JOC Article

Facile Access to Polysubstituted Indoles via a Cascade Cu-Catalyzed Arylation−Condensation Process

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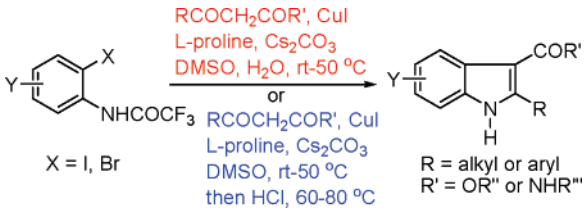
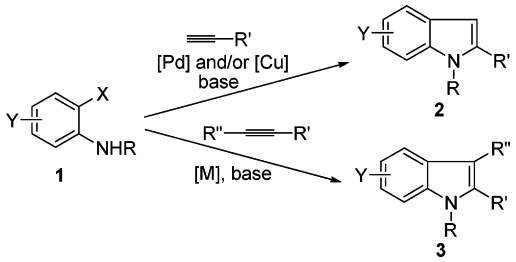


CuI/L-proline-catalyzed cross-coupling of 2-halotrifluoroacetanilides with β-keto esters and amides followed by in situ acidic hydrolysis delivered 2,3-disubstituted indoles. The halides bearing a strong electron-withdrawing group in the 4-position can undergo in situ basic hydrolysis to provide the corresponding indoles. Polysubstituted indoles can be prepared from substituted 2-halotrifluoroacetanilides with high regioselectivity.

Introduction

The indole structure is probably the most common heterocycle found in natural products.[1] Substituted indoles have been referred to as "privileged structures" owing to their excellent binding ability to many receptors.[2a] This fact led to a great number of efforts in elaborating and functionalizing indoles over the past few decades.[2−4] From the numerous methods developed for indole synthesis, one of the most attractive procedures involves the condensation of *o*-haloaniline derivatives with terminal alkynes (Scheme 1)[2,5−6] due to the ease of preparation and modification. However, as this process only delivers 2-substituted indoles **2**,[5,6] this fact promoted further research efforts to elaborate 2,3-disubstituted indoles.[7] Direct construction of 2,3-disubstituted indoles **3** from *o*-haloanilines was achieved by a palladium-catalyzed reaction of *o*-haloaniline derivatives

SCHEME 1. Assembly of Indoles via Coupling of *o*-Haloaniline Derivatives and Alkynes



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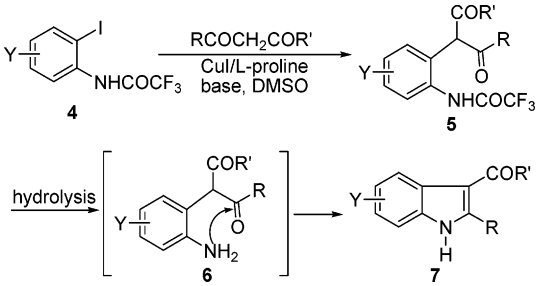
with internal alkynes.[8] Although this is an efficient process and has been used widely for the preparation of complex indoles,[9] it suffers from poor regioselectivity for most substrates.

During our studies of the amino acid promoted Ullmann reaction, we recently revealed that in some cases an ortho-substituent effect, directed by NHCOR (amido) groups, enables the coupling of 2-halotrifluoroacetanilides with phenols,[10] 2-methyl acetoacetates,[11] and primary amines[12] to occur at room temperature or even −45 °C. We envisaged that, under the influence of an ortho-substituent effect, coupling of 2-iodotrifluoroacetanilides **4** with β-keto esters[13] should proceed smoothly affording amides **5**, which, upon hydrolysis under basic or acidic conditions, would generate anilines **6** in which the free amine would attack the ketone moiety spontaneously to provide 2,3-disubstituted indoles **7** (Scheme 2). Indeed, two groups have attempted to assemble 2,3-disubstituted indoles via the Cu-promoted coupling of 2-iodoaniline with β-keto esters and β-diketones, but their coupling reactions required higher temperatures (120−130 °C), and only two examples were examined.[14]

SCHEME 2. Elaboration of 2,3-Disubstituted Indoles via a Cascade Coupling−Condensation Process

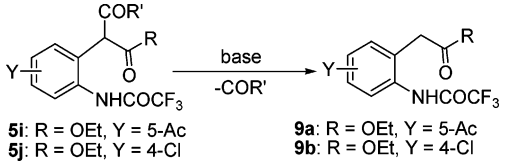


Results and Discussion

Considering that the trifluoroacetanilide moiety can be cleaved by basic hydrolysis, we initially tried to run this cascade process by introducing water to our previous reaction system.[13c] Accordingly, the reaction of 2-iodo-4-acyltrifluoroacetanilide **4a** with β-keto ester **8a** was conducted using 10% mol CuI, 20 mol % L-proline, and 4 equiv of Cs_2CO_3 in 0.5 mL of DMSO and 0.5 mL of water. To our delight, this reaction provided the desired indole **7a** in 73% yield at room temperature after 5 h (Table 1, entry 1). Encouraged by this result, we examined the reaction by using different iodides and β-keto esters. Some functionalized β-keto esters, such as benzyl substituted and olefin embodied β-keto esters **8b** and **8c** and ethyl 4-benzoxyacetoacetate **8d**, gave rise to the corresponding 2,3,5-trisubstituted indoles in satisfactory yields (Table 1, entries 2−4). Under the same conditions, β-keto amide **8e** provided indole **7e** in nearly quantitative yield (Table 1, entry 5).

Good results were also observed with iodides **4b** and **4c** that bear ester and nitro groups at the 4-position (Table 1, entries 6−8). However, when 2-iodo-5-acyl-trifluoroacetanilide **4d** was utilized, 2,3,6-trisubstituted indole **7i** was isolated in only 51% yield (entry 9), indicating that the position of the electron-withdrawing group at the 4- or 5-position of 2-iodotrifluoroacetanilides has some influence on the reaction process. In this case, a side product **9a** was produced in about 38% yield, most likely resulting from deacylation of the corresponding coupling product **5i** under basic conditions (Scheme 3). This side reaction was also observed by Parkinson and co-workers in their CuI-catalyzed coupling of aryl iodides and ethyl acetoacetate.[13g] Formation of **9a** illustrates that in this case, the cleavage step of the trifluoroacetanilide moiety is slow. This is understandable because the trifluoroacetanilide moiety in **4d** is more stable toward basic hydrolysis than in **4a**. The importance of the electronic effect to this reaction process was also demonstrated by the fact that 2-iodo-4-chlorotrifluoroacetanilide **4e** gave a poor yield of **7j** (together with about a 30% yield of **9b**; Table 1, entry 10).

SCHEME 3. Deacylation of β-Keto Esters 5i and 5j



The requirement of a strong electron-withdrawing group at the 4-position of 2-iodotrifluoroacetanilides, to ensure quick base-induced hydrolysis, limits the scope of the present indole formation process. To overcome this drawback, we decided to try acidic conditions to produce indoles from the coupling reaction products. Thus, a CuI/L-proline-catalyzed coupling reaction of 2-iodo-4-methyltrifluoroacetanilide **4f** with **8f** was carried out in DMSO at room temperature. It was found that after 5 h, the reaction was complete, and the corresponding coupling product was isolated in 85% yield, which was then treated with a solution of 22% HCl in MeOH at 80 °C for 1−2 h, affording indole **7k** in 84% yield. This result prompted us to run these two steps in a one-pot reaction. We were pleased to find that **7k** could be isolated in 67% yield after adding 37% HCl and methanol to the coupling reaction mixture and then heating at 70 °C for 1 h (Table 2, entry 1).

The newly established reaction conditions offered a solution to some problems we encountered before, which was evident from the fact that a good yield of **7j** was obtained from **4e** via the acid-induced hydrolysis strategy (Table 2, entry 2). However, no improvement was observed when applying **4d** (Table 2, entry 3), presumably due to heavy deacylation during the coupling reaction. Using 2-iodo-trifluoroacetanilide **4g** as the coupling partner, a number of activated methylene compounds was tested.

(8) For selected examples, see: (a) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921. (b) Zhou, H.; Liao, X.; Cook, J. M. *Org. Lett.* **2004**, *6*, 249. (c) Walsh, T. F.; Toupence, R. B.; Ujjainwalla, F.; Young, J. R.; Goulet, M. T. *Tetrahedron* **2001**, *57*, 5233.

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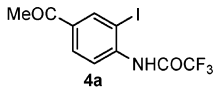
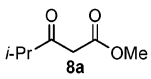
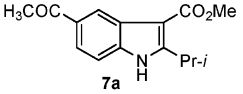
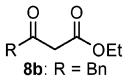
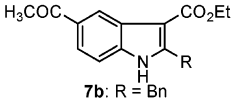
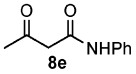
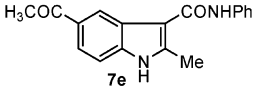
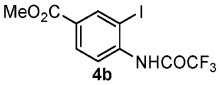
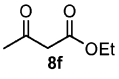
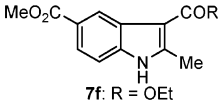
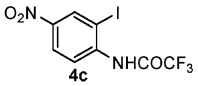
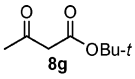
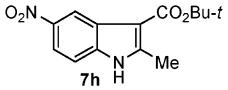
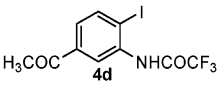
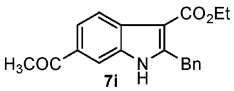
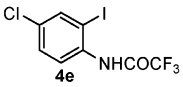
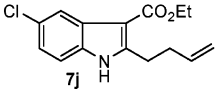
TABLE 1. Indole Synthesis via CuI/L-Proline-Catalyzed Coupling of 2-Iodotrifluoroacetanilides with β-Keto Esters and Amides with in Situ Base-Induced Hydrolysis[a]

entry	iodide	β-keto ester	indole	yield (%)[b]
1	 **4a**	 **8a**	 **7a**	73
2		 **8b**: R = Bn	 **7b**: R = Bn	86
3		**8c**: R = $(CH_2)_2CH{=}CH_2$	**7c**: R = $(CH_2)_2CH{=}CH_2$	72
4		**8d**: R = CH_2OBn	**7d**: R = CH_2OBn	67
5		 **8e**	 **7e**	99
6	 **4b**	 **8f**	 **7f**: R = OEt	69
7		**8e**	**7g**: R = NHPh	91
8	 **4c**	 **8g**	 **7h**	72
9	 **4d**	**8b**	 **7i**	51
10	 **4e**	**8c**	 **7j**	44

[a] Reaction conditions: iodide **4** (0.25 mmol), β-keto ester or acetoacetanilide **8** (0.5 mmol), CuI (0.025 mmol), L-proline (0.05 mmol), Cs_2CO_3 (1 mmol), DMSO (0.5 mL), H_2O (0.5 mL), rt, 5−24 h. [b] Isolated yield.

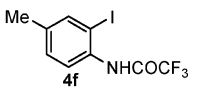
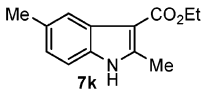
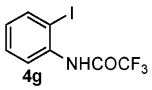
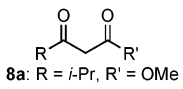
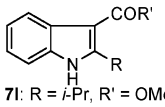
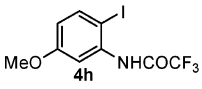
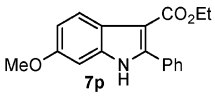
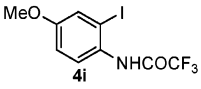
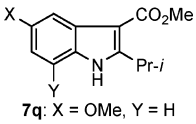
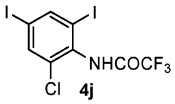
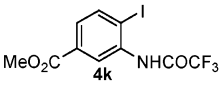
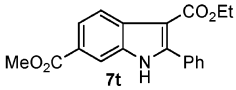
It was found that both α-aliphatic and α-aromatic β-keto esters were suitable for this process, delivering the corresponding 2-alkyl and 2-aryl indoles in good yields (Table 2, entries 4−6). It is noteworthy that *t*-butyl substituted β-keto ester **8h** worked well to afford indole **7m** in 82% yield (Table 2, entry 5), indicating that our method is suitable for the elaboration of sterically hindered indoles.

From β-keto amide **8e**, indole **7o** was prepared in 66% yield, demonstrating that variations at the 3-position of indoles are possible (Table 2, entry 7). Two 2-iodotrifluoroacetanilides bearing a methoxy group at either the 4- or the 5-position were compatible with the reaction conditions, leading to indoles **7p** and **7q** in reasonable yields (Table 2, entries 8 and 9). While 2,4-diiodo-6-chlorotrifluoroacetanilide **4j** was used, 2,3,5,7-tetrasubstituted indole **7r** was isolated as a single product (Table 2, entry 10), which provides further evidence that the ortho-substituent effect of the $NHCOCF_3$ group assists in the coupling reaction. The 5-iodo group of **7r** allows further coupling to produce more diverse indoles. The orientation of the ester group in 2-iodotrifluoroacetanilides seems to have little influence on the outcome of the reaction under acidic conditions, as good yields were observed from **4b** and **4k** (compare entries 11 and 12 in Table 2). Therefore, the process under acidic conditions is more generally applicable than the one involving base-induced hydrolysis.

We then explored if these two processes could be applied to 2-bromotrifluoroacetanilides (Table 3). It was found that the coupling step was rather sluggish at room temperature, but complete conversion could be achieved by raising the reaction temperature to 30−50 °C. For substrates with an electron-withdrawing group at the 4-position of 2-bromotrifluoroacetanilides, using mixed solvents (DMSO/H_2O) was useful for cleaving the trifluoroacetanilide moiety and directly afforded substituted indoles in good yields (Table 3, entries 1−3), while bromides bearing no electron-withdrawing groups delivered the desired indoles through acidic hydrolysis (Table 3, entries 4−7).

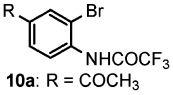
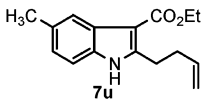
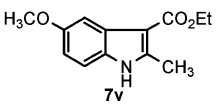
In conclusion, an efficient and high yielding cascade process for the assembly of 2,3-substituted indoles was developed, based on the CuI/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides with β-keto esters and amides followed by in situ acidic hydrolysis. It is noteworthy that this procedure can also be carried out by in situ basic hydrolysis of the trifluoroacetanilide moiety. However, this procedure requires a strong electron-withdrawing group in the 4-position of the 2-halotrifluoroacetanilides. Various functional groups survived our

TABLE 2. Indole Synthesis via CuI/L-Proline-Catalyzed Coupling of 2-Iodotrifluoroacetanilides with β-Keto Esters and Amides Followed by Acid-Induced Hydrolysis[a]

entry	iodide	β-keto ester	indole	yield (%)[b]
1	 **4f**	**8f**	 **7k**	67
2	**4e**	**8c**	**7j**	65
3	**4d**	**8b**	**7i**	53
4	 **4g**	 **8a**: R = *i*-Pr, R' = OMe	 **7l**: R = *i*-Pr, R' = OMe	87
5		**8h**: R = *t*-Bu, R' = OMe	**7m**: R = *t*-Bu, R' = OMe	82
6		**8i**: R = Ph, R' = OEt	**7n**: R = Ph, R' = OEt	77
7		**8e**	**7o**: R = Me, R' = NHPh	66
8	 **4h**	**8i**	 **7p**	66
9	 **4i**	**8a**	 **7q**: X = OMe, Y = H	61
10	 **4j**	**8a**	**7r**: X = I, Y = Cl	78
11	**4b**	**8a**	**7s**: X = CO_2Me, Y = H	70
12	 **4k**	**8i**	 **7t**	63

[a] Reaction conditions: iodide **4** (0.25 mmol), β-keto ester or acetoacetanilide **8** (0.5 mmol), CuI (0.025 mmol), L-proline (0.05 mmol), Cs_2CO_3 (1 mmol), DMSO (0.5 mL), rt, 3−20 h; then 37% HCl (2 mL), MeOH (2 mL), 60−80 °C, 0.5−2.5 h. [b] Isolated yield.

TABLE 3. Indole Synthesis via CuI/L-Proline-Catalyzed Coupling of 2-Bromotrifluoroacetanilides with β-Keto Esters[a]

entry	iodide	β-keto ester	indole	yield (%)[b]
1	 **10a**: R = $COCH_3$	**8b**	**7b**	70
2		**8c**	**7c**	60
3	**10b**: R = CO_2CH_3	**8e**	**7g**	85
4	**10c**: R = H	**8a**	**7l**	71
5		**8i**	**7n**	68
6	**10d**: R = CH_3	**8c**	 **7u**	64
7	**10e**: R = OCH_3	**8f**	 **7v**	58[c]

[a] Reaction conditions: bromide **10** (0.25 mmol), β-keto ester or acetoacetanilide **8** (0.5−0.75 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), Cs_2CO_3 (1 mmol), DMSO (0.5 mL), H_2O (0.5 mL, for entries 1−3), 30−50 °C, 24 h; then added was 37% HCl, MeOH, 60−80 °C, 1−2 h (for entries 4−7). [b] Isolated yield. [c] Coupling step took 48 h.

reaction conditions, including ketones, esters, and nitro, iodo, olefin, chloro, and benzoxy moieties. Our method allows the assembly of a wide range of substituted indoles in an efficient manner, thereby providing a useful tool in organic synthesis.

Experimental Section

General Procedure for the Synthesis of Polysubstituted Indoles from Aryl Iodides via Base-Induced Hydrolysis. A Schlenk tube was charged with aryl iodide (0.25 mmol), CuI (5 mg, 0.025 mmol), L-proline (6 mg, 0.05 mmol), and Cs_2CO_3 (326 mg, 1 mmol), evacuated, and backfilled with argon. A β-keto ester or amide (0.5 mmol), DMSO (0.5 mL), and H_2O (0.5 mL) were successively added. The reaction mixture was stirred at room temperature (rt) until the conversion was completed as monitored by TLC (5−24 h). The mixture was partitioned between ethyl acetate and saturated NH_4Cl, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 20:1 to 1:1 petroleum ether/ethyl acetate) to provide the desired product.

General Procedure for the Synthesis of Polysubstituted Indoles from Aryl Iodides via Acid-Induced Hydrolysis. A Schlenk tube was charged with aryl iodide (0.25 mmol), CuI (5 mg, 0.025 mmol), L-proline (6 mg, 0.05 mmol), and Cs_2CO_3 (326 mg, 1 mmol), evacuated, and backfilled with argon. A β-keto ester or amide (0.5 mmol) and DMSO (0.5 mL) were successively added. The reaction mixture was stirred at rt until the conversion was completed as monitored by TLC (3−20 h). To this solution, MeOH (2 mL) and 37% HCl (2 mL) were added. The resultant mixture was heated at 60−80 °C for 0.5−2.5 h. The cooled solution was partitioned between ethyl acetate and water. $NaHCO_3$ was added to neutralize the solution to pH 7−8 before the organic layer was separated. After being washed with water and brine, the solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 20:1 to 1:1 petroleum ether/ethyl acetate) to provide the desired product.

General Procedure for the Synthesis of Polysubstituted Indoles from Aryl Bromides via Base-Induced Hydrolysis. A Schlenk tube was charged with aryl bromide (0.25 mmol), CuI (10 mg, 0.05 mmol), L-proline (12 mg, 0.10 mmol), and Cs_2CO_3 (326 mg, 1 mmol), evacuated, and backfilled with argon. A β-keto ester or amide (0.5 mmol), DMSO (0.5 mL), and H_2O (0.5 mL) were successively added. After the reaction mixture was stirred at 40−50 °C for 24 h, it was partitioned between ethyl acetate and saturated NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 20:1 to 1:1 petroleum ether/ethyl acetate) to provide the desired product.

General Procedure for the Synthesis of Polysubstituted Indoles from Aryl Bromides via Acid-Induced Hydrolysis. A Schlenk tube was charged with aryl bromide (0.25 mmol), CuI (10 mg, 0.05 mmol), L-proline (12 mg, 0.10 mmol), and Cs_2CO_3 (326 mg, 1 mmol), evacuated, and backfilled with argon. A β-keto ester (0.75 mmol) and DMSO (0.5 mL) were successively added. After the resultant reaction mixture was stirred at 30−50 °C for 24−48 h, MeOH (2 mL) and 37% HCl (2 mL) were added, and then the mixture was stirred at 60−80 °C for 1−2 h. The cooled solution was partitioned between ethyl acetate and water. $NaHCO_3$ was added to neutralize the solution to pH 7−8 before the organic layer was separated. After being washed with water and brine, the solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 20:1 to 1:1 petroleum ether/ethyl acetate) to provide the desired product.

Methyl 5-Acetyl-2-isopropyl-1*H*-indole-3-carboxylate 7a. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.37 (d, J = 7.3 Hz, 6H), 2.60 (s, 3H), 3.89 (s, 3H), 4.10−4.20 (m, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.80 (dd, J = 1.4, 8.2 Hz, 1H), 8.72 (d, J = 1.4 Hz, 1H), 11.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.68, 26.67, 30.18, 50.94, 103.77, 111.03, 122.43, 123.66, 126.76, 131.27, 137.64, 155.46, 165.95, 199.08; ESI-MS m/z 260 $(M + H)^+$; HRMS calcd for $C_{15}H_{17}NO_3$ (M^+) 259.1208, found 259.1206.

Ethyl 5-Acetyl-2-benzyl-1*H*-indole-3-carboxylate 7b. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.41 (t, J = 7.3 Hz, 3H), 2.60 (s, 3H), 4.38 (q, J = 7.3 Hz, 2H), 4.59 (s, 2H), 7.12−7.45 (m, 6H), 7.80 (d, J = 8.6 Hz, 1H), 8.79 (d, J = 1.2 Hz, 1H), 11.15 (br s, 1H); ^{13}C NMR (100 MHz, d_6-acetone) δ 14.05, 25.88, 33.10, 59.40, 105.08, 111.30, 122.34, 123.28, 126.60, 126.82, 128.61, 128.81, 131.30, 138.21, 138.57, 148.12, 164.99, 197.06; ESI-MS m/z 322 $(M + H)^+$; HRMS calcd for $C_{20}H_{19}NO_3$ (M^+) 321.1365, found 321.1366.

Ethyl 5-Acetyl-2-(but-3-enyl)-1*H*-indole-3-carboxylate 7c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, J = 7.3 Hz, 3H), 2.50−2.56 (m, 2H), 2.70 (s, 3H), 3.30 (t, J = 7.3 Hz, 2H), 4.43 (q, J = 7.3 Hz, 2H), 4.97−5.09 (m, 2H), 5.84−5.90 (m, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.88 (dd, J = 1.8, 8.8 Hz, 1H), 8.82 (s, 1H), 9.68 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.58, 26.77, 27.57, 33.19, 59.93, 105.24, 111.20, 116.07, 122.45, 123.91, 126.99, 131.23, 137.14, 137.79, 149.56, 165.68, 199.45; ESI-MS m/z 286 $(M + H)^+$; HRMS calcd for $C_{17}H_{19}NO_3$ (M^+) 285.1365, found 285.1368.

Ethyl 5-Acetyl-2-(benzyloxymethyl)-1*H*-indole-3-carboxylate 7d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.3 Hz, 3H), 2.68 (s, 3H), 4.40 (q, J = 7.3 Hz, 2H), 4.71 (s, 2H), 5.13 (s, 2H), 7.20−7.45 (m, 6H), 7.90 (d, J = 8.6 Hz, 1H), 8.76 (s, 1H), 9.42 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.62, 26.71, 60.08, 65.73, 73.77, 104.35, 111.44, 122.76, 123.63, 126.66, 128.17, 128.33, 128.72, 131.65, 137.23, 137.35, 145.99, 165.21, 198.69; ESI-MS m/z 352 $(M + H)^+$; HRMS calcd for $C_{21}H_{21}NO_4$ (M^+) 351.1471, found 351.1475.

5-Acetyl-2-methyl-*N*-phenyl-1*H*-indole-3-carboxamide 7e. ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.58 (s, 3H), 2.63 (s, 3H), 7.04 (t, J = 7.6 Hz, 1H), 7.29−7.33 (m, 2H), 7.43 (d, J = 8.6 Hz, 1H), 7.72−7.79 (m, 3H), 8.41 (s, 1H), 9.76 (s, 1H), 12.01 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 13.77, 27.18, 110.55, 111.47, 120.45, 122.03, 123.53, 126.48, 129.12, 130.18, 138.00, 140.27, 141.82, 164.24, 198.02; ESI-MS m/z 293 $(M + H)^+$; HRMS calcd for $C_{18}H_{16}N_2O_2$ (M^+) 292.1212, found 292.1213.

3-Ethyl 5-Methyl 2-Methyl-1*H*-indole-3,5-dicarboxylate 7f. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.32 (t, J = 7.3 Hz, 3H), 2.63 (s, 3H), 3.82 (s, 3H), 4.26 (q, J = 7.3 Hz, 2H), 7.40 (d, J = 8.7 Hz, 1H), 7.72 (dd, J = 1.4, 8.7 Hz, 1H), 8.60 (s, 1H), 12.12 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 14.29, 14.95, 52.34, 59.58, 104.23, 111.73, 122.81, 123.12, 123.30, 127.01, 138.03, 146.95, 165.17, 167.62; ESI-MS m/z 262 $(M + H)^+$; HRMS calcd for $C_{14}H_{15}NO_4$ (M^+) 261.1001, found 261.1005.

Methyl 2-Methyl-3-(phenylcarbamoyl)-1*H*-indole-5-carboxylate 7g. ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.60 (s, 3H), 3.80 (s, 3H), 6.98−7.78 (m, 7H), 8.40 (s, 1H), 9.73 (s, 1H), 11.90 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 13.66, 52.31, 110.35, 111.53, 120.42, 121.96, 122.44, 122.92, 123.60, 126.64, 129.15, 137.95, 140.11, 141.58, 164.23, 167.75; ESI-MS m/z 309 $(M + H)^+$; HRMS calcd for $C_{18}H_{16}N_2O_3$ (M^+) 308.1161, found 308.1162.

***t*-Butyl 2-Methyl-5-nitro-1*H*-indole-3-carboxylate 7h.** ^{1}H NMR (400 MHz, d_6-acetone) δ 1.64 (s, 9H), 2.72 (s, 3H), 7.49 (d, J = 8.7 Hz, 1H), 8.01 (dd, J = 2.3, 8.7 Hz, 1H), 8.59 (d, J = 2.3 Hz, 1H), 11.27 (br s, 1H); ^{13}C NMR (100 MHz, d_6-acetone) δ 13.28, 27.93, 79.84, 106.83, 111.22, 117.11, 117.34, 126.95, 138.08, 142.73, 147.39, 163.99; ESI-MS m/z 277 $(M + H)^+$; HRMS calcd for $C_{14}H_{16}N_2O_4$ (M^+) 276.1111, found 276.1140.

Ethyl 6-Acetyl-2-benzyl-1*H*-indole-3-carboxylate 7i. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, J = 7.3 Hz, 3H), 2.61 (s, 3H), 4.45 (q, J = 7.3 Hz, 2H), 4.62 (s, 2H), 7.25−7.40 (m, 5H), 7.83 (d, J = 8.8 Hz, 1H), 7.93 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 8.67 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.62, 26.88, 34.27, 59.98, 105.08, 111.78, 121.27, 122.30, 127.31, 129.15, 129.27, 131.28,

131.80, 134.49, 136.95, 149.62, 165.28, 198.48; ESI-MS *m*/*z* 322 $(M + H)^+$; HRMS calcd for $C_{20}H_{19}NO_3$ (M^+) 321.1365, found 321.1369.

Ethyl 2-(But-3-enyl)-5-chloro-1*H*-indole-3-carboxylate 7j. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J = 7.3 Hz, 3H), 2.45−2.55 (m, 2H), 3.26 (t, J = 7.3 Hz, 2H), 4.42 (q, J = 7.3 Hz, 2H), 5.01−5.12 (m, 2H), 5.80−5.92 (m, 1H), 7.12−7.28 (m, 2H), 8.09 (d, J = 1.4 Hz, 1H), 8.64 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.65, 27.46, 32.99, 59.85, 104.15, 111.15, 116.26, 121.17, 122.79, 127.62, 128.36, 132.94, 137.27, 148.81, 165.58; ESI-MS *m*/*z* 278 $(M + H)^+$; HRMS calcd for $C_{15}H_{16}ClNO_2$ (M^+) 277.0870, found 277.0874.

Ethyl 2,5-Dimethyl-1*H*-indole-3-carboxylate 7k. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.37 (t, J = 6.9 Hz, 3H), 2.38 (s, 3H), 2.67 (s, 3H), 4.30 (q, J = 6.9 Hz, 2H), 6.93 (dd, J = 1.4, 8.2 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.84 (s, 1H); ^{13}C NMR (400 MHz, d_6-acetone) δ 13.31, 14.16, 20.99, 58.68, 103.36, 110.60, 120.82, 123.18, 127.78, 129.95, 133.39, 144.10, 165.44; ESI-MS *m*/*z* 218 $(M + H)^+$; HRMS calcd for $C_{13}H_{15}NO_2$ (M^+) 217.1103, found 217.1100.

Methyl 2-Isopropyl-1*H*-indole-3-carboxylate 7l. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 6.9 Hz, 6H), 3.94 (s, 3H), 4.11−4.15 (m, 1H), 7.20−7.35 (m, 3H), 8.11 (d, J = 8.7 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.90, 26.42, 50.91, 102.86, 110.88, 121.62, 121.85, 122.46, 127.17, 134.53, 153.81, 166.53; ESI-MS *m*/*z* 218 $(M + H)^+$; HRMS calcd for $C_{13}H_{15}NO_2$ (M^+) 217.1103, found 217.1104.

Methyl 2-*t*-Butyl-1*H*-indole-3-carboxylate 7m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 9H), 3.94 (s, 3H), 7.19−7.40 (m, 3H), 8.10−8.12 (m, 1H), 8.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.64, 33.86, 50.97, 103.59, 110.83, 121.92, 121.98, 122.40, 128.47, 132.97, 154.56, 166.14; ESI-MS *m*/*z* 232 $(M + H)^+$; HRMS calcd for $C_{14}H_{17}NO_2$ (M^+) 231.1259, found 231.1261.

Ethyl 2-Phenyl-1H-indole-3-carboxylate 7n. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3H), 4.26 (q, J = 6.9 Hz, 2H), 7.20−7.61 (m, 8H), 8.20 (d, J = 7.3 Hz, 1H), 8.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.41, 59.86, 104.61, 111.26, 122.13, 122.19, 123.24, 127.69, 128.15, 129.23, 129.72, 132.12, 135.32, 144.75, 165.66; ESI-MS *m*/*z* 266 $(M + H)^+$; HRMS calcd for $C_{17}H_{15}NO_2$ (M^+) 265.1103, found 265.1104.

2-Methyl-*N*-phenyl-1*H*-indole-3-carboxamide 7o. ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.62 (s, 3H), 6.98−7.83 (m, 9H), 9.56 (s, 1H), 11.57 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 13.68, 109.09, 111.51, 120.04, 120.25, 120.57, 121.72, 123.23, 126.78, 129.04, 135.23, 140.16, 140.42, 164.68; ESI-MS *m*/*z* 251 $(M + H)^+$; HRMS calcd for $C_{16}H_{14}N_2O$ (M^+) 250.1106, found 250.1110.

Ethyl 6-Methoxy-2-phenyl-1*H*-indole-3-carboxylate 7p. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.3 Hz, 3H), 3.85 (s, 3H), 4.30 (q, J = 7.3 Hz, 2H), 6.86 (d, J = 2.0 Hz, 1H), 6.94 (dd, J = 2.0, 8.6 Hz, 1H), 7.42−7.46 (m, 3H), 7.63−7.67 (m, 2H), 8.10 (d, J = 8.6 Hz, 1H), 8.43 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.42, 55.74, 59.77, 94.46, 104.74, 111.79, 121.89, 123.04, 128.21, 129.08, 129.61, 132.25, 136.01, 143.44, 157.12, 165.39; ESI-MS *m*/*z* 296 $(M + H)^+$; HRMS calcd for $C_{18}H_{17}NO_3$ (M^+) 295.1208, found 295.1205.

Methyl 2-Isopropyl-5-methoxy-1*H*-indole-3-carboxylate 7q. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 7.3 Hz, 6H), 3.87 (s, 3H), 3.93 (s, 3H), 4.05−4.13 (m, 1H), 6.84 (dd, J = 2.8, 8.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 2.8 Hz, 1H), 8.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.78, 26.49, 50.71, 55.86, 102.76, 103.80, 111.40, 112.18, 128.07, 129.33, 153.96, 155.66, 166.32; ESI-MS *m*/*z* 248 $(M + H)^+$; HRMS calcd for $C_{14}H_{17}NO_3$ (M^+) 247.1208, found 247.1206.

Methyl 7-Chloro-5-iodo-2-isopropyl-1*H*-indole-3-carboxylate 7r. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, J = 7.3 Hz, 6H), 3.94 (s, 3H), 4.08−4.18 (m, 1H), 7.50 (d, J = 1.4 Hz, 1H), 8.34 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.63, 26.37, 51.08, 84.61, 103.58, 117.03, 129.14, 129.61, 130.24, 131.03, 154.55, 165.27; ESI-MS *m*/*z* 378 $(M + H)^+$; HRMS calcd for $C_{13}H_{13}NO_2$-ClI (M^+) 376.9679, found 376.9684.

Dimethyl 2-Isopropyl-1*H*-indole-3,5-dicarboxylate 7s. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.36 (d, J = 7.3 Hz, 6H), 3.86 (s, 3H), 3.88 (s, 3H), 4.10−4.18 (m, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.81 (dd, J = 1.8, 8.7 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, d_6-acetone) δ 21.90, 27.22, 50.94, 51.97, 103.85, 111.88, 124.01, 124.07, 124.51, 127.57, 138.75, 156.22, 166.08, 168.19; ESI-MS *m*/*z* 276 $(M + H)^+$; HRMS calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1158, found 275.1155.

3-Ethyl 6-Methyl 2-Phenyl-1*H*-indole-3,6-dicarboxylate 7t. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.24 (t, J = 7.3 Hz, 3H), 3.88 (s, 3H), 4.24 (q, J = 7.3 Hz, 2H), 7.47−7.80 (m, 6H), 8.18 (d, J = 0.9 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, d_6-acetone) δ 13.77, 51.39, 59.30, 104.33, 113.57, 121.48, 122.26, 124.55, 127.97, 129.30, 130.01, 131.58, 131.86, 135.15, 147.43, 164.30, 167.02; ESI-MS *m*/*z* 324 $(M + H)^+$; HRMS calcd for $C_{19}H_{17}NO_4$ (M^+) 323.1158, found 323.1160.

Ethyl 2-(But-3-enyl)-5-methyl-1*H*-indole-3-carboxylate 7u. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.3 Hz, 3H), 2.46 (s, 3H), 2.46−2.51 (m, 2H), 3.23 (t, J = 7.3 Hz, 2H), 4.40 (q, J = 7.3 Hz, 2H), 4.99−5.10 (m, 2H), 5.81−5.92 (m, 1H), 7.01 (dd, J = 1.4, 8.2 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.93 (s, 1H), 8.52 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.69, 21.79, 27.62, 33.20, 59.57, 103.82, 110.39, 116.04, 121.30, 123.95, 127.55, 131.24, 132.86, 137.51, 147.55, 166.10; ESI-MS *m*/*z* 258 $(M + H)^+$; HRMS calcd for $C_{16}H_{19}NO_2$ (M^+) 257.1416, found 257.1419;

Ethyl 2-(4-Acetyl-2-(2,2,2-trifluoroacetamido)phenyl)acetate 9a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.3 Hz, 3H), 2.62 (s, 3H), 3.73 (s, 2H), 4.22 (q, J = 7.3 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.83 (dd, J = 1.4, 7.8 Hz, 1H), 8.45 (s, 1H), 10.23 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.03, 26.79, 39.05, 62.65, 124.87, 126.42, 131.31, 131.63, 134.72, 137.59, 155.66, 172.40, 197.00; ESI-MS *m*/*z* 335 $(M + NH_4)^+$; HRMS calcd for $C_{14}H_{14}F_3$-NO_4 (M^+) 317.0875, found 317.0871.

Ethyl 2-(5-Chloro-2-(2,2,2-trifluoroacetamido)phenyl)acetate 9b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.3 Hz, 3H), 3.55 (s, 2H), 4.14 (q, J = 7.3 Hz, 2H), 7.18 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = 2.3, 8.7 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 10.07 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.02, 38.70, 62.61, 116.01 (q, J = 287 Hz), 125.87, 128.08, 128.81, 131.06, 132.09, 132.95, 155.66 (q, J = 37 Hz), 172.54; ESI-MS *m*/*z* 327 $(M + NH_4)^+$; HRMS calcd for $C_{12}H_{11}ClF_3NO_3$ (M^+) 309.0380, found 309.0385.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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