JOC Note

Synthesis of N-Substituted Indole-3-carboxylic Acid Derivatives via Cu(I)-Catalyzed Intramolecular Amination of Aryl Bromides

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A variety of N-alkylated and N-arylated derivatives of methyl 1*H*-indole-3-carboxylate were synthesized efficiently via Ullmann-type intramolecular arylamination, using the CuI−K_3PO_4−DMF system. This catalytic amination procedure can be performed with good to high yields under mild conditions under an air atmosphere.

The indole nucleus is one of the most widely distributed heterocyclic ring systems in nature.[1] Also, the indole ring system has become an important structural component in many synthetic pharmaceuticals.[2] As a result, a great number of various methods for the preparation of indoles have been developed with use of intermolecular and intramolecular approaches.[3]

Recent advances of transition metal chemistry in organic synthesis have provided new versatile catalytic methodologies for the synthesis of indoles from various arene derivatives via different bond formation. Among transition metals, the most extensively investigated and employed metal for the construction of the indole ring system was palladium.[4] However, recent considerable progress in copper-catalyzed organic reactions has provided several new convenient routes to indole derivatives.[5] In the past decade, copper-catalyzed C−N bond formation via coupling between amines or amides with aryl halides has received significant attention and provided a versatile method for the synthesis of a wide range of arylamines.[6] A number of useful synthetic protocols utilizing various combinations of a copper source, a ligand, a base, and a solvent have been developed to achieve a high efficiency of the Ullmann-type amination reaction of various substrates under mild conditions.[7] On the other hand, intramolecular Ullmann coupling reactions have remained less explored. To the best of our knowledge, only a few examples of intramolecular copper-catalyzed amination of aryl (or vinyl) halides have been reported, which led to the formation of nitrogen heterocyclic compounds.[8] Application of the copper-catalyzed amination methodology for the construction of the indole ring via a key N(1)−C(7a) bond formation[9] has been demonstrated by the synthesis of pyrazolo[1,5-*a*]indoles[5b] and indole- and 6-azaindole-2-carboxylates.[5f]

Indole-3-carboxylic acids and the corresponding esters have found significant use as building blocks for the synthesis of pharmaceutically important molecules.[10] A number of effective means for the assembly of indole-3-carboxylic acid derivatives have been developed, which include either the formation of the

(1) For selected recent reviews on indole-containing natural products, see: (a) Huguchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843−868. (b) O'Connor, S. E.; Maresh, J. *Nat. Prod. Rep.* **2006**, *23*, 532–547. (c) Kawasaki, T.; Huguchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761–793. (d) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442–453. (e) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278–311. (f) Lounasmaa, M.; Tolvanen, N. *Nat. Prod. Rep.* **2000**, *17*, 175–191.

(2) For selected recent reports, see: (a) Suzen, S. *Top. Heterocycl. Chem.* **2007**, *11*, 145–178. (b) Ölgen, S.; Kaessler, K.; Nebioğlu, D.; Joachim, J. *Chem. Biol. Drug Des.* **2007**, *70*, 547–551. (c) Smart, B. P.; Oslund, R. S.; Walsh, L. A.; Gelb, M. N. *J. Med. Chem.* **2006**, *49*, 2858–2860. (d) Dandia, A.; Singh, N.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. *Bioorg. Med. Chem.* **2006**, *14*, 2409–2417.

(3) For recent reviews on indole synthesis, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075. (b) Hamphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (c) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491–2515.

(4) For reviews, see ref 3b and the following: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Patil, S.; Buolamwini, J. K. *Curr. Org. Synth.* **2006**, *3*, 477–498.

(5) For recent reports, see: (a) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625−628. (b) Zhu, Y.-M.; Qin, L.-N.; Liu, R.; Ji, S.-J.; Katayama, H. *Tetrahedron Lett.* **2007**, *48*, 6262–6266. (c) Tanimori, S.; Ura, H.; Kirihata, M. *Eur. J. Org. Chem.* **2007**, 3977–3980. (d) van den Hoogenband, A.; Lange, J. H. M.; den Hartog, J. A.; Henzen, R.; Terpstra, J. W. *Tetrahedron Lett.* **2007**, *48*, 4461–4465. (e) Ohno, H.; Ohta, Y.; Oishi, S.; Fudjii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298. (f) Barberris, C.; Gordon, D.; Thomas, C.; Zhang, X.; Cusack, K. P. *Tetrahedron Lett.* **2005**, *46*, 8877–8880.

(6) For reviews, see: (a) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166–4176. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439. (e) Corbert, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.

(7) Several supporting ligands have been introduced to achieve a high efficiency of Ullmann coupling under mild reaction conditions, among them: (a) *N*,*N*-Diethylsalicylamide: Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793–796. (b) *β*-Diketone: Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743. (c) *β*-Keto ester: Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863–3867. (d) 2-Hydroxybenzaldehyde *N*-phenylhydrazone: Jiang, Q.; Jiang, D.; Jiang, Y.; Zhao, Y. *Synlett* **2007**, 1836–1842. (e) *N*-Hydroxyimide: Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, *72*, 8943–8946. (f) Hyppuric acid : Mao, J.; Guo, J.; Song, H.; Ji, S.-J. *Tetrahedron* **2008**, *64*, 1383–1387. (g) Glyoxale bis hydrazone: Mino, T.; Harada, Y.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 614–620. (h) Amino acids: Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455. (i) Amino acids: Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y. D.; Ma, D. W. *Synthesis* **2005**, 496–499. (j) *N*,*N*-Dimethylaminoethanol: Twieg, H., Jr.; R., J.; Lu, Z. K.; Huang, S. P. D. *Tetrahedron Lett.* **2003**, 2453–2455. (k) Ethylene glycol: Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584. (l) 1,10-Phenantroline: Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317. (m) 8-Hydroxyquinoline : Liu, L.; Frohn, M.; Domingueez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135–10138. (n) 1,2-Diamines : Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428. (o) *rac*-1,1′-Binaphthol : Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672–674.

(8) (a) Pyrroles: Pan, Y.; Lu, H.; Fang, Y.; Chen, L.; Qian, J.; Wang, J.; Li, C. *Synthesis* **2007**, 1242–1246. (b) Pyrrolo[2,3-*c*]pyridine, see ref 5f. (c) 1-Aryl-1*H*-indazoles : Liu, R.; Zhu, Y.; Qin, L.; Ji, S. *Synth. Commun.* **2008**, *38*, 249–254. (d) 2-Aryl-2*H*-indazoles : Liu, R.; Zhu, Y.; Qin, L.; Ji, S.; Katayama, H. *Heterocycles* **2007**, *71*, 1755–1763. (e) Oxindoles: ref 5d. (f) *β*-Lactams: Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365–5367. (g) Other lactams: Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035–2038. (h) Indolines: Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231–234. (i) 2-Aminobenzimidazoles: Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133–136.

(9) For examples of related Pd-catalyzed N-anulation routes to indoles, see: (a) Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, 4764–4766. (b) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403–406. (c) Watanabe, M.; Yamamoto, T.; Nishiyama, M. A *Angew. Chem., Int. Ed.* **2000**, *39*, 2501–2504.

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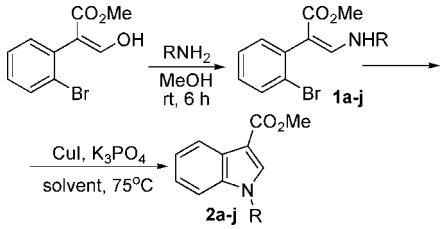
SCHEME 1. Synthesis of N-Substituted Methyl Indole-3-carboxylates via Cu(I)-Catalyzed Intramolecular Amination of Aryl Bromides



indole ring system[11] or the introduction of a substituent to the nitrogen atom.[12] All of these approaches cannot be regarded as a general approach to both N-alkyl and N-aryl derivatives of indole-3-carboxylic acid.

Herein, we wish to describe an efficient method for the synthesis of N-substituted indole-3-carboxylic acid derivatives via the copper(I)-catalyzed cyclization of N-substituted methyl 3-amino-2-(2-bromophenyl)acrylates **1**. Substrates **1** are readily achieved in nearly quantitative yields by the reaction of methyl 2-(2-bromophenyl)-2-formylacetate[13] with various primary amines. We first utilized N-benzyl derivative **1a** (Scheme 1, R = CH_2Ph), as a mixture of cis and trans isomers, to examine the possibility of indole ring formation via the Cu(I)-catalyzed intramolecular amination reaction. In 2002, Buchwald and coworkers reported an operationally simple CuI (5 mol %)−ethylene glycol (2 equiv)-catalyzed amination of aryl iodides and bromides.[7k] This amination protocol can be successfully performed in unpurified 2-propanol as a solvent and K_3PO_4 (2 equiv) as a base even without protection from air or moisture. These attractive reaction conditions (Table 1, A conditions) were used to carry out the intramolecular amination reaction of substrate **1a**. It was found that the ring closure reaction proceeded smoothly and gave a mixture of methyl 1-benzyl-1*H*-indole-3-carboxylate (**2a**, R = CH_2Ph, Scheme 1) and corresponding isopropyl ester **2a′** in 1:3 ratio and in 86% total yield after 6 h at 75 °C (bath temperature). To avoid the transesterification product we decided to investigate alternative solvents. Only a trace amount, if any, of the product was detected when the reaction was performed in dioxane, acetonitrile, and *tert*-butyl alcohol. The best yield and a significant rate enhancement were observed, however, if DMF was used as the solvent (B conditions, 91% after 4 h at 75 °C).

Using the optimal reaction protocol we applied this methodology to the synthesis of methyl 1*H*-indole-3-carboxylate with various substituents at the nitrogen atom. As shown in Table 1, both aliphatic and aromatic amines can be utilized in the Cu(I)−ethylene glycol-catalyzed synthesis of a number of indoles **2** in moderate to good yields. High yields with quantitative conversion of starting materials were achieved with unhindered amines (entries 2, 4, 13, 18, and 21). The reaction seemed to be sensitive to the steric hindrance. α-Branched alkylamines (entries 6, 10, and 14) and ortho-substituted anilines (entries 17 and 19) required longer reaction times (9 h); however, yields of **2** were moderate due to the transesterification with ethylene glycol (entry 7). Applying the ligandless conditions C resulted in the product formation in comparable yields for slightly longer reaction times (entries 2 vs 3, 4 vs 5, 6 vs 8 and 21vs 22).

The formation of N-*tert*-butyl indole **2d** under the C conditions was found to be very problematic. After long reaction time (20 h) the reaction of **1d** was only 46% complete (determined by ^{1}HNMR) with the formation of the corresponding indole **2d** in 32% yield (entry 12). The cyclization of **1d** was much slower than the reaction of all other enamines **1**.[14] Another hindered amine such as cyclohexylamine gave a similar result and the corresponding indole was prepared by using the C conditions in only 57% yield (entry 16). On the other hand, ortho-substituted anilines such as *o*-toluidine and even more sterically hindered 2,4,6-trimethylaniline under the ligandless conditions gave the corresponding indoles in good yields (entries 17 and 19). It should be noted that the reaction of 2,4,6-trimethylaniline with methyl 2-(2-bromophenyl)-2-formylacetate was much slower (48 h) than the reaction of all over amines including *tert*-butylamine (6 h). Moreover, the reaction of methyl 2-(2-bromophenyl)-2-formylacetate with weakly nucleophilic anilines such as 4-nitro- and 2-trifluoromethylanilines failed to give the desired enamines **1**, only starting materials were detected even after refluxing a toluene solution for several hours. Thus, this protocol seemed to be unsuitable for the preparation of 1-aryl-1*H*-indole-3-carboxylic acid derivatives containing strong electron-withdrawing substituents in ortho and para positions of the phenyl ring.

In summary, we have shown a new efficient method to produce N-substituted 1*H*-indole-3-carboxylic acid derivatives via copper(I)-catalyzed intramolecular C−N bond formation. Nonhindered primary alkyl and aryl amines can be involved in the reaction under mild conditions. This protocol is simple and avoids the use of an inert atmosphere without loss of yields. This method is complementary to existing methods for the construction of the indole ring.

Experimental Section

General Procedure. To a solution of methyl 2-(2-bromophenyl)-2-formylacetate[13] (500 mg, 1.94 mmol) in methanol (5 mL) was added a corresponding amine (1.94 mmol) at room temperature. After being stirred for 6 h at the same temperature solvent was evaporated to dryness under reduced pressure. A crude product was diluted with 8 mL of 2-propanol (**Conditions A**) or DMF (**Conditions B**). CuI (19 mg, 0,194 mmol), anhydrous K_3PO_4 (0.826 g, 3.9 mmol), and ethylene glycol (241 μl, 3.9 mmol) were added. The reaction mixture was heated at 75−80 °C (bath temperature) for the time specified. The reaction mixture was allowed to cool to room temperature. Solvent was evaporated to dryness under reduced pressure. Water (8 mL) was added to the residue and the mixture was extracted (3 × 4 mL) with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed in vacuo to yield the crude product that was purified by column chromatography on silica gel, using a mixture hexane/ethyl acetate (20/1) as eluent.

(10) For examples, see: (a) Reference 2b. (b) Hopkins, C. R.; Czekaj, M.; Kaye, S. S.; Gao, Z.; Pribish, J.; Pauls, H.; Liang, G.; Sides, K.; Cramer, D.; Cairns, J.; Luo, Y.; Lim, H.-K.; Vaz, R.; Rebello, S.; Maignan, S.; Dupuy, A.; Mathieu, M.; Levell, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2734–2737. (c) Söderberg, B. C. G.; Banini, S. R.; Turner, M. R.; Minter, A. R.; Arrington, A. K. *Synthesis* **2008**, 903–912, and references therein.

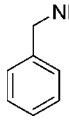
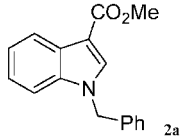
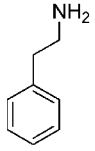
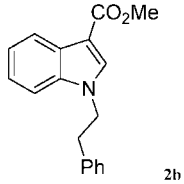
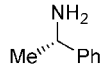
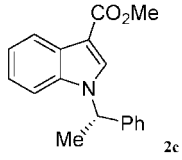
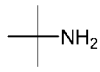
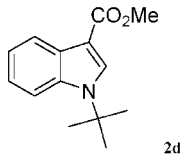
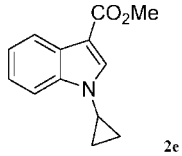
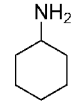
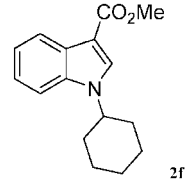
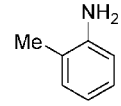
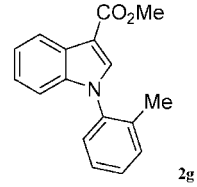
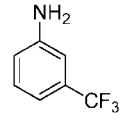
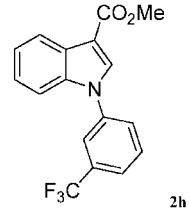
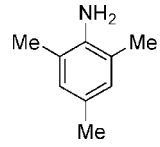
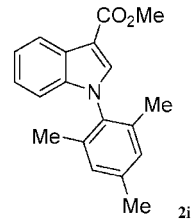
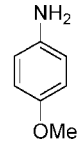
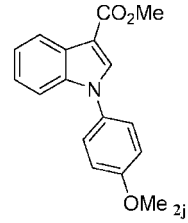
(11) For recent reports on the synthesis of indole-3-carboxylic acid derivatives, see: (a) Reference 10c. (b) Sole, D.; Serrano, O. *J. Org. Chem.* **2008**, *73*, 2476–2479.

(12) For an example of copper-catalyzed N-arylation of methyl indole-3-carboxylate, see: Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.

(13) Beautement, K.; Clough, J. M.; Godfrey, C. R. A. EP. Patent 0307101. 1989. *Chem. Abstr.* **1989**, 111. 114868.

(14) This result is consistent with the literature report on the preparation of *N-tert*-butyloxindole derivatives via Cu(I)-catalyzed intramolecular amidation, see ref 5d.

TABLE 1. Synthesis of N-Substituted Methyl Indole-3-carboxylates via Cu(I)-Catalyzed Intramolecular Amination of Aryl Bromides

#	RNH_2	Product	Conditions[a]	Yield, %[b]
1		 **2a**	A, 6h	22[c]
2			B, 4h	91 (92[d])
3			C, 6h	76
4		 **2b**	B, 4h	80
5			C, 6h	75
6		 **2c**	B, 4h	60
7			B, 9h	56[c]
8			C, 6h	60
9			C, 9h	68
10		 **2d**	B, 6h	20[e]
11			B, 9h	8[f]
12			C, 20h	32
13		 **2e**	B, 4h	78
14		 **2f**	B, 6h	25[f]
15			C, 6h	18[f]
16			C, 20h	57
17		 **2g**	C, 9h	65
18		 **2h**	B, 4h	74
19		 **2i**	C, 6h	77
20		 **2j**	A, 6h	89
21			B, 4h	94
22			C, 6h	92

[a] Conditions: (A) 5 mol % CuI, 2 equiv K_3PO_4, 2 equiv ethylene glycol, 2-propanol, 75 °C. (B) 5 mol % CuI, 2 equiv K_3PO_4, 2 equiv ethylene glycol, DMF, 75 °C. (C) 5 mol % CuI, 2 equiv K_3PO_4, DMF, 75 °C. [b] All yields refer to isolated products. [c] Corresponding isopropyl ester was also obtained in 64% yield. [d] Performed under argon. [e] Corresponding ester of ethylene glycol was obtained in 45% yield (determined by ^{1}HNMR). [f] Yield was determined by ^{1}H NMR.

Conditions C. ethylene glycol was not used.

The general procedure was followed to afford the following compounds:

Methyl 1-(2-phenylethyl)-1*H*-indole-3-carboxylate (2b). Yield 0.434 g (80%, conditions B), pale-yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (t, J = 7.5 Hz, 2H), 3.88 (s, 3H), 4.36 (t, J = 7.5 Hz, 2H), 7.05−7.07 (m, 2H), 7.22−7.39 (m, 8H), 7.65 (s, 1H), 8.17 (dd, J = 6.0, 3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.4, 48.7, 51.0, 106.9, 109.9, 121.8, 121.9, 122.8, 126.7, 127.0, 128.7, 128.8, 134.3, 136.3, 137.7, 165.5. MS, *m*/*z* (%) 279 (M^+, 26), 188 (100), 174 (9), 135 (15), 128 (16), 104 (24), 91 (38), 77 (21), 65 (14), 59 (8), 51 (15), 43 (39). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found: C, 77.38; H, 6.09.

(*S*)-Methyl 1-(1-Phenylethyl)-1*H*-indole-3-carboxylate (2c). Yield 0.367 g (68%, conditions C), pale-yellow amorphous solid. (*S*)-(−)-1-Phenylethylamine ($[\alpha]^{20}_D$ −31.8 (neat), 80% ee) was used. $[\alpha]^{23}_D$ +120.63 (*c* 11.06, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (d, J = 7.5 Hz, 3H), 3.92 (s, 3H), 5.66 (q, J = 7.5 Hz, 1H), 7.10−7.33 (m, 8H), 8.03 (s, 1H), 8.18 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 51.0, 55.7, 107.4, 110.7, 121.7, 122.1, 122.8, 125.9, 126.9, 127.9, 129.0, 131.7, 136.7, 141.3, 165.6. MS, *m*/*z* (%) 279 (M^+, 33), 175 (27), 144 (22), 105 (100), 77 (18), 51 (8). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found: C, 77.44; H, 6.15.

Methyl 1-*tert*-Butyl-1*H*-indole-3-carboxylate (2d). Yield 0.114 g (32%, conditions C), pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 9H), 3.92 (s, 3H), 7.22−7.31 (m, 2H), 7.68 (dd, J = 6.1, 2.6 Hz, 1H), 8.03 (s, 1H), 8.26 (dd, J = 5.5, 3.08 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 50.9, 57.0, 105.8, 113.9, 121.4, 121.9, 122.0, 129.1, 132.3, 133.0, 165.7. MS, *m*/*z* (%) 231 (M^+, 45), 175 (66), 144 (100), 130 (5), 116 (22), 103 (7), 89 (27), 84 (8), 75 (11), 63 (16), 57 (66), 41 (75). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.71; H, 7.38.

Methyl 1-Cyclopropyl-1*H*-indole-3-carboxylate (2e). Yield 0.328 g (78%, conditions B), tan amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02−1.21 (m, 4H), 3.39−3.47 (m, 1H), 3.92 (s, 3H), 7.25−7.36 (m, 2H), 7.61 (dd, J = 6.5, 3.3 Hz, 1H), 7.87 (s, 1H), 8.17 (dd, J = 6.4, 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.2, 27.6, 51.0, 107.0, 110.8, 121.7, 122.2, 122.8, 126.7, 134.5, 137.9, 165.5. MS, *m*/*z* (%) 215 (M^+, 60), 200 (29), 184 (70), 156

(100), 143 (17), 128 (45), 115 (40), 101 (31), 89 (27), 75 (45), 63 (35), 59 (10), 51 (39), 39 (85). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.57; H, 6.12.

Methyl 1-Cyclohexyl-1*H*-indole-3-carboxylate (2f). Yield 0.284 g (57%, conditions C), pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.16−1.34 (m, 2H), 1.39−1.55 (m, 2H), 1.59−1,75 (m, 2H), 1.85−1.97 (m, 2H), 2.08−2.19 (m, 2H), 3,95 (s, 3H), 4.14−4.26 (m, 1H), 7.25−7.34 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 8.18 (dd, J = 6, 3.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 25.5, 25.8, 33.4, 50.9, 52,2, 106.9, 110.1, 121.8, 121.9, 122.5, 125.0, 132.8, 134.2, 165.7. MS, *m*/*z* (%) 257 (M^+, 64), 226 (10), 175 (46), 170 (15), 154 (15), 149 (21), 144 (100), 130 (11), 115 (30), 103 (7), 89 (35), 83 (19), 75 (12), 63 (20), 59 (17), 55 (70), 51 (15), 41 (75). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.71; H, 7.47.

Methyl 1-(2-Methylphenyl)-1*H*-indole-3-carboxylate (2g). Yield 0.336 g (65%, conditions C), pale-yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.92 (s, 3H), 7.00 (d, J = 8.2 Hz, 1H), 7.17−7.44 (m, 6H), 7.86 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 51.1, 108.4, 111.1, 121.6, 122.2, 123.3, 126.1, 127.1, 127.9, 129.2, 131.4, 134.8, 135.6, 137.0, 137.7, 165.6. MS, *m*/*z* (%) 265 (M^+, 66), 234 (70), 204 (45), 191 (8), 178 (16), 143 (8), 133 (7), 115 (32), 106 (7), 102 (42), 95 (9), 91 (67), 77 (40), 65 (100), 51 (77), 39 (97). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found: C, 77.01; H, 5.67.

Methyl 1-(3-(Trifluoromethyl)phenyl)-1*H*-indole-3-carboxylate (2h). Yield 0.460 g (74%, conditions B), tan solid. Mp 129−131 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.22−7.37 (m, 2H), 7.46 (d, J = 8.2 Hz, 1H), 7.65−7.80 (m, 4H), 8.01 (s, 1H), 8.25 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.2, 110.1, 110.6, 121.6 (q, J_{C-F} = 3.7), 122.1, 122.9, 123.5 (q, J_{C-F} = 273.2 Hz) 123.9, 124.4 (q, J_{C-F} = 3.7 Hz), 127.0 (br), 127.9, 130.6, 132.5 (q, J_{C-F} = 33.1 Hz), 133.6, 136.4, 139.1 (br), 165.1. MS, *m*/*z* (%) 319 (M^+, 69), 288 (100), 233 (12), 191 (22), 145 (20), 125 (6), 115 (11), 95 (14), 89 (22), 75 (26), 69 (16), 63 (27), 50 (17), 39 (16). Anal. Calcd for $C_{17}H_{12}F_3NO_2$: C, 63.95; H, 3.79. Found: C, 63.91; H, 3.82.

Methyl 1-(2,4,6-Trimethylphenyl)-1*H*-indole-3-carboxylate (2i). Yield 0.438 g (77%, conditions B), tan solid. Mp 113−115 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 6H), 2.41 (s, 3H), 3,98 (s, 3H), 6.93 (d, J = 7.7 Hz, 1H), 7.05 (s, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.81 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 21.1, 51.1, 108.4, 110.7, 121.6, 122,2, 123.3, 126.1, 129.2, 133.4. 134.7, 136.4, 137.1, 139.0, 165.7. MS, *m*/*z* (%) 293 (M^+, 44), 262 (36), 234 (34), 218 (46), 204 (23), 143 (24), 130 (14), 124 (35), 115 (74), 109 (40), 102 (34), 95 (23), 91 (80), 77 (84), 63 (55), 51 (67), 45 (7), 39 (100). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.75; H, 6.52.

Supporting Information Available: Experimental procedures for starting materials, full characterization data for previously known compounds, and copies of ^{1}H, ^{13}C, and mass spectra for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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