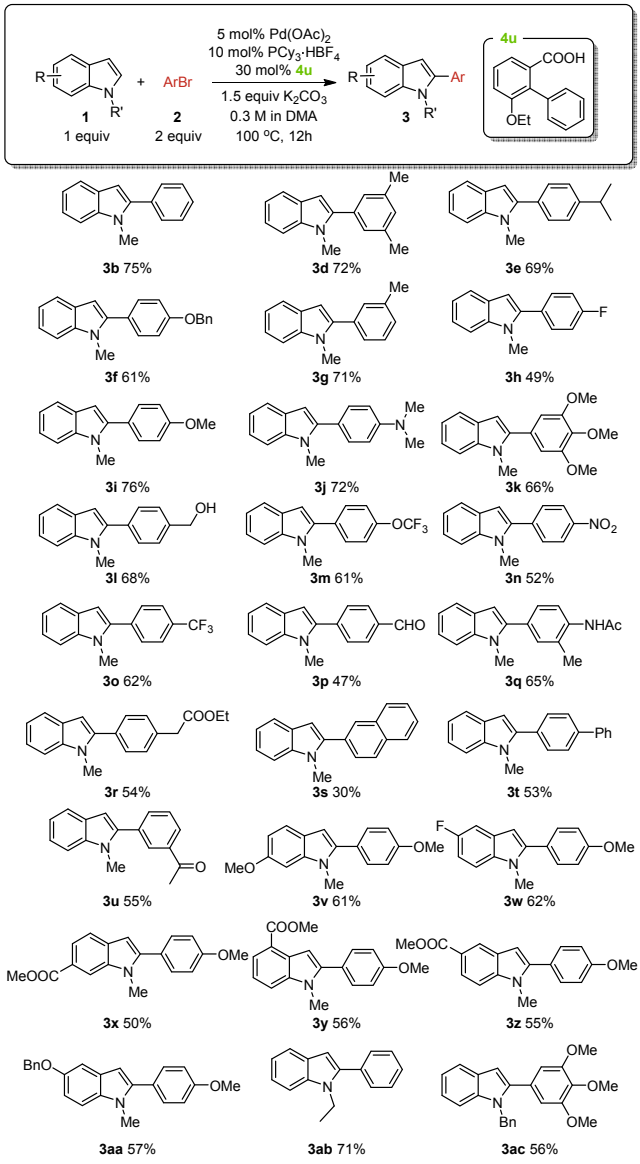
Scheme 2. Influence of Carboxylic Acid Loading on Reaction Outcome



[a]Conditions: *N*-methylindole (0.3 mmol), Aryl halide (2.0 eq.), $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), carboxylic acid **4u** (x eq.), K_2CO_3 (1.5 eq.) in DMA (0.3 M), 100 °C, 12 h. Calculated yields by GC-MS using benzophenone as internal standard.

With these conditions in hand, we then explored the scope of this regioselective indole direct arylation (scheme 3). While keeping the indole coupling partner constant, the reaction proved to be quite reliable with a variety of *para*- or *meta*-substituted aryl bromides. Both electron-donating as well as electron-withdrawing group were generally well tolerated. Functional groups such as methoxy (**3i**, **3k**), free alcohol (**3l**), nitro (**3n**), amine (**3j**), aldehyde (**3p**), ester (**3r**) and ketone (**3u**) were also suitable for the reaction. As exceptions however, the use of 3 or 4-bromo-benzonitrile was not tolerated.[11] With regards to the indole coupling partner, C4-, C5- and C-6-substitutions were also tolerated. The presence of electron-withdrawing and –donating groups had little impact on the positive outcome, providing yields ranging from 50-62%. Some other alkyl substitutions are also possible on the indole's nitrogen. For example, an ethyl (**3ab**) and a benzyl (**3ac**) group were compatible. The presence of protecting groups such as acyl or tosyl however suppressed the reactivity towards C–H functionalization.

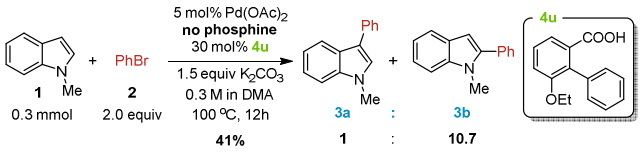
Scheme 3. Palladium-Catalyzed Regioselective C-2 Indole Arylation



[a]Conditions: *N*-methylindole derivative (0.3 mmol), Aryl halide (2.0 eq.), $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), carboxylic acid **4u** (0.3 eq.), K_2CO_3 (1.5 eq.) in DMA (0.3 M), 100 °C, 12 h. Isolated yields of the major regioisomer are shown.

It was demonstrated by Hartwig in 2011[12] that there are some cases of C–H functionalization reactions proceeding via CMD where the phosphine ligand is actually superfluous. In such scenarios, it is likely that the carboxylate acts as main ligand. It is thus conceivable that the use of a bulky carboxylic acid with a biaryl motif like the ones prepared in this study could act both as ligand and proton shuttle. With this mindset, a reaction was attempted without additional ligand. The results are shown in Scheme 4. A yield of 40% was obtained with a regioselectivity similar to the one we obtain in the presence of a phosphine ligand. These results correlate well with the study from Hartwig, suggesting that the role of the phosphine ligand in this case might be simply to provide some stability to the palladium in off-catalytic cycle intermediates.

Scheme 4. Phosphine-Free Direct Arylation



In summary, we designed a library of biarylcarboxylic acids proton shuttles in the hope of finding a structural motif that would allow better yield and selectivity in the C2-direct arylation of indole. We found that an electron-donating substituent at the 3-position of the 2-arylbenzoic acid additive increased both the parameters significantly. The generality of this approach was then demonstrated with a variety of indole and aryl bromides. We hope that this report will trigger further interest in the development of tunable proton shuttles for application in diverse C–H functionalization reactions.

Experimental Section

General information. All the reactions were carried out in oven-dried Schlenk tubes under argon atmosphere. The following chemicals were purchased and used as received: Palladium diacetate (Sigma-Aldrich), Tricyclohexylphosphonium tetrafluoroborate (Sigma-Aldrich), Potassium carbonate (Sinopharm Chemical Reagent Co., Ltd), N,N-Dimethylacetamide (J&K), 1-Methylindole (Adamas-beta,), Bromobenzene (Sinopharm Chemical Reagent Co., Ltd,), Pivalic acid (Ding Chemistry), 3-Nitro-2-phenylbenzoic acid (Hopschem), Bromoethane (Energy Chemical), 2-Bromo-3-hydroxybenzaldehyde (Bide Pharmatech Ltd), 6-Methoxyindole (Meryer), 5-Fluoroindole (Adamas-beta), Methyl 1-Methylindole-6-carboxylate (Accela), Methyl 1-methyl-1H-indole-4-carboxylate (Bide Pharmatech Ltd), Methyl indole-5-carboxylate (J&K), 5-(Benzyloxy)indole (Adamas-beta). All other commercial reagents were purchased from commercial vendors and used without further purification unless otherwise noted. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer at 295 K in $CDCl_3$ unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra of compound **4s** were recorded on a Bruker 400 MHz spectrometer at 295 K in DMSO-d_6. ^{19}F NMR were reported as 19F exp. comp. pulse decoupling (F19CPD) unless otherwise noted. HRMS analysis was performed on Finnigan LCQ advantage Max Series MS System. Gas chromatographic (GC) analysis was acquired on a Shimadzu GC-2010 plus Series GC system equipped with a flame-ionization detector. Infrared spectra were recorded on a Nicolet 8700 (Thermo Scientific Instrument Co. U.S.A) Fourier Transform Infrared Spectrometer (FT-IR), and were reported in wave numbers (cm^{-1}). Melting point was performed on X-4 Melting-point Apparatus with Microscope. HRMS were recorded with an Orbitrap analyser. Organic solutions were concentrated under reduced pressure on Buchi rotary evaporator. Column chromatographic purification of products was accomplished using forced-flow chromatography on Silica Gel (300-400 mesh).

General procedure for palladium-catalyzed indole arylation using various carboxylic acids (Scheme 1): $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), carboxylic acid **4** (30 mol%) and K_2CO_3 (1.5 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with argon (three cycles). To these solids, DMA (0.3 M), bromobenzene (1.0 equiv, 0.3 mmol) and 1-methylindole (1.1 equiv, 0.33 mmol) were added consecutively under a positive flow of argon. The reaction mixture was stirred at 100°C for 12 hours. The yield was determined by GC with benzophenone as internal standard.

General procedure for the evaluation of different 4u loading on the reaction outcome (Scheme 2) $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), carboxylic acid **4u** (x mol%) and K_2CO_3 (1.5 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with argon (three cycles). To these solids, DMA (0.3 M), bromobenzene (2.0 equiv, 0.6 mmol) and 1-methylindole (1.0 equiv, 0.3 mmol) were added consecutively under a positive flow of argon. The reaction mixture was stirred at 100°C for 12 hours. The yield was determined by GC using benzophenone as internal standard.

General procedure for palladium-catalyzed regioselective indole arylation (Scheme 3): $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), carboxylic acid **4u** (30 mol%) and K_2CO_3 (1.5 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and backfilled with argon (three cycles). To these solids, DMA (0.3 M), aryl bromide (2.0 equiv.) and indole (0.3 mmol) (if the indole is a solid, it was added together with $Pd(OAc)_2$) were added consecutively under a positive flow of argon. The reaction mixture was stirred at 100 °C for 12 hours. In order to remove DMA, the reaction mixture was poured into 50 mL of ice water and the resulting mixture was extracted with ethyl acetate (4 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo and purified by column chromatography.

2-phenyl-1-methylindole (3b). The compound was prepared following the general procedure using 1-methylindole and bromobenzene as reactants. The product was isolated by column chromatography (PE:EA = 100:1) as a light yellow solid (46.6 mg, 75%). Spectral data is consistent with previous reports.[13] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.48 – 7.42 (m, 2H), 7.42 – 7.33 (m, 2H), 7.28 – 7.21 (m, 1H), 7.17 – 7.11 (m, 1H), 6.56 (s, 1H), 3.72 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.7, 138.5, 133.0, 129.5, 128.6, 128.1, 128.0, 121.8, 120.6, 120.0, 109.7, 101.8, 31.3. **HRMS (APCI)** calcd for $C_{15}H_{14}N^+$ [(M+H)$^+$]: 208.1121; found: 208.1120.

2-(3,5-dimethylphenyl)-1-methylindole (3d). The compound was prepared following the general procedure using 1-methylindole and 1-bromo-3,5-dimethylbenzene as reactants. The product was isolated by column chromatography (PE:EA = 100:1) as a light yellow solid (50.8 mg, 72%). Spectral data is consistent with previous reports.[14] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.22 (dd, 1H), 7.13 (d, *J* = 10.2 Hz, 3H), 7.04 (s, 1H), 6.52 (s, 1H), 3.73 (s, 3H), 2.38 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.0, 138.4, 138.1, 132.9, 129.7, 128.2, 127.3, 121.6, 120.5, 119.9, 109.7, 101.6, 31.3, 21.5. **HRMS (APCI)** calcd for $C_{17}H_{18}N^+$ [(M+H)$^+$]: 236.1434; found: 236.1436.

2-(4-isopropylphenyl)-1-methylindole (3e). The compound was prepared following the general procedure using 1-methylindole and 1-bromo-4-isopropylbenzene as reactants. The product was isolated by column chromatography (PE:EA

= 100:1) as a light yellow solid (51.6 mg, 69%). Spectral data is consistent with previous reports.[15] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.32 (dd, *J* = 10.7, 8.3 Hz, 3H), 7.25 – 7.20 (m, 1H), 7.16 – 7.10 (m, 1H), 6.53 (s, 1H), 3.72 (s, 3H), 2.96 (hept, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H **^{13}C NMR (101 MHz, $CDCl_3$)** δ 148.8, 141.8, 138.4, 130.4, 129.4, 128.1, 126.7, 121.6, 120.5, 119.9, 109.7, 101.4, 34.1, 31.3, 24.1. **HRMS (APCI)** calcd for $C_{18}H_{20}N^+$ [(M+H)$^+$]: 250.1590; found: 250.1595.

2-(4-(benzyloxy)phenyl)-1-methylindole (3f). The compound was prepared following the general procedure using 1-methylindole and 1-(benzyloxy)-4-bromobenzene as reactants. The product was isolated by column chromatography (PE:EA = 50:1) as a light yellow solid (57.4 mg, 61%). Spectral data is consistent with previous reports.[16] **^{1}H NMR (400 MHz, CDCl3)** δ 7.61 (d, J = 7.8 Hz, 1H), 7.48 – 7.37 (m, 6H), 7.33 (dd, J = 7.6, 5.0 Hz, 2H), 7.25 – 7.18 (m, 1H), 7.15 – 7.10 (m, 1H), 7.07 – 7.03 (m, 2H), 6.49 (s, 1H), 5.09 (s, 2H), 3.69 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.8, 141.5, 138.3, 136.9, 130.7, 128.8, 128.2, 128.1, 127.6, 125.6, 121.5, 120.4, 119.9, 115.0, 109.6, 101.2, 70.2, 31.2. **HRMS (APCI)** calcd for C22H20NO$^+$ [(M+H)$^+$]: 314.1539; found: 314.1543.

1-methyl-2-(*m*-tolyl)-indole (3g). The compound was prepared following the general procedure using 1-methylindole and 1-(benzyloxy)-4-bromobenzene as reactants. The product was isolated by column chromatography (PE:EA = 100:1) as a light yellow solid (47.1 mg, 71%). Spectral data is consistent with previous reports.[17] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.33 (ddd, *J* = 17.0, 11.0, 6.4 Hz, 4H), 7.25 – 7.19 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.55 (s, 1H), 3.74 (s, 3H), 2.43 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.9, 138.4, 138.3, 132.9, 130.2, 128.8, 128.5, 128.1, 126.6, 121.7, 120.6, 119.9, 109.7, 101.6, 31.3, 21.7. **HRMS (APCI)** calcd for $C_{16}H_{16}N^+$ [(M+H)$^+$]: 222.1277; found: 222.1279.

2-(4-fluorophenyl)-1-methylindole (3h). The compound was prepared following the general procedure using 1-methylindole and 1-bromo-4-fluorobenzene as reactants. The product was isolated by column chromatography (PE:EA = 100:1) as a light yellow solid (33.1 mg, 49%). Spectral data is consistent with previous reports.[18] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.18 – 7.10 (m, 3H), 6.52 (s, 1H), 3.70 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.7 (d, *J* = 247.7 Hz), 140.6, 138.4, 131.2 (d, *J* = 8.1 Hz), 129.0 (d, *J* = 3.3 Hz), 128.0, 121.9, 120.6, 120.1, 115.7 (d, *J* = 21.6 Hz), 109.8, 101.8, 31.2. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -113.80 (s). **HRMS (APCI)** calcd for $C_{15}H_{13}FN^+$ [(M+H)$^+$]: 226.1027; found: 226.1029.

2-(4-methoxyphenyl)-1-methylindole (3i). The compound was prepared following the general procedure using 1-methylindole and 1-bromo-4-methoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 50:1) as a light yellow solid (54.1 mg, 76%). Spectral data is consistent with previous reports.[19] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.23 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.04 – 6.99 (m, 2H), 6.51 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.6, 141.6, 138.3, 130.8, 128.1, 125.4, 121.5, 120.4, 119.9, 114.1, 109.6, 101.1, 55.5, 31.2. **HRMS (APCI)** calcd for $C_{16}H_{16}NO^+$ [(M+H)$^+$]: 238.1226; found: 238.1228.

***N,N*-dimethyl-4-(1-methylindol-2-yl)aniline (3j).** The compound was prepared following the general procedure using 1-methylindole and 4-bromo-*N,N*-dimethylaniline as reactants. The product was isolated by column chromatography (PE:EA = 10:1) as a light yellow solid (54.1 mg, 72%). Spectral data is consistent with previous reports.[20] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 8.8, 1.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.14 – 7.08 (m, 1H), 6.78 (dd, *J* = 8.7, 1.5 Hz, 2H), 6.47 (d, *J* = 2.3 Hz, 1H), 3.70 (s, 3H), 2.98 (s, 6H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.2, 142.4, 138.2, 130.4, 128.3, 121.1, 120.7, 120.1, 119.7, 112.2, 109.5, 100.4, 40.6, 31.2. **HRMS (APCI)** calcd for $C_{17}H_{19}N_2^+$ [(M+H)$^+$]: 251.1543; found: 251.1546.

1-methyl-2-(3,4,5-trimethoxyphenyl)-indole (3k). The compound was prepared following the general procedure using 1-methylindole and 5-bromo-1,2,3-trimethoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow solid (58.9 mg, 66%). Spectral data is consistent with previous reports.[21] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.27 (ddd, *J* = 8.2, 5.7, 1.2 Hz, 1H), 7.19 – 7.13 (m, 1H), 6.73 (s, 2H), 6.57 (s, 1H), 3.94 (s, 3H), 3.92 (s, 6H), 3.77 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 153.3, 141.6, 138.4, 138.1, 128.5, 127.9, 121.8, 120.5, 120.1, 109.7, 106.8, 101.5, 61.1, 56.3, 31.3. **HRMS (APCI)** calcd for $C_{18}H_{20}NO_3^+$ [(M+H)$^+$]: 298.1438; found: 298.1439.

(4-(1-methylindol-2-yl)phenyl)methanol (3l). The compound was prepared following the general procedure using 1-methylindole and (4-bromophenyl)methanol as reactants. The product was isolated by column chromatography (PE:EA = 5:1) as a light yellow solid (48.4 mg, 68%). Spectral data is consistent with previous reports.[22] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.35 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.17 – 7.11 (m, 1H), 6.56 (d, *J* = 0.5 Hz, 1H), 4.74 (s, 2H), 3.73 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.34, 140.60, 138.48, 132.27, 129.62, 128.03, 127.22, 121.84, 120.58, 120.01, 109.74, 101.81, 65.11, 31.30. **IR (neat/cm^{-1})** 3345, 3053, 3026, 2939, 2916, 1611, 1498, 1465, 1431, 1412, 1382, 1359, 1340, 1316, 1043, 1020, 1006, 825, 783, 751, 734. **HRMS (APCI)** calcd for $C_{16}H_{16}NO^+$ [(M+H)$^+$]: 238.1226; found: 238.1230.

1-methyl-2-(4-(trifluoromethoxy)phenyl)-indole (3m). The compound was prepared following the general procedure using 1-methylindole and 1-bromo-4-(trifluoromethoxy)benzene as reactants. The product was isolated by column chromatography (PE:EA = 50:1) as a light yellow solid (53.3 mg, 61%) **M. P.** 76.5-77.8 °C **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.28 (m, 1H), 7.22 – 7.18 (m, 1H), 6.60 (s, 1H), 3.76 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 149.0, 140.1, 138.6, 131.7, 130.8, 128.0, 122.2, 121.2, 120.8, 120.7 (q, *J* = 257.5 Hz), 120.2, 109.8, 102.3, 31.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -57.68 (s). **IR (neat/cm^{-1})** 3054, 2945, 1541, 1497, 1478, 1466, 1434, 1341, 1317, 1306, 1260, 1224, 1204, 1172, 1166, 1101, 860, 784, 751, 744, 736. **HRMS (APCI)** calcd for $C_{16}H_{13}F_3NO^+$ [(M+H)$^+$] 292.0944, found 292.0948.

1-methyl-2-(4-nitrophenyl)-indole (3n). The compound was prepared following the general procedure using 1-methylindole and 1-bromo-4-nitrobenzene as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow solid (39.4 mg, 52 %). Spectral data is consistent with previous reports.[23] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.39 – 8.27 (m, 2H), 7.73 – 7.64 (m, 3H), 7.41 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.22 – 7.15 (m, 1H), 6.72 (d, *J* = 0.6 Hz, 1H), 3.81 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.10, 139.36, 139.04, 129.62, 127.82, 124.03, 123.10, 121.16, 120.60, 110.03, 104.20, 31.71. **IR (neat/cm^{-1})** 3057,

2920, 2849, 1560, 1533, 1510, 1465, 1454, 1343, 1318, 1107, 866, 854, 791, 750, 704, 696. **HRMS (APCI)** calcd for $C_{15}H_{13}N_2O_2^+$ [(M+H)$^+$]: 253.0972; found: 253.0980.

1-methyl-2-(4-(trifluoromethyl)phenyl)-indole (3o). The compound was prepared following the general procedure using 1-methylindole and 1-bromo-4-(trifluoromethyl)benzene as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow solid (51.2 mg, 62 %). Spectral data is consistent with previous reports.[18] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.65 (t, *J* = 8.7 Hz, 3H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.22 – 7.15 (m, 1H), 6.64 (s, 1H), 3.78 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 139.7, 138.7, 136.4, 129.8 (q, *J* = 32.5 Hz), 129.4, 127.8, 125.5 (q, *J* = 3.7 Hz), 122.4, 121.8 (q, *J* = 205.8 Hz), 120.8, 120.2, 109.8, 102.8, 31.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -62.51 (s). **HRMS (APCI)** calcd for $C_{16}H_{13}F_3N^+$ [(M+H)$^+$]: 276.0995; found: 276.1000.

4-(1-methylindol-2-yl)benzaldehyde (3p). The compound was prepared following the general procedure using 1-methylindole and 4-bromobenzaldehyde as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow solid (33.2 mg, 47 %). Spectral data is consistent with previous reports.[24] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.08 (s, 1H), 8.08 – 7.91 (m, 2H), 7.73 – 7.61 (m, 3H), 7.40 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.31 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.22 – 7.13 (m, 1H), 6.70 (d, *J* = 0.5 Hz, 1H), 3.80 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.9, 139.1, 138.2, 137.9, 134.4, 129.1, 128.6, 126.9, 121.7, 120.0, 119.4, 109.0, 102.6, 30.7. **IR (neat/cm^{-1})** 3052, 2922, 2852, 2735, 1702, 1604, 1567, 1466, 1389, 1359, 1341, 1318, 1305, 1207, 1168, 843, 786, 750. **HRMS (APCI)** calcd for $C_{16}H_{14}NO^+$ [(M+H)$^+$]: 236.1070; found: 236.1074.

***N*-(2-methyl-4-(1-methylindol-2-yl)phenyl)acetamide (3q).** The compound was prepared following the general procedure using 1-methylindole and *N*-(4-bromo-2-methylphenyl)acetamide as reactants. The product was isolated by column chromatography (PE:EA = 2:1) as a light yellow solid (54.3 mg, 65 %). **M. P.** 162.0-163.5 °C **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 – 7.83 (m, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.27 – 7.21 (m, 1H), 7.13 (t, *J* = 7.4 Hz, 2H), 6.51 (s, 1H), 3.72 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.6, 141.2, 138.4, 135.5, 131.5, 129.8, 129.4, 128.0, 127.8, 123.4, 121.7, 120.5, 119.9, 109.7, 101.6, 31.3, 24.5, 18.0. **IR (neat/cm^{-1})** 3274, 3050, 2922, 1666, 1612, 1587, 1518, 1465, 1433, 1369, 1339, 1301, 1266, 1242, 1009, 837, 784, 751, 736, 702. **HRMS (APCI)** calcd for $C_{18}H_{19}N_2O^+$ [(M+H)$^+$]: 279.1492; found: 279.1496.

ethyl 2-(4-(1-methylindol-2-yl)phenyl)acetate (3r). The compound was prepared following the general procedure using 1-methylindole and ethyl 2-(4-bromophenyl)acetate as reactants. The product was isolated by column chromatography (PE:EA = 10:1) as a light yellow solid (47.5 mg, 54 %) **M. P.** 64.3-66.2 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.41 – 7.31 (m, 3H), 7.23 (dd, *J* = 14.2, 6.1 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.55 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.66 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.5, 141.3, 138.5, 134.0, 131.7, 129.6, 129.5, 128.1, 121.8, 120.6, 120.0, 109.7, 101.8, 61.1, 41.2, 31.3, 14.3. **IR (neat/cm^{-1})** 3053, 2979, 2936, 1734, 1611, 1502, 1465, 1431, 1415, 1385, 1367, 1339, 1315, 1251, 1223, 1157, 1031, 826, 781, 750, 736. **HRMS (APCI)** calcd for $C_{19}H_{20}NO_2^+$ [(M+H)$^+$]: 294.1489; found: 294.1490.

1-methyl-2-(naphthalen-2-yl)indole (3s). The compound was prepared following the general procedure using 1-methylindole and 2-bromonaphthalene as reactants. The product was isolated by column chromatography (PE:EA = 100:1) as a light yellow solid (23.2 mg, 30 %) Spectral data is consistent with previous reports.[25] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.03 – 7.90 (m, 4H), 7.69 (dd, *J* = 15.3, 8.1 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.71 (s, 1H), 3.84 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.7, 138.6, 133.4, 132.8, 130.3, 128.4, 128.3, 128.2, 128.2, 127.9, 127.3, 126.7, 126.5, 121.9, 120.6, 120.1, 109.8, 102.2, 31.5. **HRMS (APCI)** calcd for $C_{19}H_{16}N^+$ [(M+H)$^+$]: 258.1277; found: 258.1279.

2-([1,1'-biphenyl]-4-yl)-1-methylindole (3t). The compound was prepared following the general procedure using 1-methylindole and 4-bromo-1,1'-biphenyl as reactants. The product was isolated by column chromatography (PE:EA = 100:1) as a light yellow solid (45.1 mg, 53 %) Spectral data is consistent with previous reports.[26] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 – 7.67 (m, 2H), 7.65 (dd, *J* = 5.2, 3.3 Hz, 3H), 7.61 – 7.55 (m, 2H), 7.47 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.41 – 7.34 (m, 2H), 7.29 – 7.23 (m, 1H), 7.19 – 7.11 (m, 1H), 6.61 (s, 1H), 3.78 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.3, 140.8, 140.6, 138.6, 131.8, 129.8, 129.0, 128.1, 127.7, 127.3, 127.2, 121.9, 120.6, 120.0, 109.8, 101.9, 31.4. **HRMS (APCI)** calcd for $C_{21}H_{18}N^+$ [(M+H)$^+$]: 284.1434; found: 284.1438.

1-(3-(1-methylindol-2-yl)phenyl)ethan-1-one (3u). The compound was prepared following the general procedure using 1-methylindole and 1-(3-bromophenyl)ethan-1-one as reactants. The product was isolated by column chromatography (PE:EA = 40:1) as a light yellow oil (41.1 mg, 55 %) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.11 (t, *J* = 1.6 Hz, 1H), 8.03 – 7.94 (m, 1H), 7.75 – 7.69 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.20 – 7.12 (m, 1H), 6.62 (s, 1H), 3.76 (s, 3H), 2.66 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 198.0, 140.4, 138.6, 137.5, 133.9, 133.5, 129.2, 129.0, 128.0, 127.8, 122.2, 120.8, 120.2, 109.8, 102.4, 31.4, 26.9. **IR (neat/cm^{-1})** 3055, 2923, 2852, 1686, 1602, 1580, 1538, 1464, 1418, 1385, 1356, 1341, 1315, 1279, 1266, 1237, 1201, 783, 750, 736, 696, 589. **HRMS (APCI)** calcd for $C_{17}H_{16}NO^+$ [(M+H)$^+$]: 250.1226; found: 250.1230.

6-methoxy-2-(4-methoxyphenyl)-1-methylindole (3v). The compound was prepared following the general procedure using 6-methoxy-1-methylindole and 1-bromo-4-methoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 50:1) as a light yellow solid (48.9 mg, 61 %) Spectral data is consistent with previous reports.[27] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.53 – 7.48 (m, 1H), 7.45 – 7.41 (m, 2H), 7.03 – 6.99 (m, 2H), 6.85 – 6.82 (m, 2H), 6.44 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.69 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.4, 156.3, 140.6, 139.0, 130.6, 125.6, 122.4, 121.0, 114.1, 109.6, 100.9, 93.5, 55.9, 55.5, 31.3.

5-fluoro-2-(4-methoxyphenyl)-1-methylindole (3w). The compound was prepared following the general procedure using 5-fluoro-1-methylindole and 1-bromo-4-methoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 50:1) as a light yellow solid (47.5 mg, 62 %) **M. P.** 107.2-108.9 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.04 (dd, *J* = 12.0, 4.8 Hz, 3H), 6.92 (t, *J* = 9.2 Hz, 1H), 6.49 (s, 1H), 3.89 (s, 3H), 3.68 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.8 (d, *J* = 237.1 Hz), 159.6, 142.1 (d, *J* = 3.8 Hz), 138.3 (d, *J* = 12.0 Hz), 130.6, 125.1, 124.5, 121.0 (d, *J* = 10.0 Hz), 114.1, 108.4 (d, *J* = 24.4 Hz), 101.1, 96.1 (d, *J* = 26.2 Hz), 55.5, 31.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -120.94 (s). **IR**

(neat/cm^{-1}) 3035, 3001, 2942, 2908, 2836, 1612, 1584, 1575, 1548, 1498, 1467, 1426, 1357, 1294, 1281, 1250, 1176, 1081, 1036, 958, 832, 808, 612, 568. **HRMS (APCI)** calcd for $C_{16}H_{15}FNO^+$ [(M+H)$^+$] 256.1132, found 256.1152.

methyl 2-(4-methoxyphenyl)-1-methylindole-6-carboxylate (3x). The compound was prepared following the general procedure using methyl 1-methylindole-6-carboxylate and 1-bromo-4-methoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow solid (44.3 mg, 50 %) **M. P.** 153.9-155.3 ^oC **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 (s, 1H), 7.84 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.07 – 6.98 (m, 2H), 6.54 (s, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.79 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.4, 159.9, 144.9, 137.6, 131.8, 130.8, 124.6, 122.8, 121.1, 119.8, 114.2, 112.1, 101.6, 55.5, 52.0, 31.4. **IR (neat/cm^{-1})** 3009, 2947, 2841, 1712, 1610, 1493, 1464, 1437, 1337, 1306, 1289, 1251, 1231, 1177, 1109, 1032, 873, 838, 825, 788, 743. **HRMS (APCI)** calcd for $C_{18}H_{18}NO_3^+$ [(M+H)$^+$]: 296.1281; found: 296.1287.

methyl 2-(4-methoxyphenyl)-1-methylindole-4-carboxylate (3y). The compound was prepared following the general procedure using methyl 1-methylindole-4-carboxylate and 1-bromo-4-methoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow solid (49.6 mg, 56 %) Spectral data is consistent with previous reports.[15] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.26 (dd, *J* = 9.0, 6.6 Hz, 1H), 7.14 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 3.98 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.3, 159.8, 143.8, 139.2, 130.8, 127.8, 124.8, 123.5, 121.0, 120.6, 114.4, 114.2, 102.6, 55.5, 51.8, 31.4. **IR (neat/cm^{-1})** 3065, 2997, 2947, 2837, 1709, 1611, 1575, 1496, 1451, 1433, 1385, 1363, 1347, 1262, 1251, 1200, 1178, 1143, 1121, 1036, 837, 791, 752.

methyl 2-(4-methoxyphenyl)-1-methylindole-5-carboxylate (3z). The compound was prepared following the general procedure using methyl 1-methylindole-5-carboxylate and 1-bromo-4-methoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow solid (48.7 mg, 55%). **M. P.** 98.0-100.2 ^oC. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 – 7.40 (m, 2H), 7.24 (d, *J* = 2.6 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.91 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.45 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.70 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.5, 154.4, 142.2, 133.7, 130.7, 128.4, 125.5, 114.1, 111.7, 110.4, 102.2, 100.8, 56.1, 55.5, 31.3. **IR (neat/cm^{-1})** 3032, 2995, 2943, 2834, 1735, 1613, 1575, 1544, 1498, 1477, 1453, 1430, 1386, 1345, 1287, 1249, 1218, 1204, 1176, 1141, 1035, 943, 836, 790, 739. **HRMS (APCI)** calcd for $C_{18}H_{18}NO_3^+$ [(M+H)$^+$] 296.1281, found 296.1287.

5-(benzyloxy)-2-(4-methoxyphenyl)-1-methylindole (3aa). The compound was prepared following the general procedure using 5-(benzyloxy)-1-methylindole and 1-bromo-4-methoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 30:1) as a light yellow solid (58.7 mg, 57%) **M. P.** 161.1-163.0 ^oC. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.40 (dd, *J* = 15.8, 8.0 Hz, 4H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 7.17 (s, 1H), 6.99 (t, *J* = 8.6 Hz, 3H), 5.13 (s, 2H), 3.87 (s, 3H), 3.69 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.6, 153.6, 142.2, 137.9, 133.9, 130.7, 128.6, 128.4, 127.8, 127.7, 125.4, 114.1, 112.4, 110.4, 103.9, 100.8, 71.1, 55.5, 31.3. **IR (neat/cm^{-1})** 3063, 3033, 3006, 2917, 2835, 1609, 1579, 1574, 1545, 1466, 1451, 1431, 1375, 1342, 1291, 1243, 1189, 1174, 1134, 1099, 1022, 829, 801, 795, 783, 743, 705, 692. **HRMS (APCI)** calcd for $C_{23}H_{22}NO_2^+$ [(M+H)$^+$] 344.1645, found 344.1671.

1-ethyl-2-phenylindole (3ab). The compound was prepared following the general procedure using 1-ethylindole and bromobenzene as reactants. The product was isolated by column chromatography (PE:EA = 50:1) as a light yellow solid (47.1 mg, 71 %) Spectral data is consistent with previous reports.[28] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.59 – 7.48 (m, 4H), 7.46 (dd, *J* = 9.2, 4.7 Hz, 2H), 7.33 – 7.26 (m, 1H), 7.20 (dd, *J* = 10.5, 4.4 Hz, 1H), 6.59 (s, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.2, 137.2, 133.3, 129.5, 128.6, 128.4, 128.0, 121.6, 120.7, 119.9, 110.0, 102.2, 38.9, 15.5. **HRMS (APCI)** calcd for $C_{16}H_{16}N^+$ [(M+H)$^+$]: 222.1277; found: 222.1279.

1-benzyl-2-(3,4,5-trimethoxyphenyl)-indole (3ac). The compound was prepared following the general procedure using 1-benzylindole and 5-bromo-1,2,3-trimethoxybenzene as reactants. The product was isolated by column chromatography (PE:EA = 20:1) as a light yellow oil (62.7 mg, 56 %) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 – 7.65 (m, 1H), 7.33 – 7.27 (m, 2H), 7.23 (t, *J* = 3.7 Hz, 2H), 7.21 – 7.14 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 2H), 6.65 (d, *J* = 2.8 Hz, 1H), 6.60 (d, *J* = 3.5 Hz, 2H), 5.37 (s, 2H), 3.86 (s, 3H), 3.60 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 153.2, 141.8, 138.7, 138.3, 137.9, 128.9, 128.2, 128.1, 127.2, 125.8, 122.1, 120.6, 120.4, 110.2, 106.2, 101.9, 61.0, 55.8, 47.9. **IR (neat/cm^{-1})** 3058, 2999, 2935, 2830, 1601, 1582, 1497, 1462, 1453, 1415, 1347, 1305, 1238, 1127, 1006, 844, 786, 750, 732, 696. **HRMS (APCI)** calcd for $C_{24}H_{24}NO_3^+$ [(M+H)$^+$]: 374.1751; found: 374.1756.

Reaction with no phosphine (Scheme 4). $Pd(OAc)_2$ (5 mol%), carboxylic acid **4u** (30 mol%) and K_2CO_3 (1.5 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with argon (three cycles). To these solids, DMA (0.3 M), bromobenzene (2.0 equiv, 0.6 mmol) and 1-methylindole (1.0 equiv, 0.3 mmol) were added consecutively under a positive flow of argon. The reaction mixture was stirred at 100^{o}C for 12 hours. The yield was determined by GC with benzophenone as internal standard (41% total yield, 3a : 3b = 1 : 10.7).

Preparation of biaryl carboxylic acids 4

General procedure A:

1) Ester formation : Thionyl chloride (3.6 equiv.) was added dropwise to the solution of *ortho*-bromobenzoic acid (1.0 equiv.) in DCM (2 M) at 0 °C. The mixture was stirred at rt for 1h before methanol (50 mL) was added dropwise. The solution was stirred at rt for 12 h (or at reflux temperature for 2 h). Excess SOCl2 and methanol were removedunder reduced pressure. The residue was dissolved in ethyl acetate, washed with water and 5% sodium hydroxide solution, dried over MgSO4, filtered, and concentrated in vacuo to give crude methyl 2-bromobenzoate, which was used in the next step without further purification

2) Suzuki-Miyaura reaction : [29] An oven-dried resealable Schlenk tube was charged with Pd(OAc)2 (5.0 mol%), dppf (6.0 mol%), methyl 2-bromobenzoate (1.0 equiv.), arylboronic acid (2.0 equiv.), and K3PO4 (3.0 equiv.). The vessel was evacuated and filled with argon (three cycles) and then DME (0.4 M) was injected into the Schlenk tube under argon atmosphere. The mixture was stirred vigorously at 80 °C for 12h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na2SO4 and concen-

trated. The crude methyl 2-arylbenzoate was purified by column chromatography.

3) Ester saponification: the methyl 2-arylbenzoate and 50% potassium hydroxide (0.5 mL/mmol substrate) were stirred overnight in methanol (0.3 M). The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was washed with ether and acidified to pH 2. The aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography .[5]

General procedure B:

1) Phenol alkylation: A suspension of 2-bromo-3-hydroxybenzaldehyde (1 equiv.), K_2CO_3 (3 equiv.) and alkyl halide (3.0 equiv.) in DMF (0.5 M) was stirred at 60°C for 3 h. The reaction was then quenched with water and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude 2-bromo-3-alkoxybenzaldehyde was purified by column chromatography.

2) Suzuki-Miyaura reaction :[29] An oven-dried resealable Schlenk tube was charged with $Pd(OAc)_2$ (5.0 mol%), dppf (6.0 mol%), 2-bromo-3-alkoxybenzaldehyde (1.0 equiv.), arylboronic acid (2.0 equiv.), and K_3PO_4 (3.0 equiv.). The vessel was evacuated and filled with argon (three cycles) and then DME (0.4 M) was injected into the Schlenk tube under argon atmosphere. The mixture was stirred vigorously at 80 °C for 12h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude 2-aryl-3-alkoxybenzaldehyde was purified by column chromatography.

3) Aldehyde oxidation: The 2-aryl-3-alkoxybenzaldehyde was dissolved in methanol (0.5 M) and 50% KOH (0.35 ml/mmol substrate) was added. A 30% hydrogen peroxide solution (0.96 ml/mmol substrate) was then slowly added dropwise. The mixture was stirred for half an hour at 65 °C and cooled to room temperature. After removing methanol under reduced pressure, the resulting mixture was acidified to pH = 2, diluted with water and extracted with ethyl acetate. the combined organic layers was dried over anhydrous Na_2SO_4 and concentrated. The crude material was purified by column chromatography.

General Procedure C: According to the reported literature:[30]6 In a glove box, a 25 mL of the Schlenk tube equipped with a stir bar was charged with $Pd(OAc)_2$ (8 mol%), ligand (8 mol%), benzoic acid (0.2 mmol), iodobenzene (2.0 equiv), Ag_2CO_3 (0.5 equiv), Cs_2CO_3 (0.5 equiv). The tube was fitted with a rubber septum and taken out of the glove box. HFIP (1 mL) was added to the Schlenk tube though the rubber septum using syringe and then the septum was replaced by a Teflon screwcap under argon flow. The reaction mixture was stirred at 30°C for 36 h. Upon completion, diluted HCl (15 mL) was added to the reaction mixture with stirring followed by water (15 mL). The resulting reaction mixture was extracted twice with ether (50 mL x 2) and the combined organic fractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography.

[1,1'-biphenyl]-2-carboxylic acid (4b). Following general procedure A, 2-bromobenzoic acid (5 mmol) and phenylboronic acid were used. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get white solid, yield 80%, 792mg. Spectral data is consistent with previous reports.[31] **1H NMR (400 MHz, $CDCl_3$)** δ 10.96 (s, 1H), 7.96 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.57 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 – 7.32 (m, 7H). **13C NMR (101 MHz, $CDCl_3$)** δ 173.7, 143.6, 141.2, 132.2, 131.4, 130.8, 129.5, 128.6, 128.2, 127.5, 127.3.

5-methoxy-[1,1'-biphenyl]-2-carboxylic acid (4c). The compound was prepared following general procedure C using 4-methoxybenzoic acid (5 mmol) and iodobenzene as reactants. The product was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 4:1) as the eluent to get a white solid (582mg 51%). Spectral data is consistent with previous reports.[32] **1H NMR (400 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 8.7 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.33 – 7.28 (m, 2H), 6.91 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.82 (d, *J* = 2.6 Hz, 1H), 3.86 (s, 3H). **13C NMR (101 MHz, $CDCl_3$)** δ 172.0, 162.4, 146.3, 141.3, 133.4, 128.4, 127.9, 127.3, 121.0, 116.7, 112.6, 55.5.

5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid (4d). The compound was prepared following general procedure C using 4-(trifluoromethyl)benzoic acid (5 mmol) and iodobenzene as reactants. The product was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 2:1) as the eluent to get a white solid (559 mg, 42%). **1H NMR (400 MHz, $CDCl_3$)** δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.65 (s, 1H), 7.45 – 7.39 (m, 3H), 7.37 – 7.32 (m, 2H). **13C NMR (101 MHz, $CDCl_3$)** δ 172.2, 144.1, 139.7, 133.9 (q, J = 32.8 Hz), 132.7, 132.7, 131.2, 128.5, 128.3, 128.2 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.9 Hz). **19F NMR (376 MHz, $CDCl_3$)** δ -63.08 (s). **HRMS (ESI)** calcd for $C_{14}H_9O_2F_3Na+$ [(M+Na)+] 289.0447, found 289.0439.

5-nitro-[1,1'-biphenyl]-2-carboxylic acid (4e). The compound was prepared following general procedure C using 4-nitrobenzoic acid (5 mmol) and iodobenzene as reactants. The product was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 1:1) as the eluent to get a white solid (352 mg, 29%). Spectral data is consistent with previous reports.[33] **1H NMR (400 MHz, $CDCl_3$)** δ 8.26 (d, *J* = 7.1 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 3H), 7.40 – 7.31 (m, 2H). **13C NMR (101 MHz, $CDCl_3$)** δ 171.9, 149.7, 144.9, 138.7, 134.9, 131.8, 128.7, 128.4, 126.0, 122.0.

2'-methyl-[1,1'-biphenyl]-2-carboxylic acid (4f). The compound was prepared following general procedure A using 2-bromobenzoic acid (5 mmol) and o-tolylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (711 mg 67%). Spectral data is consistent with previous reports.[34] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 – 8.02 (m, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.28 – 7.17 (m, 4H), 7.10 – 7.06 (m, 1H), 2.07 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.8, 143.7, 141.3, 135.4, 132.5, 131.4, 130.9, 129.7, 129.3, 128.6, 127.4, 127.3, 125.4, 20.1.

2'-methoxy-[1,1'-biphenyl]-2-carboxylic acid (4g). The compound was prepared following general procedure A using 2-bromobenzoic acid (5 mmol) and (2-methoxyphenyl)boronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 4:1) as the eluent to get a white solid (798 mg 70%).

Spectral data is consistent with previous reports.[35] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 (td, *J* = 7.7, 1.2 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.04 (td, *J* = 7.4, 0.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 3.70 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.0, 156.2, 139.2, 132.4, 131.7, 130.8, 130.3, 129.9, 129.2, 127.2, 121.0, 110.7, 55.1.

2-(naphthalen-1-yl)benzoic acid (4h). The compound was prepared following general procedure A using 2-bromobenzoic acid (5 mmol) and 1-naphtylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (732 mg 59%). Spectral data is consistent with previous reports.[36] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.04 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.88 (dd, *J* = 16.1, 8.2 Hz, 2H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H), 7.52 – 7.42 (m, 4H), 7.39 – 7.32 (m, 2H), 7.28 (dd, *J* = 7.0, 1.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.4, 142.1, 139.3, 133.4, 132.4, 132.3, 132.1, 131.0, 130.2, 128.3, 127.8, 127.7, 126.1, 125.7, 125.6, 125.2.

3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (4i). The compound was prepared following general procedure A using 2-bromobenzoic acid (5 mmol) and 3,5-dimethylphenylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (803 mg 71%). Spectral data is consistent with previous reports.[37] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.94 – 7.91 (m, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 – 7.34 (m, 2H), 6.98 (dd, *J* = 10.2, 0.6 Hz, 3H), 2.34 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.8, 143.6, 141.0, 137.7, 132.1, 131.3, 130.7, 129.5, 129.2, 127.1, 126.5, 21.4.

2',4',6'-trimethyl-[1,1'-biphenyl]-2-carboxylic acid (4j). The compound was prepared following general procedure A using 2-bromobenzoic acid (5 mmol) and 2,4,6-trimethylphenylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (240 mg 20%). Spectral data is consistent with previous reports.[38] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.60 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.91 (s, 2H), 2.34 (s, 3H), 1.92 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.4, 142.7, 137.7, 136.6, 135.2, 133.0, 131.3, 131.2, 127.9, 127.1, 21.1, 20.5.

6-methyl-[1,1'-biphenyl]-2-carboxylic acid (4k). The compound was prepared following general procedure A using 2-bromo-3-methyl-benzoic acid (5 mmol) and phenylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (657 mg 62%). Spectral data is consistent with previous reports.[37] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.16 – 7.13 (m, 2H), 2.09 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.3, 142.7, 140.1, 137.7, 134.1, 130.2, 128.6, 128.1, 128.1, 127.2, 127.1, 20.9.

2',6-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (4l). The compound was prepared following general procedure A using 2-bromo-3-methylbenzoic acid (5 mmol) and o-tolylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (543 mg 48%). Spectral data is consistent with previous reports.[39] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.16 – 7.13 (m, 2H), 2.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 142.7, 140.1, 137.7, 134.1, 130.2, 128.6, 128.1, 128.1, 127.2, 127.1, 20.9.

2'-methoxy-6-methyl-[1,1'-biphenyl]-2-carboxylic acid (4m). The compound was prepared following general procedure A using 2-bromo-3-methylbenzoic acid (5 mmol) and 2-methoxyphenylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 3:1) as the eluent to get a white solid (605 mg 55%). **M. P.** 129.8-130.9°C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.05 – 6.98 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 3H), 2.11 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.5, 156.5, 139.3, 138.2, 134.1, 130.5, 129.9, 128.9, 128.8, 128.0, 127.1, 120.6, 110.9, 55.6, 20.5. **HRMS (ESI)** calcd for $C_{15}H_{14}O_3Na^+$ $[(M+Na)^+]$ 265.0835, found 265.0830.

6-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid (4n). The compound was prepared following general procedure A using 2-bromo-3-(trifluoromethyl)benzoic acid (5 mmol) and phenylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 4:1) as the eluent to get a white solid (678 mg 51%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.93 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.57 (td, *J* = 7.9, 0.6 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.25 – 7.20 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.6, 141.8, 136.4, 133.1, 132.8, 130.5 (q, *J* = 29.6 Hz), 129.6 (q, *J* = 5.4 Hz), 129.2 (q, *J* = 1.2 Hz), 128.1, 127.7, 127.4, 123.6 (q, *J* = 549.2, 274.6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -57.09 (s). **HRMS (ESI)** calcd for $C_{14}H_9O_2F_3Na^+$ $[(M+Na)^+]$ 289.0447, found 289.0444.

5,6-difluoro-[1,1'-biphenyl]-2-carboxylic acid (4o). The compound was prepared following general procedure A using 2-bromo-3,4-difluorobenzoic acid (5 mmol) and phenylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (550 mg 47%). **M. P.** 152.1-154.0°C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (ddd, *J* = 8.8, 5.0, 1.9 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.30 – 7.26 (m, 2H), 7.25 – 7.20 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.9, 153.5 (dd, *J* = 257.2, 14.2 Hz), 148.2 (dd, *J* = 247.8, 12.7 Hz), 134.0 (dd, *J* = 14.4, 1.0 Hz), 132.7 (d, *J* = 2.2 Hz), 129.2 (d, *J* = 1.2 Hz), 128.5, 128.3, 127.4 (dd, *J* = 7.9, 4.5 Hz), 126.4 (dd, *J* = 3.6, 0.9 Hz), 116.1 (d, *J* = 17.7 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -129.23 (d, *J* = 22.0 Hz), -137.74 (d, *J* = 22.0 Hz). **IR (neat/cm^{-1})** 3436, 3056, 2928, 2874, 1709, 1618, 1587, 1577, 1493, 1438, 1423, 1407, 1295, 1281, 1105, 953, 765, 756, 697. **HRMS (ESI)** calcd for $C_{13}H_8O_2F_2Na^+$ $[(M+Na)^+]$ 257.0385, found 257.0377.

1-phenyl-2-naphthoic acid (4p). The compound was prepared following general procedure A using 1-bromo-2-naphtoic acid (5 mmol) and phenylboronic acid as reactants.

The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a white solid (931 mg 75%). Spectral data is consistent with previous reports.[40] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 8.7 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 2H), 7.61 – 7.53 (m, 2H), 7.51 – 7.39 (m, 4H), 7.35 – 7.28 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.6, 142.9, 138.7, 135.3, 132.9, 129.7, 128.2, 128.0, 128.0, 128.0, 127.9, 127.6, 126.8, 126.7, 126.0.

6-methoxy-[1,1'-biphenyl]-2-carboxylic acid (4q). The compound was prepared following general procedure B using 2-bromo-3-hydroxybenzaldehyde (5 mmol), iodomethane and phenylboronic acid as reactants. The 2-arylbenzalhedyde intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 20:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 3:1) as the eluent to get a white solid (798 mg 70%). Spectral data is consistent with previous reports.[41] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.42 – 7.33 (m, 4H), 7.27 (d, *J* = 1.7 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.13 (dd, *J* = 8.3, 0.9 Hz, 1H), 3.75 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.9, 157.2, 136.4, 131.9, 131.8, 129.6, 128.5, 127.9, 127.3, 122.3, 114.8, 56.2. **HRMS (ESI)** calcd for $C_{14}H_{12}O_3Na^+$ [$(M+Na)^+$] 251.0679, found 251.0673.

6-amino-[1,1'-biphenyl]-2-carboxylic acid (4s). The compound was prepared following general procedure A using 3-amino-2-bromobenzoic acid (10 mmol) and phenylboronic acid as reactants. The methyl ester intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 4:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate/acetic acid (PE:EA:AcOH = 1:1:0.02) as the eluent to get a red solid (852 mg 40%). **^{1}H NMR (400 MHz, DMSO)** δ 7.47 – 7.37 (m, 6H), 7.30 – 7.25 (m, 2H). **^{13}C NMR (101 MHz, DMSO)** δ 168.6, 135.0, 134.0, 133.9, 132.8, 129.4, 128.5, 128.3, 127.9, 125.5, 124.0. **HRMS (ESI)** calcd for $C_{13}H_{11}O_2NNa^+$ [$(M+Na)^+$] 236.0682, found 236.0679.

6-((4-methylphenyl)sulfonamido)-[1,1'-biphenyl]-2-carboxylic acid (4t). Following a literature procedure :[42] To a mixture of TsCl (715 mg, 3.75 mmol) in pyridine (7.5 mL) at 0°C was added 6-amino-[1,1'-biphenyl]-2-carboxylic acid (**4s**) (533 mg, 2.5 mmol) and the resulting reaction mixture stirred for 20 h at room temperature. Removal of the solvent under vacuum yielded a residue which was purified by column chromatography (PE:EA = 1:1) to afford the product **4t** as a light yellow solid (90%, 826mg). **M. P.** 146.8-148.0 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.70 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.42 – 7.39 (m, 3H), 7.35 (dt, *J* = 2.7, 1.9 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.20 (dd, *J* = 8.6, 0.6 Hz, 2H), 6.63 – 6.60 (m, 2H), 6.29 (s, 1H), 2.41 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.0, 144.3, 135.9, 135.6, 134.9, 134.3, 130.3, 129.8, 129.1, 128.8, 128.6, 128.5, 127.4, 127.0, 125.2, 21.7. **IR (neat/cm^{-1})** 3537, 3459, 3275, 3065, 3028, 2923, 1712, 1698, 1636, 1597, 1578, 1499, 1463, 1390, 1324, 1290, 1167, 1090, 975, 854, 816, 761, 747, 697, 665, 556. **HRMS (ESI)** calcd for $C_{20}H_{17}O_4NNaS^+$ [$(M+Na)^+$] 390.0770, found 390.0768.

6-ethoxy-[1,1'-biphenyl]-2-carboxylic acid (4u). The compound was prepared following general procedure B using 2-bromo-3-hydroxybenzaldehyde (10 mmol), bromoethane and phenylboronic acid as reactants. The 2-arylbenzalhedyde intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 50:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 5:1) as the eluent to get a yellow solid (1.80 g 76%). **M. P.** 122.9-125.1 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.39 – 7.31 (m, 4H), 7.27 (d, *J* = 1.7 Hz, 1H), 7.25 (d, *J* = 1.4 Hz, 1H), 7.12 (dd, *J* = 8.2, 0.9 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.9, 156.5, 136.3, 132.2, 131.7, 129.6, 128.3, 127.6, 127.0, 122.2, 116.4, 64.7, 14.6. **HRMS (ESI)** calcd for $C_{15}H_{14}O_3Na^+$ [$(M+Na)^+$] 265.0835, found 265.0837.

6-ethoxy-4'-methoxy-[1,1'-biphenyl]-2-carboxylic acid (4v). The compound was prepared following general procedure B using 2-bromo-3-hydroxybenzaldehyde (5 mmol), bromoethane and 4-methoxyphenylboronic acid as reactants. The 2-arylbenzalhedyde intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 40:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 3:1) as the eluent to get a light yellow solid (884 mg 65%). **M. P.** 119.6-121.7 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.21 (dt, 2H), 7.10 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.91 (dt, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.6, 158.8, 156.7, 132.1, 131.9, 130.9, 128.6, 128.1, 122.4, 116.4, 113.3, 64.8, 55.3, 14.7. **IR (neat/cm^{-1})** 3437, 3065, 2978, 2959, 2931, 2882, 2838, 2649, 2571, 1698, 1611, 1591, 1577, 1515, 1465, 1452, 1443, 1412, 1395, 1302, 1257, 1239, 1175, 1112, 1054, 828, 770, 758. **HRMS (ESI)** calcd for $C_{16}H_{16}O_4Na^+$ [$(M+Na)^+$] 295.0941, found 295.0936.

6-ethoxy-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (4w). The compound was prepared following general procedure B using 2-bromo-3-hydroxybenzaldehyde (5 mmol), bromoethane and 3,5-dimethylphenylboronic acid as reactants. The 2-arylbenzalhedyde intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 50:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 4:1) as the eluent to get a light yellow solid (946 mg 70%). **M. P.** 143.7-145.4 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.96 (s, 1H), 6.91 (s, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 2.32 (s, 6H), 1.25 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.5, 156.6, 137.1, 136.0, 132.3, 132.0, 129.1, 128.2, 127.6, 122.3, 116.5, 64.8, 21.5, 14.7. **HRMS (ESI)** calcd for $C_{17}H_{18}O_3Na^+$ [$(M+Na)^+$] 293.1148, found 293.1140.

6-ethoxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid (4x). The compound was prepared following general procedure B using 2-bromo-3-hydroxybenzaldehyde (5 mmol), bromoethane and 4-(trifluoromethyl)phenylboronic acid as reactants. The 2-arylbenzalhedyde intermediate was purified using petroleum ether/ethyl acetate (PE:EA = 50:1). The carboxylic acid was isolated by column chromatography, using petroleum ether/ethyl acetate (PE:EA = 3:1) as the eluent to get a white solid (868 mg 56%). **M. P.** 168.0-169.2 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 8.3, 0.9 Hz, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.7, 156.5, 140.6, 131.2, 131.1, 130.1, 129.2 (q, *J* = 32.3 Hz), 129.1, 124.6 (q, *J* = 271.9 Hz), 124.6 (q, *J* = 3.7 Hz), 122.7, 116.6, 64.8, 14.6. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -62.30 (s). **IR (neat/cm^{-1})** 3424, 3072, 2988, 2914, 2880, 2676, 2643, 2571, 1705, 1616, 1594, 1580, 1454, 1405, 1325, 1303, 1262, 1158, 1119, 1066, 868, 836, 760. **HRMS (APCI)** calcd for $C_{16}H_{14}O_3F_3^+$ [$(M+H)^+$] 311.0890, found 311.0890.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H, ^{13}C and ^{19}F (if applicable) NMR spectra.

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Notes

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