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Additive-Free Copper(I)-Mediated Synthesis of 5- or 6-Brominated 2-Aryl-1*H*-Indole-3-Carboxylates from α,α-Dibromo β-Iminoesters

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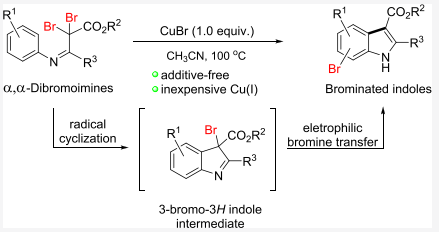
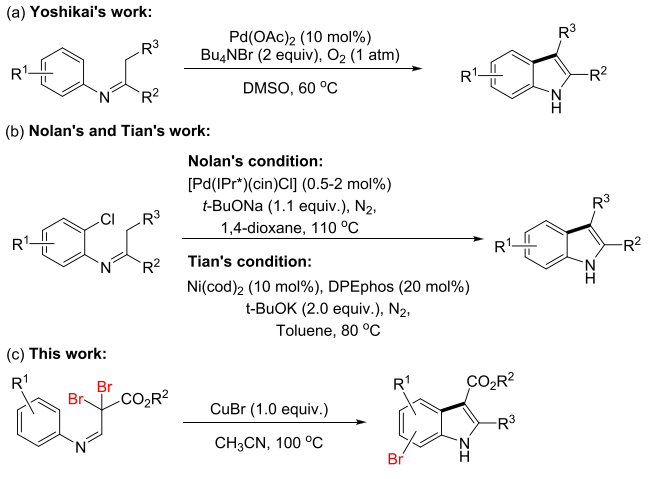
ABSTRACT: Additive-free copper(I)-bromide-mediated radical cyclization reactions of α,α-dibromo β-iminoesters were investigated, enabling the synthesis of a series of 5- or 6-brominated 2-aryl-1*H*-indole-3-carboxylates in moderate to good yields. The mechanistic study showed that (i) the bromine atom originated from the substrates and (ii) the bromination might be related to a 3-bromo-3*H* indole intermediate via an electrophilic bromine atom transfer. Furthermore, the practicality of this method was demonstrated by gram-scale synthesis and the potential for product derivatization toward other valuable multisubstituted indoles.



Imines and their derivatives are versatile intermediates and have been transformed to a variety of *N*-heterocycles with significant biological activity.[1] However, as synthetic precursors for constructing an indole skeleton, they are rarely reported, even though indoles are privileged motifs found extensively in natural products, pharmaceuticals, and materials.[2] In 2012, Yoshikai et al. developed a palladium-catalyzed aerobic oxidative cyclization of *N*-aryl imines derived from common anilines and ketones to afford corresponding indoles (Scheme 1a).[3] This approach not only represents a breakthrough for indole synthesis from simple starting materials but also opens a new reaction manifold for exploitation. Subsequent to this work, Nolan et al. reported palladium *N*-heterocycle carbene-catalyzed α-arylation of imines leading to highly substituted indoles and azaindoles (Scheme 1b).[4a] Very recently, Tian et al. developed the same elegant transformation by using a Ni $(cod)_2$/DPEphos system in place of a palladium *N*-heterocycle carbene (Scheme 1b).[4b] Exciting as these achievements are, they are limited in that they all require relatively expensive metal catalysts and additives. Thus, an alternative method to the synthesis of indoles from imines under a relatively simple reaction system would be desirable.

Scheme 1. Literature Report and Present Work



Recently, we reported an efficient method for the synthesis of functionalized α,α-dihaloimines.[5] During the course of our research on the potential utility of these imines, we observed that our dibromoimines could be transformed into an indole skeleton by treatment of a stoichiometric amount of $Cu(acac)_2$ in refluxing CH_3CN.

This interesting result spurred us to do further investigation on the formation of the indole structure based on this biased substrate by using copper metal. In the past few decades, it has been extensively used as a promoter in cross-coupling reactions of organic halides with diverse partners for the construction of carbon−carbon and carbon−heteroatom bonds. Among them, for the synthesis of complex halogenated cyclic systems, copper-catalyzed/mediated halogen atom transfer radical cyclization (ATRC) is regarded as a powerful strategy, wherein activated mono-, di-, and trihalo derived compounds are commonly used substrates and a Cu(I)−halogen derived complex has proven to be more effective.[6] To our knowledge, this strategy for the synthesis of indole derivatives is rare, and Steves et al. reported an elegant Cu(I)Cl-catalyzed chlorine atom transfer radical cyclization of *N*-(indolylmethyl)-trichloroacetamides to synthesize 3,3-spiro-3*H*-indoles.[7] In-

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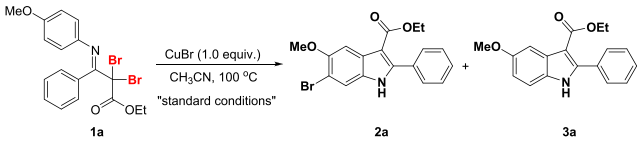
spired by previous works, we envisioned that exposure of our dibromoimines to the conditions in concert with known ATRC reactions may provide a new access to brominated indoles.

Herein, we report an additive-free copper(I)-mediated cyclization of α,α-dibromo β-iminoesters for the synthesis of multisubstituted bromoindoles. In particular, the C6−Br indole scaffold is found in the core of Arbidol and several drug candidates,[8] while the direct synthetic methods to this framework are rather limited.[9] After extensive studies, our dibromoimine substrates with an ester group, such as **1a**, were found to be particularly suitable for this process (Table 1).

Table 1. Selected Optimization Studies[a]



1a 2a 3a

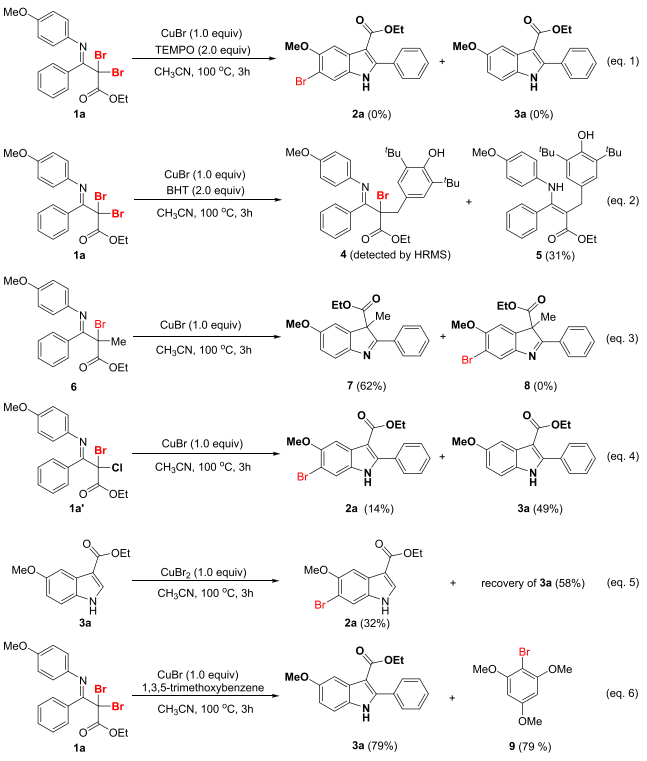
entry[b]	variation from standard conditions	2a (%)	3a (%)
1	none	78	-
2	w/o CuBr	<5	-
3	$CuBr{\cdot}SMe_2$ instead of CuBr	75	-
4	CuCl instead of CuBr	53	-
5	CuI instead of CuBr	28	23
6	Cu_2O instead of CuBr	68	10
7	CuCN instead of CuBr	61	-
8	CuBr (50%)	42	-
9	DMAP (1.0 equiv) was used	41	32
10	TMEDA (1.0 equiv) was used	11	53
11	2,2′-bipyridine (1.0 equiv) was used	45	39
12	1,10-phenanthroline (1.0 equiv) was used	43	42
13	1,4-dioxane instead of CH_3CN	70	-
14	DCE instead of CH_3CN	59	22
15	80 °C	57	-
16	120 °C	66	-

[a]Reaction conditions: run on a 0.3 mmol scale for 3 h in a 15 mL sealed tube. [b]Yield of isolated products. DMAP = 4-dimethylaminopyridine. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. DCE = 1,2-dichloroethane.

Careful optimization of the reaction conditions eventually afforded C6−Br indole **2a**[10] exclusively in 78% yield using CH_3CN as the solvent in a sealed tube at 100 °C (entry 1). Interestingly, in the absence of CuBr, a trace amount of **2a** was still observed along with some unidentified products (entry 2). Variation of the Cu(I) salts led to a decreased yield (entries 3−7). A smaller amount of CuBr gave a lower yield (entry 8). A collection of amines were employed as potential ligands in view of their demonstrated versatility in radical cyclization. However, they also led to a decreased yield of **2a** and increased amount of undesired **3a**, indicating that basicity of the ligand plays a negative role in this reaction (entries 9−12). A survey of the solvent effect revealed CH_3CN to be optimal (entries 13 and 14). Finally, variation of reaction temperatures gave unsatisfied results, as a lower temperature led to lower conversion, while a higher temperature caused more decomposition of **1a** (entries 15 and 16).

With the optimal conditions in hand, we realized that this reaction may not have proceeded via atom transfer radical cyclization as we initially anticipated, with one bromine atom present in the final product **2a**. In order to gain a better understanding of the reaction mechanism, some control experiments were carried out (Scheme 2). In the radical

Scheme 2. Control Experiments



trapping experiments, the formation of either **2a** or **3a** was completely suppressed when 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was added under the optimal conditions (Scheme 2, eq 1). The addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) also inhibited the reaction, and meanwhile, an adduct of the debromo-**1a** radical with BHT (**4**) was detected by HRMS but was unable to be isolated. Compound **5** could be separated from the reaction mixture, likely derived from the decomposition of **4** (Scheme 2, eq 2). These results indicated that this reaction may initiate via a radical intermediate generated by clipping one of the C−Br bonds in the substrate. Wondering about the role of each bromine atom in **1a**, compound **6**, in which one of the bromine atoms was replaced with amethyl group, was prepared and thus subjected to the optimal conditions (Scheme 2, eq 3). This reaction afforded 3*H*-indole **7** exclusively, without any brominated products **8**. When using α-bromo-α-chloro β-iminoester **1a**′ instead of **1a** (Scheme 2, eq 4), a small amount of **2a** was still obtained probably due to the fact that this reaction was initiated with partial cleavage of the C−Cl bond in **1a**′. These results revealed that the formation of **2a** was not via a classical ATRC reaction and the second bromine atom in **1a** is key to final product **2a** formation and efficiency. In addition, treatment of **3a** with 1 equiv of $CuBr_2$ could afford **2a** with recovery of more than half of the unreacted **3a** (Scheme 2, eq 5), suggesting that this reaction pathway may be involved but unlikely dominant. Furthermore, when subjecting 1,3,5-trimethoxybenzene into this reaction, the brominated products **9** and **3a** were obtained with equal yields (Scheme 2, eq 6), implying that the bromination step of **2a** may proceed via a electrophilic bromine transfer. Recently, Yeung's group developed a series

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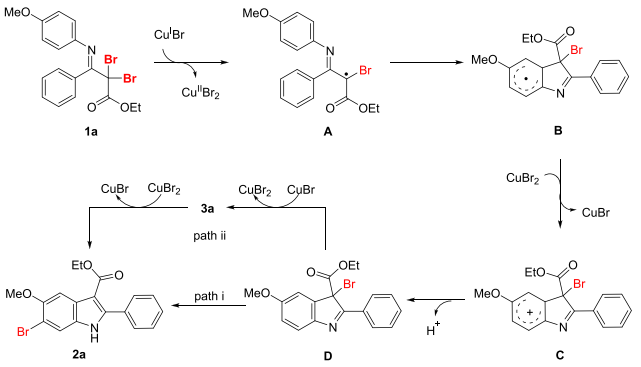
of indole-catalyzed bromination reactions in lipophilic solvent, in which the unstable methyl 3-bromo-3*H*-indole-3-carboxylate is believed to be the key intermediate, providing a highly active electrophilic bromine atom.[11]

Based on the above experimental results and Yeung's works, a plausible mechanism involving intermediate **A** is proposed as shown in Scheme 3. Homolytic cleavage of one of the C−Br

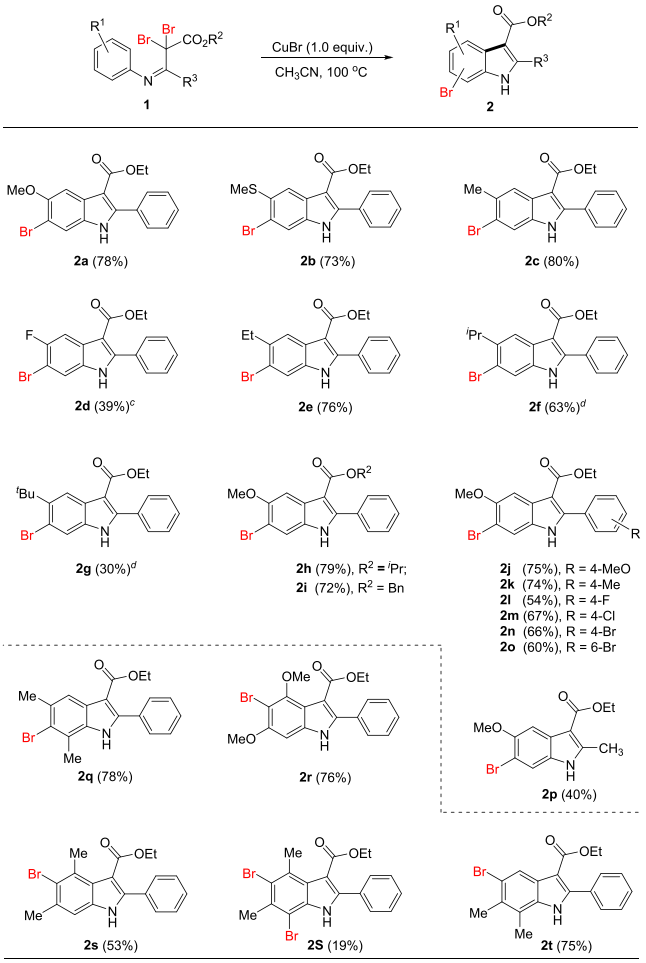
Scheme 3. Plausible Mechanism



bonds in **1a** by CuBr form the alkyl radical **A** and $CuBr_2$, followed by intramolecular addition to the *N*-aryl ring in the intermediate **A** affording the aryl radical intermediate **B**, which sequentially undergoes single-electron oxidation by $CuBr_2$. Finally, deprotonation of the intermediate **C** offers unstable intermediate **D**. There are two potential ways for intermediate **D** to form C6−Br indole **2a**: (i) directly delivering **2a** by intramolecular electrophilic bromine transfer to the electronically favored site and (ii) being decomposed into indole **3a** with the aid of Cu(I)Br, along with its oxidization to $Cu(II)Br_2$, which subsequently reacts with **3a**, yielding **2a** in the end.

Following the optimal conditions, we next examined the scope of this process (Table 2). First, the substituents ($\mathbf{R^1}$) on the *N*-aryl group were varied to evaluate the effect on the reaction efficiency. Compared with the electron-withdrawing group in *para*-position of the *N*-aryl group (**2d**), the electron-donating group enhanced the reaction efficiency significantly (**2a**−**2c**). These results could be attributed to the fact that electron-donating groups increase the electron density on the phenyl ring and thus facilitate intramolecular electrophilic bromine transfer. In the absence of a *para*-substituent or the substituents on the *ortho*- or *meta*-positions of an *N*-aryl group, the reaction efficiency vanished, and no desired products were obtained. Furthermore, steric hindrance on the *N*-aryl group influenced the reaction efficiency. The ethyl substituent proceeded smoothly under optimal conditions, affording **2e** in comparable yield; nevertheless, the more bulky groups such as isopropyl and *tert*-butyl substituents produced decreased yields (**2f**, **2g**), even with higher reaction temperatures and longer reaction times. It should be pointed out that, in the cases of **2d**, **2f**, and **2g**, a considerable amount of corresponding nonbrominated indoles were generated, presumably due to the decomposition of the 3-bromo-3*H*-indole intermediates. As expected, isopropyl (**2h**) and benzyl (**2i**) groups in the ester moiety ($\mathbf{R^2}$) had no adverse effect on the reaction efficiency. Further scope examination showed that substituents on the aryl ring ($\mathbf{R^3}$ = Ar) with electron-donating and electron-withdrawing groups all worked well; albeit, the presence of MeO (**2j**) or Me (**2k**) brought about slightly

Table 2. Substrate Scope[a,b]



[a]Reaction conditions: run on a 0.3 mmol scale for 3 h in a 15 mL sealed tube. [b]Yield of isolated products. [c]120 °C, 6 h. [d]5 h.

higher yields than those of F, Cl, and Br (**2l**−**2o**). For starting material **1p** ($\mathbf{R^3}$ = Me), because of its temperature-sensitive nature, the desired C6−Br indole **2p** was obtained in relatively low yield. Additionally, aiming to substantially expand the generality of this reaction, the substrate scope with respect to disubstituents on the *N*-aryl ring was also investigated. To our delight, all the tested substrates (**1q**−**1t**) were competent in this transformation, giving the brominated indoles in good yield. Surprisingly, a small amount of dibrominated indole **2S** was observed in the case of **1s**, probably arising from the further bromination of **2s** by $CuBr_2$ in the reaction mixture.[12] The location of bromine substituent in **2q**−**2t** was determined by ^{1}H−^{1}H NOESY experiments. Some α,α-dichloro β-iminoesters were also employed to investigate this reaction. Contrary to expectation, the corresponding chlorinated indoles were not observed in our experiments. Instead, nonchlorinated indoles were obtained as major products accompanied by some unidentified side-products. The unsuccessful cases may be attributed to the lesser electrophilic property of chlorine than that of bromine, and thus, the unstable 3-chloro-3*H*-indole intermediate is prone to be decomposed into the corresponding nonchlorinated indole in this process.[13]

To test the practicality of this method, a gram-scale reaction was performed, and a similar yield of **2a** was obtained (Scheme 4). Some representative transformations were employed to

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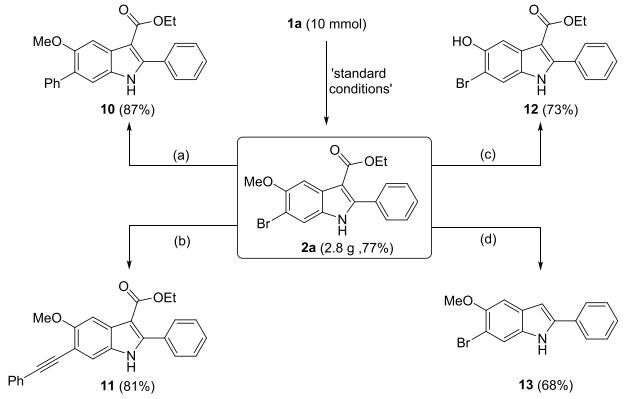
Scheme 4. Multigram Synthesis and Further Transformations



[a]Reagents and conditions: (a) phenylboric acid, $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (2.0 equiv), N_2, toluene, 100 °C, 2 h; (b) phenylacetylene, CuI (5 mol %), $Pd(PPh_3)_2Cl_2$ (10 mol %), Et_3N/THF, N_2, 80 °C, 5 h; (c) BBr_3 (1.3 equiv), DCM, 0 °C, 6 h; (d) 1N NaOH (4 equiv), THF, 90 °C, 20 h.

extend the utility of the product **2a**. Palladium-catalyzed cross-coupling reactions of **2a** with phenylboronic acid and phenylacetylene proceed smoothly to afford **10** and **11**, respectively. The methyl group in **2a** could be easily removed in the presence of BBr_3/DCM to give **12**. Hydrolysis of **2a** in refluxing a 1N NaOH solution delivered the decarboxylated **13** as the only product.

In conclusion, we have introduced a new synthetic route to 5- or 6-brominated 2-aryl-1*H*-indole-3-carboxylates from *α*,*α*-dibromo *β*-iminoesters via copper(I)-mediated radical cyclization/electrophilic bromination cascade in one pot. The protocol enables the facile synthesis of various C6−Br and other brominated indoles from readily available starting materials. Further derivatization of the product highlights the utility of this method. Hopefully, our approach has augmented the numerous methods that have been reported for the indole synthesis.

EXPERIMENTAL SECTION

General Information. All the substrates and solvents for the synthesis of compounds were purchased from a commercial source and used as received without any further purification. All the *α*,*α*-dibromo *β*-iminoesters were synthesized using earlier reported methods.[5b] Thin layer chromatography was performed on plates (GF254) supplied by Yantai Chemicals (China), and visualization was accomplished using UV light, iodine stains, or potassium permanganate solution. Silica gel (200−300 mesh) supplied by Tsingdao Haiyang Chemicals (China) was used for column chromatography purification with a hexane/ethyl acetate mixture as the eluent. ^{1}H NMR spectra were measured on a Bruker (400 or 500 MHz) spectrometer. ^{13}C NMR spectra were measured on a Bruker (100 or 126 MHz) spectrometer with complete proton decoupling. ^{19}F NMR spectra were measured on a Bruker (376 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform: *δ* 7.26, acetone: *δ* 2.05, dimethyl sulfoxide: *δ* 2.50), carbon (chloroform *δ* 77.16, acetone: *δ* 206.26, 29.84, dimethyl sulfoxide: *δ* 39.52), or tetramethylsilane (TMS *δ* 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded on Q-TOF mass spectrometer, Waters. Melting points were measured on an MP90, Mettler Toledo.

General Procedure for the Synthesis of Brominated Indoles. To a 15 mL sealed tube was added **1** (0.30 mmol, 1.0 equiv), CuBr (0.30 mmol, 1.0 equiv), and dry CH_3CN (3 mL, 0.1 M). The resulting mixture was heated at 100 °C in an oil bath until the complete consumption of starting material as monitored by TLC or GC−MS analysis (During the reaction, the sealed tube was let to cool down before the samples could be taken out for TLC or GC−MS analysis.). After cooling, the reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated in vacuo, and the obtained residue was purified by silica gel column chromatography (ethyl acetate (EA)/hexane) to afford the desired product. Structural assignments (**2q**−**2s**) were made with additional information from ^{1}H−^{1}H NOESY experiments.

*Ethyl 6-Bromo-5-methoxy-2-phenyl-1H-indole-3-carboxylate (**2a**).* 87 mg, 78% yield; white solid; R_f = 0.24 (EA/hexane = 1:5, *V*:*V*); mp 212−214 °C; ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 12.09 (s, 1H), 7.70−7.68 (m, 3H), 7.65 (s, 1H), 7.65 (s, 1H), 7.51−7.46 (m, 3H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) *δ* 164.3, 150.8, 145.1, 131.6, 130.7, 129.9, 129.0, 127.8, 127.7, 115.8, 106.8, 103.3, 102.8, 59.1, 56.1, 14.0; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{18}H_{16}BrNNaO_3$ 396.0206, found 396.0205.

*Ethyl 6-Bromo-5-(methylthio)-2-phenyl-1H-indole-3-carboxylate (**2b**).* 85 mg, 73% yield; white solid; R_f = 0.33 (EA/hexane = 1:5, *V*:*V*); mp 179−181 °C; ^{1}H NMR (500 MHz, chloroform-*d*) *δ* 8.58 (s, 1H), 8.08 (s, 1H), 7.62 (brs, 2H), 7.58 (s, 1H), 7.43 (brs, 3H), 4.28 (q, *J* = 7.0 Hz, 2H), 2.56 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) *δ* 165.1, 145.3, 133.8, 132.4, 131.6, 129.7, 129.6, 128.3, 128.1, 120.0, 117.6, 115.3, 104.3, 60.0, 17.1, 14.4; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{18}H_{17}BrNO_2S$ 390.0158, found 390.0149.

*Ethyl 6-Bromo-5-methyl-2-phenyl-1H-indole-3-carboxylate (**2c**).* 86 mg, 80% yield; white solid; R_f = 0.42 (EA/hexane = 1:5, *V*:*V*); mp 187−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 12.13 (s, 1H), 8.00 (s, 1H), 7.68 (brs, 2H), 7.63 (s, 1H), 7.49 (brs, 3H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 1.21 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) *δ* 164.1, 145.2, 134.9, 131.5, 129.9, 129.3, 129.0, 127.8, 127.1, 122.5, 118.1, 114.8, 102.5, 59.1, 23.0, 14.1; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{18}H_{17}BrNO_2$ 358.0437, found 358.0431.

*Ethyl 6-Bromo-5-fluoro-2-phenyl-1H-indole-3-carboxylate (**2d**).* 42 mg, 39% yield; white solid; R_f = 0.38 (EA/hexane = 1:5, *V*:*V*); mp 163−165 °C; ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 12.37 (s, 1H), 7.86 (d, *J* = 10 Hz, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.69−7.67 (m, 2H), 7.52−7.48 (m, 3H), 4.20 (q, *J* = 7.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) *δ* 163.9, 154.0 (d, *J* = 233.9 Hz), 146.7, 132.6, 131.1, 129.9, 129.4, 127.9, 127.3 (d, *J* = 9.9 Hz), 115.8, 107.3 (d, *J* = 26 Hz), 103.3 (d, *J* = 4.4 Hz), 102.7 (d, *J* = 24.5 Hz), 59.4, 14.1; ^{19}F NMR (376 MHz, DMSO-d_6) *δ* −117.09; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{17}H_{13}BrFNNaO_2$ [M + Na]$^+$ 384.0006, found 384.0007.

*Ethyl 6-Bromo-5-ethyl-2-phenyl-1H-indole-3-carboxylate (**2e**).* 85 mg, 76% yield; white solid; R_f = 0.48 (EA/hexane = 1:5, *V*:*V*); mp 148−150 °C; ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 8.56 (s, 1H), 8.09 (s, 1H), 7.59 (brs, 2H), 7.54 (s, 1H), 7.41 (brs, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.89 (q, *J* = 7.2 Hz, 2H), 1.30 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*) *δ* 165.3, 145.1, 136.9, 134.5, 131.9, 129.7, 129.4, 128.3, 127.6, 122.1, 119.3, 114.9, 104.5, 59.9, 29.8, 15.1, 14.4; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{19}H_{19}BrNO_2$ 372.0594, found 372.0590.

*Ethyl 6-Bromo-5-isopropyl-2-phenyl-1H-indole-3-carboxylate (**2f**).* 73 mg, 63% yield; white solid; R_f = 0.57 (EA/hexane = 1:5, *V*:*V*); mp 156−158 °C; ^{1}H NMR (500 MHz, chloroform-*d*) *δ* 8.42 (s, 1H), 8.18 (s, 1H), 7.65−7.61 (m, 2H), 7.59 (s, 1H), 7.46−7.43 (m, 3H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.50−3.45 (m, 1H), 1.34 (d, *J* = 6.5 Hz, 6H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) *δ* 165.2, 145.2, 141.1, 134.3, 131.9, 129.7, 129.5, 128.3, 127.7, 119.6, 119.5, 114.9, 104.7, 59.9, 33.0, 23.6, 14.4; HRMS (ESI-

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TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{20}BrNNaO_2$ 408.0570, found 408.0560.

*Ethyl 6-Bromo-5-(tert-butyl)-2-phenyl-1H-indole-3-carboxylate (**2g**)*. 36 mg, 30% yield; white solid; R_f = 0.42 (EA/hexane = 1:5, *V*:*V*); mp 156−158 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.50 (s, 1H), 8.23 (d, J = 1.0 Hz, 1H), 7.68−7.66 (m, 2H), 7.49 (d, J = 1.5 Hz, 1H), 7.48−7.47 (m, 3H), 4.31 (q, J = 7.0 Hz, 2H), 1.42 (s, 9H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.2, 147.2, 145.0, 132.3, 131.9, 129.8, 129.6, 128.7, 128.3, 124.0, 117.7, 106.0, 104.1, 59.9, 35.2, 31.9, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}BrNO_2$ 400.0907, found 400.0908.

*Isopropyl 6-Bromo-5-methoxy-2-phenyl-1H-indole-3-carboxylate (**2h**)*. 92 mg, 79% yield; white solid; R_f = 0.27 (EA/hexane = 1:5, *V*:*V*); mp 146−148 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.47 (s, 1H), 7.79 (s, 1H), 7.62−7.60 (m, 2H), 7.56 (s, 1H), 7.44−7.42 (m, 3H), 5.20−5.14 (m, 1H), 3.97 (s, 3H), 1.25 (d, J = 6.0 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 164.8, 151.9, 145.0, 132.1, 130.4, 129.7, 129.4, 128.2, 128.2, 115.5, 108.4, 105.1, 104.1, 67.3, 56.7, 22.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{18}BrNNaO_3$ 4100362, found 410.0358.

*Benzyl 6-Bromo-5-methoxy-2-phenyl-1H-indole-3-carboxylate (**2i**)*. 94 mg, 72% yield; white solid; R_f = 0.27 (EA/hexane = 1:5, *V*:*V*); mp 168−171 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.46 (s, 1H), 7.69 (s, 1H), 7.59 (brs, 2H), 7.56 (s, 1H), 7.41 (brs, 3H), 7.31 (brs, 5H), 5.27 (s, 2H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 164.9, 152.0, 145.4, 136.3, 131.8, 130.3, 129.7, 129.5, 128.6, 128.4, 128.4, 128.2, 128.1, 115.6, 108.4, 104.5, 104.1, 66.0, 56.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}BrNO_3$ 436.0543, found 436.0539.

*Ethyl 6-Bromo-5-methoxy-2-(4-methoxyphenyl)-1H-indole-3-carboxylate (**2j**)*. 91 mg, 75% yield; white solid; R_f = 0.22 (EA/hexane = 1:5, *V*:*V*); mp 172−174 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.54 (s, 1H), 7.73 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.51 (s, 1H), 6.90 (d, J = 8.5 Hz, 2H), 4.28 (q, J = 7.0 Hz, 2H), 3.96 (s, 3H), 3.81 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.5, 160.6, 151.8, 145.3, 131.0, 130.3, 128.2, 124.1, 115.5, 113.7, 108.0, 104.1, 104.0, 59.9, 56.7, 55.5, 14.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}BrNO_4$ 404.0492, found 404.0475.

*Ethyl 6-Bromo-5-methoxy-2-(p-tolyl)-1H-indole-3-carboxylate (**2k**)*. 86 mg, 74% yield; white solid; R_f = 0.24 (EA/hexane = 1:5, *V*:*V*); mp 170−172 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.60 (s, 1H), 7.73 (s, 1H), 7.49 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 2.35 (s, 3H), 1.29 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*) δ 165.5, 151.8, 145.5, 139.5, 130.4, 129.4, 128.9, 128.8, 128.1, 115.6, 108.1, 104.2, 104.0, 59.9, 56.7, 21.5, 14.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{18}BrNNaO_3$ 410.0362, found 410.0355.

*Ethyl 6-Bromo-2-(4-fluorophenyl)-5-methoxy-1H-indole-3-carboxylate (**2l**)*. 64 mg, 54% yield; white solid; R_f = 0.26 (EA/hexane = 1:5, *V*:*V*); mp 161−163 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.13 (s, 1H), 7.74−7.70 (m, 2H), 7.67 (s, 1H), 7.62 (s, 1H), 7.36−7.32 (m, 2H), 4.19 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.2, 161.5, 150.8, 144.1, 132.2 (d, J = 8.5 Hz), 130.6, 127.9 (d, J = 3.3 Hz), 127.5, 115.8, 114.8 (d, J = 21.6), 106.8, 103.2, 102.9, 59.1, 56.2, 14.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ −112.29; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{15}BrFNNaO_3$ 414.0112, found 414.0099.

*Ethyl 6-Bromo-2-(4-chlorophenyl)-5-methoxy-1H-indole-3-carboxylate (**2m**)*. 82 mg, 67% yield; white solid; R_f = 0.52 (EA/hexane = 1:5, *V*:*V*); mp 152−154 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.73 (s, 1H), 7.73 (s, 1H), 7.54 (s, 1H), 7.53−7.51 (m, 2H), 7.38−7.35 (m, 2H), 4.27 (q, J = 7.0 Hz, 2H), 3.95 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.2, 152.1, 143.7, 135.6, 131.0, 130.4, 130.3, 128.5, 128.0, 115.6, 108.8, 105.0, 104.1, 60.1, 56.7, 14.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}BrClNO_3$ 407.9997, found 407.9978.

*Ethyl 6-Bromo-2-(4-bromophenyl)-5-methoxy-1H-indole-3-carboxylate (**2n**)*. 90 mg, 66% yield; white solid; R_f = 0.41 (EA/hexane = 1:5, *V*:*V*); mp 163−165 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.57 (s, 1H), 7.74 (s, 1H), 7.56 (s, 1H), 7.55−7.52 (m, 2H), 7.49−7.46 (m, 2H), 4.28 (q, J = 7.0 Hz, 2H), 3.96 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.2, 152.1, 143.6, 131.5, 131.2, 130.8, 130.4, 128.0, 123.9, 115.7, 108.8, 105.0, 104.0, 60.1, 56.7, 14.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}Br_2NO_3$ 451.9491, found 451.9472.

*Ethyl 6-Bromo-2-(2-bromophenyl)-5-methoxy-1H-indole-3-carboxylate (**2o**)*. 82 mg, 60% yield; white solid; R_f = 0.26 (EA/hexane = 1:5, *V*:*V*); mp 183−186 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 11.04 (s, 1H), 7.83 (s, 1H), 7.74−7.72 (m, 2H), 7.55−7.52 (m, 1H), 7.51−7.47 (m, 1H), 7.44−7.40 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.96 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, acetone-d_6) δ 164.8, 152.5, 144.2, 135.3, 133.2, 132.8, 131.7, 131.4, 128.2, 127.9, 124.6, 116.9, 108.6, 106.7, 104.3, 59.8, 56.8, 14.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}Br_2NO_3$ 451.9491, found 451.9476.

*Ethyl 6-Bromo-5-methoxy-2-methyl-1H-indole-3-carboxylate (**2p**)*. 37 mg, 40% yield; white solid; R_f = 0.16 (EA/hexane = 1:5, *V*:*V*); mp 158−160 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.22 (s, 1H), 7.67 (s, 1H), 7.49 (s, 1H), 4.39 (q, J = 7.0 Hz, 2H), 3.95 (s, 3H), 2.71 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.9, 151.7, 144.4, 129.6, 127.7, 115.0, 107.2, 104.9, 103.7, 59.7, 56.7, 14.7, 14.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{14}BrNNaO_3$ 334.0049, found 334.0044.

*Ethyl 6-Bromo-5,7-dimethyl-2-phenyl-1H-indole-3-carboxylate (**2q**)*. 87 mg, 78% yield; white solid; R_f = 0.48 (EA/hexane = 1:5, *V*:*V*); mp 145−147 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.91 (s, 1H), 7.87 (s, 1H), 7.65−7.63 (m, 2H), 7.50−7.48 (m, 3H), 4.16 (q, J = 7.0 Hz, 2H), 2.60 (s, 3H), 2.47 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.2, 145.4, 134.1, 131.7, 130.3, 130.0, 128.9, 127.6, 126.1, 121.3, 121.2, 119.8, 103.1, 59.0, 24.3, 17.7, 14.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}BrNO_2$ 372.0594, found 372.0586.

*Ethyl 5-Bromo-4,6-dimethoxy-2-phenyl-1H-indole-3-carboxylate (**2r**)*. 92 mg, 76% yield; white solid; R_f = 0.46 (EA/hexane = 1:5, *V*:*V*); mp 151−153 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.74 (s, 1H), 7.56−7.54 (m, 2H), 7.43−7.38 (m, 3H), 6.80 (s, 1H), 4.28 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 166.0, 144.4, 142.7, 140.6, 131.6, 129.1, 128.7, 128.6, 126.6, 121.9, 108.4, 107.6, 106.6, 61.6, 60.9, 56.1, 14.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{18}BrNNaO_4$ 426.0311, found 426.0309.

*Ethyl 5-Bromo-4,6-dimethyl-2-phenyl-1H-indole-3-carboxylate (**2s**)*. 59 mg, 53% yield; white solid; R_f = 0.36 (EA/hexane = 1:5, *V*:*V*); mp 147−149 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.40 (s, 1H), 7.51−7.49 (m, 2H), 7.41−7.38 (m, 3H), 7.07 (s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.71 (s, 3H), 2.50 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 167.3, 140.5, 134.5, 133.4, 132.0, 130.7, 129.0, 128.6, 125.2, 122.0, 110.2, 107.7, 61.0, 25.1, 21.2, 14.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{18}BrNNaO_2$ 394.0413, found 394.0416.

*Ethyl 5,7-Dibromo-4,6-dimethyl-2-phenyl-1H-indole-3-carboxylate (**2S**)*. 26 mg, 19% yield; white solid; R_f = 0.26 (EA/hexane = 1:5, *V*:*V*); mp 149−151 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.35 (s, 1H), 7.56−7.54 (m, 2H), 7.44−7.40 (m, 3H), 4.23 (q, J = 7.0 Hz, 2H), 2.65 (s, 3H), 2.43 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 167.1, 140.6, 134.1, 132.0, 129.1, 128.7, 128.6, 127.9, 127.9, 126.5, 119.4, 118.3, 108.6, 61.0, 20.1, 16.1, 14.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{17}Br_2NNaO_2$ 471.9518, found 471.9514.

*Ethyl 5-Bromo-6,7-dimethyl-2-phenyl-1H-indole-3-carboxylate (**2t**)*. 83 mg, 75% yield; white solid; R_f = 0.52 (EA/hexane = 1:5, *V*:*V*); mp 146−148 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.11 (s, 1H), 7.66−7.63 (m, 2H), 7.50−7.48 (m, 3H), 4.16 (q, J = 7.0 Hz, 2H), 2.52 (s, 3H), 2.41 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.1, 145.6, 135.0, 131.6, 130.3, 128.9, 128.4, 127.6, 126.4, 121.6, 121.4, 118.5, 102.7, 59.0, 19.1, 14.7, 14.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}BrNO_2$ 372.0594, found 372.0590.

Procedure for the Synthesis of 5. To a 15 mL sealed tube was added **1a** (137 mg, 0.30 mmol, 1.0 equiv), CuBr (43 mg, 0.30 mmol,

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1.0 equiv), BHT (132 mg, 0.6 mmol, 2.0 equiv), and dry CH_3CN (3 mL, 0.1 M). The resulting mixture was heated at 100 °C in an oil bath for 3 h. After cooling, the reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated in vacuo, and the obtained residue was purified by silica gel column chromatography (EA/hexane = 1:15) to afford compound **5**.

*Ethyl 2-Bromo-2-(3,5-di-tert-butyl-4-hydroxybenzyl)-3-((4-methoxyphenyl)amino)-3-phenylpro panoate (**5**).* 47 mg, 31% yield; yellow solid; R_f = 0.55 (EA/hexane = 1:5, *V*:*V*); mp 171−173 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.30−7.28 (m, 2H), 7.22−7.20 (m, 3H), 6.75 (s, 2H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.50 (d, *J* = 9.0 Hz, 2H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.63 (s, 3H), 3.18 (s, 2H), 1.14 (s, 18H), 1.10 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 185.9, 166.0, 158.9, 157.7, 146.7, 140.6, 132.5, 131.7, 129.9, 129.4, 128.9, 127.6, 113.3, 99.7, 66.5, 59.2, 55.4, 41.0, 34.8, 29.4, 14.4; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{33}H_{42}NO_4$ 516.3108, found 516.3104.

Procedure for the Synthesis of 7. To a 15 mL sealed tube was added **6** (117 mg, 0.30 mmol, 1.0 equiv), CuBr (43 mg, 0.30 mmol, 1.0 equiv), and dry CH_3CN (3 mL, 0.1 M). The resulting mixture was heated at 100 °C in an oil bath for 3 h. After cooling, the reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated in vacuo, and the obtained residue was purified by silica gel column chromatography (EA/hexane = 1:10) to afford compound **7.**

*Ethyl 5-Methoxy-3-methyl-2-phenyl-3H-indole-3-carboxylate (**7**).* 58 mg, 62% yield; yellow oil; R_f = 0.28 (EA/hexane = 1:10, *V*:*V*); mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.88 (m, 2H), 7.64−7.59 (m, 1H), 7.48−7.40 (m, 3 H), 6.98−6.90 (m, 2H), 4.19−4.10 (m, 1H), 4.03−3.94 (m, 1H), 3.84 (s, 3H), 1.70 (s, 3H), 0.99 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.1, 171.8, 158.9, 148.7, 143.6, 132.3, 130.7, 128.8, 128.1, 121.8, 114.2, 107.7, 62.3, 61.9, 55.9, 21.3, 13.9; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{19}H_{20}NO_3$ 310.1438, found 310.1434.

Procedure for the Synthesis of 3a and 9 from 1a. To a 15 mL sealed tube was added **1a** (137 mg, 0.3 mmol, 1.0 equiv), CuBr (43 mg, 0.30 mmol, 1.0 equiv), 1,3,5-trimethoxybenzene (101 mg, 0.6 mmol, 2.0 equiv), and dry CH_3CN (3 mL, 0.1 M). The resulting mixture was heated at 100 °C in an oil bath for 3 h. After cooling, the reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated in vacuo, and the obtained residue was purified by silica gel column chromatography (EA/hexane = 1:20−1:10) to afford **3a** and **9** with equal yields.

*Ethyl 5-Methoxy-2-phenyl-1H-indole-3-carboxylate (**3a**).* 70 mg, 79% yield; white solid; R_f = 0.24 (EA/hexane = 1:5, *V*:*V*); mp 188−190 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.06 (s, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.58−7.56 (m, 2H), 7.36−7.33 (m, 3H), 7.18 (d, *J* = 9 Hz, 1H), 6.88 (dd, *J* = 2.5, 9.0 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.9, 155.7, 145.1, 132.2, 130.4, 129.6, 129.0, 128.6, 128.0, 113.3, 112.2, 104.1, 103.6, 59.7, 55.7, 14.3; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{18}H_{17}NNaO_3$ 318.1101, found 318.1088.

*2-Bromo-1,3,5-trimethoxybenzene (**9**).* 59 mg, 79% yield; white solid; R_f = 0.55 (EA/hexane = 1:5, *V*:*V*); mp 98−100 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 6.16 (s, 2H), 3.86 (s, 6H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 160.6, 157.6, 92.1, 91.7, 56.5, 55.6; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_9H_{11}BrNaO_3$ 268.9784, found 268.9783.

Procedure for the Synthesis of 10. Under N_2 atmosphere, to a solution of **2a** (93 mg, 0.25 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (15 mg, 0.0125 mmol, 5 mol %) in dry toluene (5 mL, 0.05 M) was added K_2CO_3 (70 mg, 0.5 mmol, 2 equiv) and $PhB(OH)_2$ (61 mg, 0.5 mmol, 2 equiv). The vigorously stirred mixture was heated to 100 °C in an oil bath for 2 h (monitored by TLC). After cooling, the mixture was filtered through a pad of Celite, and the filter cake was washed with EA. The organic mixture was concentrated in vacuo, and the residue was purified by column chromatography (EA/hexane = 1:10) to afford **10**.

*Ethyl 5-Methoxy-2,6-diphenyl-1H-indole-3-carboxylate (**10**).* 81 mg, 87% yield; white solid; R_f = 0.24 (EA/hexane = 1:5, *V*:*V*); mp 238−240 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.75 (s, 1H), 7.81 (s, 1H), 7.62−7.60 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.43−7.41 (m, 2H), 7.39 (brs, 3H), 7.34−7.31 (m, 1H), 7.23 (brs, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.7, 153.1, 145.0, 139.2, 132.2, 130.3, 129.9, 129.6, 129.2, 128.2, 128.1, 128.1, 128.0, 126.9, 113.1, 104.3, 103.2, 59.8, 56.0, 14.3; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{24}H_{22}NO_3$ 372.1594, found 372.1592.

Procedure for the Synthesis of 11. Compound **2a** (373 mg, 1 mmol, 1.0 equiv), $Pd(PPh_3)Cl_2$ (21 mg, 0.05 mmol, 5 mol %), and CuI (19 mg, 0.1 mmol, 10 mol %) were added into a 50 mL two-neck round-bottom flask equipped with a reflux condenser, which was evacuated and backfilled with N_2 three times. Then, phenylacetylene (153 mg, 1.5 mmol, 1.5 equiv), Et_3N (5 mL, 0.2 M), and THF (5 mL, 0.2 M) were added, and the resulting mixture was stirred at 80 °C in an oil bath for 5 h (monitored by TLC). After cooling, the reaction mixture was filtered through a pad of Celite and washed with EA. The filtrate was concentrated in vacuo, and the obtained residue was then purified by silica gel column chromatography (EA/hexane = 1:25−1:10) to afford **11**.

*Ethyl 5-Methoxy-2-phenyl-6-(phenylethynyl)-1H-indole-3-carboxylate (**11**).* 320 mg, 81% yield; yellow solid; R_f = 0.21 (EA/hexane = 1:5, *V*:*V*); mp 173−175 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.16 (s, 1H), 7.70−7.69 (m, 2H), 7.64 (s, 1H), 7.56 (s, 1H), 7.55 (brs, 2H), 7.51−7.49 (m, 3H), 7.44−7.40 (m, 3H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.3, 155.2, 146.1, 131.6, 131.2, 129.9, 129.1, 128.9, 128.7, 128.3, 127.8, 123.1, 116.2, 107.4, 103.1, 101.9, 92.0, 87.4, 59.8, 59.1, 55.7, 14.1; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{22}NO_3$ 396.1594, found 396.1597.

Procedure for the Synthesis of 12. To a solution of **2a** (373 mg, 1 mmol, 1.0 equiv) in dry DCM (10 mL, 0.1 M) was added BBr_3 (0.125 mL, 25.6 mg, 1.3 mmol, 1.3 equiv) at −20 °C, and the resulting mixture was stirred at 0 °C. TLC indicated completion of the reaction (6 h), and water was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with DCM (10 mL × 3). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EA/hexane = 1:10) to afford compound **12.**

*Ethyl 6-Bromo-5-hydroxy-2-phenyl-1H-indole-3-carboxylate (**12**).* 263 mg, 73%; yellow solid; R_f = 0.41 (EA/hexane = 1:3, *V*:*V*); mp 205−207 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.80 (s, 1H), 7.70 (s, 1H), 7.67−7.64 (m, 2H), 7.52 (s, 1H), 7.48−7.46 (m, 3H), 4.17 (q, *J* = 7.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.3, 149.0, 145.2, 131.7, 130.3, 129.8, 128.9, 127.9, 127.8, 115.2, 106.5, 106.1, 102.1, 59.0, 14.2; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{17}H_{15}BrNO_3$ 360.0230, found 360.0226.

Procedure for the Synthesis of 13. To a solution of **2a** (93 mg, 0.25 mmol, 1.0 equiv) in THF (5 mL, 0.05 M) was added 1N NaOH (1 mL, 4.0 equiv), and the resulting mixture was stirred at 90 °C in an oil bath for 20 h. After cooling, 1 N HCl was introduced into the reaction mixture to adjust the pH value (2−3). The reaction mixture was extracted with ethyl acetate (20 mL × 3), washed with saturated brine, and dried over Na_2SO_4. Then, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (EA/hexane = 1:10) to afford compound **13**.

*6-Bromo-5-methoxy-2-phenyl-1H-indole (**13**).* 51 mg, 68% yield; white solid; R_f = 0.53 (EA/hexane = 1:5, *V*:*V*); mp 160−162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.49 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.55 (s, 1H), 7.49−7.44 (m, 2H), 7.35−7.31 (m 1H), 7.19 (s, 1H), 6.85 (d, *J* = 1 Hz, 1H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 149.4, 138.9, 132.5, 131.9, 128.9, 128.6, 127.6, 125.0, 115.1, 105.9, 102.3, 98.7, 56.3; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{12}BrNNaO$ 323.9994, found 323.9980.

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■ ASSOCIATED CONTENT

Supporting Information

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NMR spectra of synthesized compounds (**2a−2t**, **3a**, **5**, **7**, **9−13**), $^{1}H-^{1}H$ NOESY experiments of **2q−2t**, X-ray crystallography data (**2a**) (PDF)

FAIR data, including the primary NMR FID files, for compounds **2a−2o** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **2q−2t**, **3a**, **5**, **7**, and **9−13** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **2q−2t** (ZIP)

Accession Codes

CCDC 2035288 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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