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Copper-Catalyzed Synthesis of Multisubstituted Indoles Through Tandem Ullmann-Type C-N Formation and Cross-dehydrogenative Coupling Reactions

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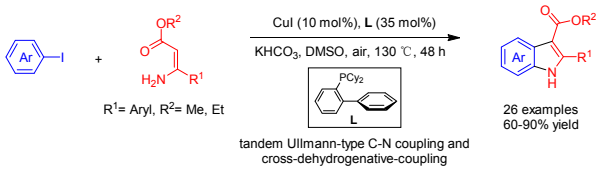
Abstract



Multisubstituted indoles were synthesized via a one-pot tandem copper-catalyzed Ullmann-type C-N bond formation/intramolecular cross-dehydrogenative coupling process at 130 ℃ in DMSO. The methodology allows practical and modular assembly of indoles in good to excellent yields from readily available aryl iodides and enamines.

The indole subunit represents an important heterocyclic motif that widely exists in natural products,[1] pharmaceuticals and agrochemicals,[2] and advanced organic functional materials.[3] In particular, indole scaffolds are generally utilized as “privileged structures” for drug discovery and development, numerous substituted indoles display a wide range of biological activities, for example, anticancer, antibacterial, anti-inflammatory and so on.[4]

Since the first report of Fischer indole synthesis,[5] a variety of powerful methods have been well established for the construction of indole scaffold over the last hundred years.[6] Despite the availability of numerous procedure, the development of new, more efficient and atom economical methods is still highly desirable. Over the past decades, transition-metal-catalyzed inter- and intramolecular C–C and/or C–N bond forming reaction has emerged as one of the most powerful routes for the synthesis of indoles.[7] Among the various transition metal catalysis, copper-mediated

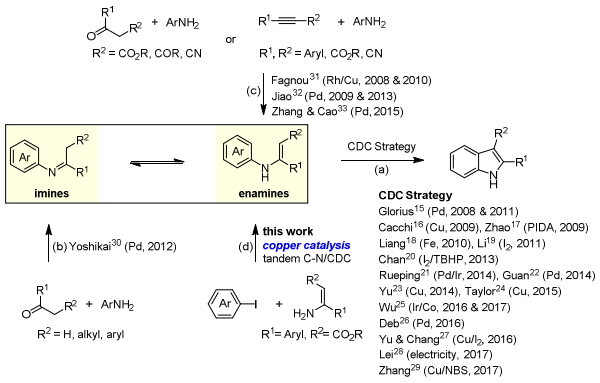
Ullmann-type C-heteroatom[8] and C-C cross-coupling reactions[9] have received increased attention in the synthesis of heterocycles[10] due to their economic attractiveness, excellent functional group tolerance and potential in large-scale applications. As an attractive alternative strategy for the construction of heterocycles, copper-catalyzed C–H functionalization[11] has aroused great interest due to its improved atom and step economy. These copper-catalyzed cross-coupling reactions have been employed for the synthesis of indoles.[12]

Various methodologies have been established to construct indole backbone through transition metal-catalyzed C–H activation.[7f, 13] Initiated by the first examples of Pd-catalyzed intramolecular cross-dehydrogenative coupling (CDC) reaction to synthesize carbazoles and dibenzofurans,[14] specific CDC strategy has recently been receiving considerable attention for the synthesis of indoles from enamines and imines (Scheme 1). In 2008, Glorius reported an efficient synthesis of indoles via Pd-catalyzed oxidative cyclization of *N*-aryl enaminones/esters with $Cu(OAc)_2$ as the oxidant.[15] Subsequent to this original work, much effort has been focused on the improvement of this transformation. Different transition metals, oxidants, and reaction conditions have been widely explored to enlarge the substrate scope and improve the efficiency (Scheme 1, path a).[16-29] To render the process more efficient and easier, domino reactions have evolved as highly economic alternative to CDC approaches by using simple and easily available substrates. Due to the possible tautomerization of imines to enamines, recently, Yoshikai group[30] developed a new route to indoles through Pd-catalyzed two fold C-H bond cleavage from *N*-aryl imines directly derived from simple and obtainable anilines and ketones (Scheme 1, path b). In addition, one-pot methods have also been established to provide indoles through sequential addition/Rh or Pd-catalyzed CDC reaction of anilines and alkynes by Fagnou,[31] Jiao,[32] and Zhang,[33] respectively (Scheme 1, path c).

As described above, copper catalysis can be used in the formation of C-heteroatom and C-C bonds through either classical Ullmann-type reactions or oxidative C-H functionalization. Merging fundamentally different copper catalysis into one operation is no doubt very challenging, however, such sequential one-pot process

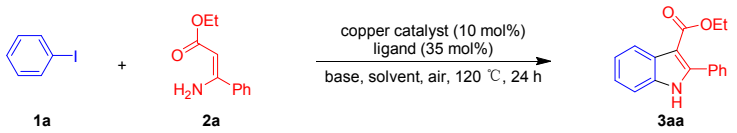
would provide a straightforward method for the synthesis of heterocycles. In a continuation of our efforts to develop metal-catalyzed new synthetic protocols involving C-H activation for the construction of heterocyclic frameworks,[34] herein we report a one-pot synthesis of multisubstituted indoles through a sequential Cu-catalyzed Ullmann-type C-N formation and cross-dehydrogenative coupling (Scheme 1, path d).[35]

Scheme 1. Pathways for the Synthesis of Indoles Based on CDC Strategy



Iodobenzene **1a** and enamine **2a** were selected as the coupling partners for a copper-catalyzed synthesis of indole **3aa**. Reaction optimization results were summarized in Table 1. Initially, a survey of reaction media was conducted in the presence of CuI/1,10-phenanthroline **L1** (phen) widely used for Ullmann-type C-N bond formation.[8] With K_2CO_3 as the base, reactions carried out in polar solvents such as DMF, DMA and DMSO at 120 ℃ gave a similar yield, whereas the use of 1,4-dioxane and toluene led to lower yields (entries 1-5). As the best result was obtained when DMSO was used (**3aa** was isolated in 35% yield, entry 3), the effect of various bases (NEt_3, KOH, Na_2CO_3, Li_2CO_3, K_3PO_4, $NaHCO_3$, $KHCO_3$, and NaO*t*-Bu) on the reaction was then investigated in DMSO (entries 6–13). $KHCO_3$ was found to be the best base to achieve **3aa** in 48% yield (entry 12). After an extensive screen of copper catalysts [CuCl, CuBr, $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$, $CuBr_2$, Cu_2O, $CuSO_4$, and CuI], we found the nature of copper sources greatly influences the efficiency of twofold arylation process (entries 14-21), the use of CuI gave the best result in 48% yield by

Table 1. Optimization of Reaction Conditions for Cu-Catalyzed Synthesis of Indole **3a**[a]



1a **2a** **3aa**

entry	catalyst/ ligand[b]	base/solvent	yield %[c]	entry	catalyst/ligand[b]	base/solvent	yield %[c]
1	CuI/L1	K_2CO_3, DMF	28	19	$CuBr_2$/L1	$KHCO_3$, DMSO	25
2	CuI/L1	K_2CO_3, DMA	30	20	Cu_2O/L1	$KHCO_3$, DMSO	25
3	CuI/L1	K_2CO_3, DMSO	35	21	$CuSO_4 \cdot 5H_2O$/L1	$KHCO_3$, DMSO	45
4	CuI/L1	K_2CO_3, 1,4-dioxane	8	22	CuI/L2	$KHCO_3$, DMSO	38
5	CuI/L1	K_2CO_3, toluene	15	23	CuI/L3	$KHCO_3$, DMSO	35
6	CuI/L1	NEt_3, DMSO	5	24	CuI/L4	$KHCO_3$, DMSO	40
7	CuI/L1	KOH, DMSO	17	25	CuI/L5	$KHCO_3$, DMSO	45
8	CuI/L1	Na_2CO_3, DMSO	25	26	CuI/PCy_3	$KHCO_3$, DMSO	43
9	CuI/L1	Li_2CO_3, DMSO	20	27	CuI/$P^tBu_3 \cdot HBF_4$	$KHCO_3$, DMSO	32
10	CuI/L1	K_3PO_4, DMSO	30	28	CuI/L6	$KHCO_3$, DMSO	69
11	CuI/L1	$NaHCO_3$, DMSO	42	29	CuI/L7	$KHCO_3$, DMSO	40
12	CuI/L1	$KHCO_3$, DMSO	48	30	CuI/L8	$KHCO_3$, DMSO	41
13	CuI/L1	NaO*t*-Bu, DMSO	36	31	CuI/L9	$KHCO_3$, DMSO	33
14	CuCl/L1	$KHCO_3$, DMSO	45	32[d]	CuI/L6	$KHCO_3$, DMSO	80 (15)[e]
15	CuBr/L1	$KHCO_3$, DMSO	47	33[f]	CuI/L6	$KHCO_3$, DMSO	88/82[g]/50[h]
16	$Cu(OAc)_2$/L1	$KHCO_3$, DMSO	15	34[f]	CuCl/L6	$KHCO_3$, DMSO	75
17	$Cu(OTf)_2$/L1	$KHCO_3$, DMSO	18	35[f]	CuBr/L6	$KHCO_3$, DMSO	78
18	$CuCl_2$/L1	$KHCO_3$, DMSO	30	36[f]	CuI/L6	$KHCO_3$, DMSO	65[i]/76[j]

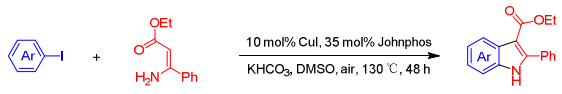
[a]Reaction conditions: **2a** (0.2 mmol), **1a** (0.24 mmol), base (0.4 mmol), catalyst (0.02 mmol), ligand (0.07 mmol) , solvent (1.0 mL). [b]L1 = 1,10-phenanthroline, L2 = (1*E*,2*E*)-N^1,N^2-dimesitylethane-1,2-diimine, L3 = N^1,N^2-diphenylethane-1,2-diamine, L4 = N^1,N^2-bis(2,6-diisopropylphenyl)ethane-1,2-diamine, L5 = 1,3-bis(2,6-diisopropylphenyl)imidazolinium tetrafluoroborate, L6 = Johnphos, L7 = Mephos, L8 = Davephos, L9 = x-phos. [c]Isolated yield. [d]130 ℃. [e]O_2. [f]130 ℃ for 48 h. [g]N_2. [h]Without Johnphos (**L6**). [i]10 mol% **L6**. [j]20 mol% **L6**.

using $KHCO_3$ and excess phen in DMSO after 24 h (entry 12). In order to increase the yield of **3aa**, we then investigated the effect of ligands (nitrogen-based bidentate ligands **L1-L4**, *N*-heterocyclic carbene ligand **L5**, and phosphorus ligands **L6-L9**) on the reaction (entries 22-31). Sterically hindered biaryl phosphine Johnphos (**L6**)[36] performed best, and the yield was improved to 69% (entry 28). We carried out a set of experiments to reveal the crucial role of the reaction temperature and time (entries 32 and 33). With the reaction temperature and time increasing, higher yields were obtained (69% vs 80% vs 88%, entries 28, 32 and 33). In addition, **3aa** was isolated in only 15% yield when the reaction was carried out under O_2 (entry 32) and was formed in good yield under an air atmosphere. A higher ratio of ligand to Cu is preferable to afford a better result [65% (1:1), 76% (2:1), and 88% (3:1); entries 33

and 36]. Finally, it is worth to note that the microwave-promoted tandem cyclization can provide **3aa** in 78% yield within 12 hours at 130 ℃. In general, excess Johnphos (**L6**) for CuI was found to be the best catalyst system with $KHCO_3$ as the base in DMSO at 130 ℃ for 48 h.

Encouraged by the above results, we then explored the scope and generality of the present process. First, the limitations were assessed with different aryl iodides **1** using enamine **2a** as the substrate (Table 2). As shown in Table 2, all monosubstituted (including *ortho*-, *meta*-, and *para*-substituted substrates, entries 2-11 and 14-16), disubstituted (entry 13), or fused aryl iodides (entry 12) underwent the reaction smoothly and afforded the corresponding indoles in good yields (60-90%). In addition, both aryl bromide and chloride smoothly underwent the cyclization to afford the desired product in 70% and 50% yield, respectively. The yield for the aryl halide substrates follows the order aryl iodide > aryl bromide > aryl chloride (entry 1, Table 2). For the *para*- and *ortho*-substituted aryl iodides, both electron-donating and -withdrawing groups, such as −Me, −OMe, −F, −Cl, $-CF_3$, $-CO_2Et$, and $-CO_2Me$, were tolerant under the reaction conditions (Table 2, **3ba**-**3ka**). The incorporation of the group in the *ortho* and *meta* positions of aryl iodide seemed not to hamper the reaction, and the corresponding indoles can be obtained in high yields (Table 2, entries 9, 13, 14 and 15). When *meta*-substituted aryl iodides (**1n**, **1o** and **1p**) were used, regioselectivity issues surfaced in the cross-dehydrogenative coupling process, and a mixture of two regioisomers was obtained (Table 2, entries 14-16). Intramolecular aromatic C−H vinylation occurred at two different sites to give products **3na**, **3pa** and **3oa**, respectively (Table 2, entries 14-16). The ring-fused 1-iodonaphthalene also participated in this reaction and afforded product **3la** in 81% yield (Table 2, entry 12). When extending the substrate scope from aryl iodide to vinyl iodide, for example, (*E*)-(2-iodovinyl)benzene **1q**, the reaction cannot proceed to give the corresponding pyrrole product**.** In addition, the use of heteroaromatic 2-iodopyridine **1r** led to the formation of 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **3ra** through Ullmann-type C-N cross coupling and intramolecular amidation in 60% yield.

Table 2. Variation of the Aryl Iodide Substrates[a]



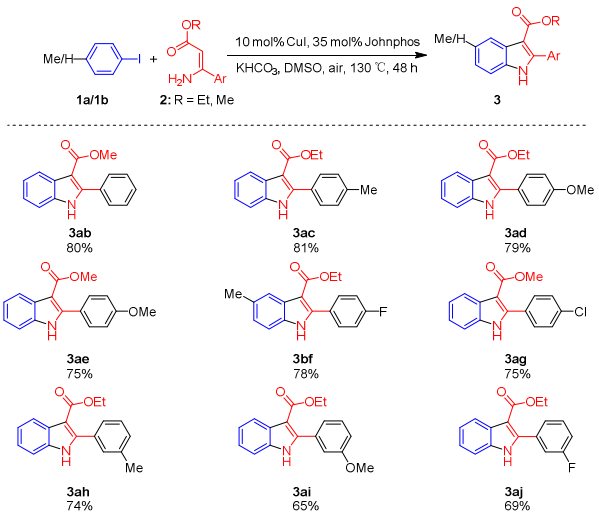
1 2a 3

entry	S-1	P-3	yield[b]	entry	S-1	P-3	yield[b]
1	X = I X = Br X = Cl	3aa	88 70 50	10	1j	3ja	80
2	1b	3ba	82	11	1k	3ka	78
3	1c	3ca	79	12	1l	3la	81
4	1d	3da	75	13	1m	3ma	90
5	1e	3ea	60	14[c]	1n	3na 3n'a (6-Me/4-Me)	89 (1.7:1)
6	1f	3fa	80	15[c]	1o	3oa 3o'a (6-MeO/4-MeO)	80 (1:1)
7	1g	3ga	70	16	1p	3pa 3p'a	45% 39%
8	1h	3ha	65				
9	1i	3ia	85				

[a]Reaction conditions: **2a** (0.2 mmol), aryl iodides **1** (0.24 mmol), 2.0 equiv of $KHCO_3$, 10 mol% of CuI, 35 mol% of Johnphos, DMSO (1.0 mL), 130 ℃, 48 h, air. [b]Isolated yield. [c]The ratio of the regioisomers was determined by NMR analysis.

Next, enamine substrates were examined in this process. As shown in Scheme 2, a great variety of enamines **2a**-**2j** can be smoothly converted into the corresponding indoles in good yields (65-81%). Several functional groups (such as Me, OMe, F, and Cl) are tolerated in the aryl fragment of enamine, and the electronic nature of the aromatic motifs does not seem to affect the efficiency of this transformation. However, when the scope of substrates is extended to aliphatic and carbocyclic enamines, for example, ethyl (*Z*)-3-aminobut-2-enoate **2k** and 3-aminocyclohex-2-en-1-one **2l**, the reaction did not give the corresponding products. Enamine substrates with an aromatic ketone or nitro group were also examined under the standard conditions, however, no product can be obtained**.**

Scheme 2. Variation of the enamine unit[a,b]

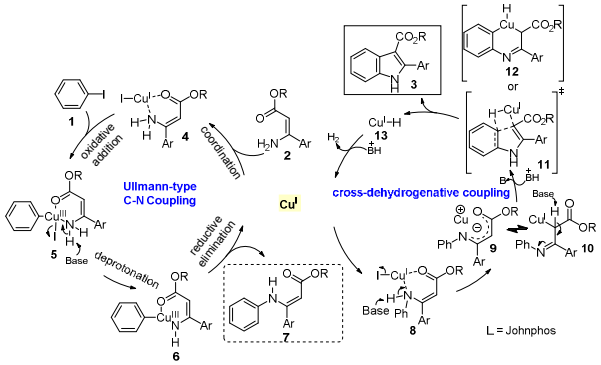


[a]Reaction conditions: **2** (0.2 mmol), aryl iodides **1a** or **1b** (0.24 mmol), 2.0 equiv of $KHCO_3$, 10 mol% of CuI, 35 mol% of Johnphos, DMSO (1.0 mL), 130 ℃, 48 h, air. [b] Isolated yield.

To gain insight into the mechanism of the reaction, some designed control experiments were conducted. First, the cyclization of the *N*-methyl derivative of **2a** with iodobenzene **1a** was attempted, only *N*-arylated intermediate was obtained in 92% yield and no indole product was observed. Second, *N*-phenyl derivative of **2a** (Ullmann coupling intermediate) was carried out under the optimized reaction conditions, the desired **3aa** was obtained in 70% yield. On the basis of the results described above and the previous mechanistic studies,[16, 37] a plausible catalytic cycle for the synthesis of indoles was outlined in Scheme 3. The initial step involved the coordination of enamine **2** to the Cu(I) center to form 4, which was followed by an intermolecular oxidative addition of aryl iodide **1**, affording an intermediate complex **5**. The resulting complex **5** reacted with base to form Cu-N bond and afforded an intermediate complex **6**, which preceded the formation of *N*-aryl enamine **7** and regeneration of catalytic Cu(I) species (Ullmann-type C-N coupling process).[8d] The coordination of *N*-arylation intermediate **7** to CuI led to the formation of complex **8**, which was then transformed into a new C-Cu(I) intermediate **10** through the sequential deprotonation of N-H and complexation of the resulting carbanion by Cu^+ under basic conditions. The further deprotonation of the ester *α*-carbon of **10**

yielded the carbanion which attacked the C_2-position of *N*-aryl moiety, and this C–C bond formation proceeded rapidly when preceded by re-protonation of the N-atom of intermediate **10** from B^+-H. Hydride transfer to the Cu(I) center then finished the formation of indole product **3** and gave Cu-H **13**. However, an alternative pathway via reductive elimination of six-membered copper-cycle intermediate **12** to give **3** could not be completely ruled out.[16] Finally, Cu-H species reacted with the conjugate acid of base, affording hydrogen and regenerating the active copper catalyst for the next Ullmann-type C-N reaction (CDC process).[37]

Scheme 3. Proposed mechanism for sequential Cu-catalyzed annulation of **1** and **2**.



In summary, we have developed a Cu(I)-catalyzed 2-fold arylation process through a tandem Ullmann-type C-N and cross-dehydrogenative coupling sequence. This method allows the synthesis of multisubstituted indoles from enamines and aryl iodides in high yields. Considering the valuable structure of the products and good functionality tolerance, this tandem reaction could be of synthetic utility for the discovery of drugs.

EXPERIMENTAL SECTION

General Experimental Methods. Chemicals were all purchased from commercial supplies and used without further purification unless otherwise stated. Solvents were dried and purified according to the standard procedures before use. Reactions were monitored by analytical thin-layer chromatography (TLC). All reactions were conducted in dried glassware. Purification of reaction products was done by flash chromatography with 230–400 mesh silica gel. Enamine substrates were prepared

according to the literature methods.[38] Melting points were determined on a melting point apparatus in open capillaries and are uncorrected. Infrared spectra of samples were recorded from 4,000 to 500 cm^{-1} in ATR (attenuated total reflectance) mode using an FT-IR instrument. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer, and ^{13}C NMR spectra were recorded at 100, 125 or 150 MHz. Unless otherwise stated, deuterochloroform ($CDCl_3$) was used as a solvent. Chemical shifts (δ) are given in parts per million downfield relative to tetramethylsilane (TMS). Chemical shifts for carbon resonances are reported in parts per million and are referenced to the carbon resonance of the solvent $CHCl_3$ (δ = 77.16 ppm). The splitting patterns are reported as s (singlet), d (doublet), dd (double doublet), td (triplet of doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Coupling constants are given in hertz. High-resolution mass spectra were recorded on a BIO TOF Q mass spectrometer equipped with an electrospray ion source (ESI), operated in the positive mode.

General Procedures for Synthesis of Indole Derivatives. A 10 mL Schlenk tube or standard vial equipped with a magnetic stirring bar was charged with enamines (0.2 mmol, 1.0 equiv), aryl iodides (0.24 mmol, 1.2 equiv) and $KHCO_3$ (40 mg, 0.4 mmol, 2.0 equiv), and then CuI (0.02 mmol, 3.8 mg) and Johnphos (0.07 mmol, 24.5 mg) were added. Finally, dimethyl sulfoxide (1.0 mL) was added to the mixture via syringe at room temperature under air. The tube was sealed and put into a preheated oil bath at 130 ℃ for 48 h. The mixture was cooled to room temperature, quenched with water (3 mL), and diluted with ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with 2 × 5 mL of ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel (H), eluting with 10−15% ethyl acetate/petroleum ether.

*Ethyl 2-phenyl-1H-indole-3-carboxylate (**3aa**).* Yield, 88% (46.6 mg); white solid, mp 147-149 ℃ (lit.[25a] mp 150−152 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.23 – 8.21 (m, 1H), 7.63 – 7.61 (m, 2H), 7.42 – 7.39 (m, 3H), 7.35 – 7.33 (m, 1H), 7.29 – 7.23

(m, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 144.7, 135.3, 132.2, 129.7, 129.3, 128.2, 127.7, 123.3, 122.3, 122.2, 111.2, 104.8, 59.8, 14.4.

*Ethyl 5-methyl-2-phenyl-1H-indole-3-carboxylate (**3ba**).* Yield, 82% (45.8 mg); white solid, mp 152-154 ℃ (lit.[25a] mp 155−157 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.02 (s, 1H), 7.61 – 7.59 (m, 2H), 7.40 – 7.38 (m, 3H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.3 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 144.5, 133.6, 132.3, 131.6, 129.7, 129.1, 128.1, 128.0, 124.8, 121.8, 110.8, 104.3, 59.7, 21.8, 14.4.

*Ethyl 5-methoxy-2-phenyl-1H-indole-3-carboxylate (**3ca**).*[25a] Yield, 79% (46.6 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.49 – 7.37 (m, 3H), 7.25 (d, *J* = 7.2 Hz, 1H), 6.91 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 154.6, 143.9, 131.1, 129.1, 128.5, 127.9, 127.5, 126.9, 112.3, 110.0, 103.1, 102.5, 58.6, 54.6, 13.2.

*Ethyl 5-fluoro-2-phenyl-1H-indole-3-carboxylate (**3da**).* Yield, 75% (42.5 mg); white solid, mp 149-151 ℃ (lit.[25a] mp 152−154 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.87 (dd, *J* = 10.1, 2.5 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.45 – 7.38 (m, 3H), 7.27 (dd, *J* = 8.7, 4.5 Hz, 1H), 7.00 (td, *J* = 9.0, 2.6 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 159.2 (d, $^1J_{C\text{-}F}$ = 235 Hz), 146.0, 131.66 (d, $^3J_{C\text{-}F}$ = 9 Hz), 129.5, 129.4, 128.4 (d, $^3J_{C\text{-}F}$ = 11 Hz), 128.2, 111.9, 111.8, 111.6 (d, $^2J_{C\text{-}F}$ = 26 Hz), 107.5 (d, $^2J_{C\text{-}F}$ = 25 Hz), 104.9 (d, $^4J_{C\text{-}F}$ = 4 Hz), 59.9, 14.3.

*Ethyl 5-chloro-2-phenyl-1H-indole-3-carboxylate (**3ea**).* Yield, 60% (35.9 mg); white solid, mp 148-150 ℃ (lit.[25a] mp 151−153 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.20 (d, *J* = 1.9 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.46 – 7.40 (m, 3H), 7.28 (d, *J* = 9.2 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 145.6, 133.5, 131.6, 129.6, 129.5, 128.8, 128.2, 127.9, 123.6, 121.8, 112.0, 104.5, 59.9, 14.3.

*Ethyl 2-phenyl-5-(trifluoromethyl)-1H-indole-3-carboxylate (**3fa**).*[25a] Yield, 80% (53.3

mg); white solid, mp 180-184 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.54 (s, 1H), 7.65 (dd, *J* = 6.3, 2.9 Hz, 2H), 7.53 – 7.41 (m, 5H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 146.0, 136.5, 131.3, 129.7, 129.6, 128.3, 127.1, 125.1 (q, $^1J_{C\text{-}F}$ = 270 Hz), 124.5 (q, $^2J_{C\text{-}F}$ = 32 Hz), 120.1 (q, $^3J_{C\text{-}F}$ = 4 Hz), 111.4, 105.5, 60.1, 14.3.

*3-Ethyl 5-methyl 2-phenyl-1H-indole-3,5-dicarboxylate (**3ga**).*[25b] Yield, 70% (45.2 mg); white solid, mp 156-160 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 1.1 Hz, 1H), 8.74 (s, 1H), 7.97 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.66 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.40 (d, *J* = 8.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 164.9, 145.7, 137.7, 131.5, 129.6, 128.3, 127.3, 125.1, 124.7, 124.1, 113.8, 110.8, 105.8, 60.0, 52.1, 14.3.

*Diethyl 2-phenyl-1H-indole-3,5-dicarboxylate (**3ha**).* Yield, 65% (43.8 mg); white solid, mp 190-192 ℃; IR (KBr, cm^{-1}): 3276, 1704, 1677, 1471, 1446, 1430, 1316, 1285, 1274, 1241, 1128, 1115, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.88 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 3.9 Hz, 2H), 7.45 (m, 3H), 7.40 (d, *J* = 8.5 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 163.9, 144.7, 136.7, 130.4, 128.6, 128.5, 127.2, 126.2, 123.9, 123.6, 123.3, 109.8, 104.7, 59.8, 58.9, 13.4, 13.2. HRMS-ESI: $[M+H]^+$ calcd for $C_{20}H_{20}NO_4$ *m/z* 338.1392, found *m/z* 338.1394.

*Ethyl 7-methyl-2-phenyl-1H-indole-3-carboxylate (**3ia**).*[25a] Yield, 85% (47.4 mg); white solid, mp 150-152 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.47 – 7.37 (m, 3H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 144.2, 134.7, 132.3, 129.7, 129.1, 128.1, 127.3, 123.8, 122.3, 120.2, 119.9, 105.3, 59.7, 16.5, 14.3.

*Ethyl 7-fluoro-2-phenyl-1H-indole-3-carboxylate (**3ja**).* Yield, 80% (45.3 mg); white solid, mp 143-145 ℃ (lit.[29] mp 140−142 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.66 (dd, *J* = 6.4, 2.6 Hz, 2H), 7.52 – 7.35 (m, 3H), 7.18 (td, *J* = 8.0, 5.0 Hz, 1H), 6.98 (dd, *J* = 10.7, 8.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 149.1 (d, $^1J_{C\text{-}F}$ = 243 Hz), 145.0, 131.5,

130.98 (d, $^{3}J_{C\text{-}F}$ = 4 Hz), 129.7, 129.5, 128.2, 123.6 (d, $^{2}J_{C\text{-}F}$ = 14 Hz), 122.3 (d, $^{3}J_{C\text{-}F}$ = 6 Hz), 117.95 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 108.1 (d, $^{2}J_{C\text{-}F}$ = 15 Hz), 105.6 (d, $^{4}J_{C\text{-}F}$ = 2 Hz), 59.9, 14.3.

*Ethyl 7-chloro-2-phenyl-1H-indole-3-carboxylate (**3ka**).* Yield, 78% (46.7 mg); white solid, mp 145-147 ℃ (lit.[29] mp 145−147 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.76 – 7.60 (m, 2H), 7.54 – 7.42 (m, 3H), 7.27 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 139.7, 127.2, 126.3, 124.5, 124.3, 123.8, 123.0, 117.6, 117.3, 115.6, 111.2, 100.7, 54.7, 9.1.

*Ethyl 2-phenyl-1H-benzo[g]indole-3-carboxylate (**3la**).* Yield, 81% (51.1 mg); white solid, mp 205-207 ℃ (lit.[25a] mp 204−206 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.32 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.66 (m, 3H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.50 – 7.37 (m, 4H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 141.2, 131.2, 129.7, 129.0, 128.7, 127.9, 127.9, 127.1, 124.9, 123.6, 123.1, 121.8, 120.3, 120.0, 118.4, 105.4, 58.8, 13.3.

*Ethyl 4,6-dimethyl-2-phenyl-1H-indole-3-carboxylate (**3ma**).*[25b] Yield, 90% (52.7 mg); white solid, mp 120-122 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.54 – 7.52 (m, 2H), 7.46 – 7.36 (m, 3H), 6.99 (s, 1H), 6.84 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 2.41 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 139.3, 135.0, 132.2, 131.5, 130.0, 127.7, 127.6, 127.3, 124.3, 122.6, 107.6, 106.1, 59.4, 20.4, 20.1, 12.9.

*Mixture of ethyl 6-methyl-2-phenyl-1H-indole-3-carboxylate (**3na**) and ethyl 4-methyl-2-phenyl-1H-indole-3-carboxylate (**3n'a**).*[25a] Yield, 89% (49.7 mg); yellow oil, the ratio (**3na**:**3n'a** = 1.7:1) is determined by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 – 9.25 (s, 2.6$H_{overlap}$), 8.18 (d, *J* = 8.2 Hz, 1.7H_{3na}), 7.83 (d, *J* = 7.7 Hz, 1$H_{3n'a}$), 7.68 – 7.57 (m, 3.5H_{3na}), 7.53 – 7.51 (m, 2.7$H_{overlap}$), 7.40 – 7.36 (m, 8.4$H_{overlap}$), 7.18 – 7.15 (m, 3.5H_{3na}), 7.08 (m, 2.6$H_{overlap}$), 4.31 – 4.23 (m, 5.2$H_{overlap}$), 2.75 (s, 3$H_{3n'a}$), 2.48 (s, 5H_{3na}), 1.33 (t, *J* = 7.1 Hz, 5H_{3na}), 1.21 (t, *J* = 7.1 Hz, 3$H_{3n'a}$).

*Mixture of ethyl 6-methoxy-2-phenyl-1H-indole-3-carboxylate (**3oa**) and ethyl 4-methoxy-2-phenyl-1H-indole-3-carboxylate (**3o'a**).*[25a] Yield, 80% (47.2 mg); yellow

oil; the ratio (**3oa**:**3o'a** = 1:1) is determined by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 – 8.97 (br, $2H_{overlap}$), 8.05 (d, *J* = 8.8 Hz, $1H_{3oa}$), 7.54 (d, *J* = 3.7 Hz, $2H_{3oa}$), 7.46 (d, *J* = 2.3 Hz, $2H_{3o'a}$), 7.27 (m, $6H_{overlap}$), 7.07 (t, *J* = 8.0 Hz, $1H_{3o'a}$), 6.95 – 6.81 (m, $2H_{overlap}$), 6.72 (s, $1H_{3oa}$), 6.53 (d, *J* = 7.9 Hz, $1H_{3o'a}$), 4.24 (q, *J* = 7.1 Hz, $4H_{overlap}$), 3.81 (s, $3H_{3o'a}$), 3.67 (s, $3H_{3oa}$), 1.26 (t, *J* = 7.1 Hz, $3H_{3oa}$), 1.18 (t, *J* = 7.1 Hz, $3H_{3o'a}$).

*Ethyl 6-chloro-2-phenyl-1H-indole-3-carboxylate (**3pa**).*[25a] Yield, 45% (26.9 mg); white solid, mp 145-148 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.42 – 7.37 (m, 3H), 7.31 (d, *J* = 1.4 Hz, 1H), 7.22 (dd, *J* = 8.6, 1.7 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 144.3, 134.6, 130.6, 128.6, 128.5, 127.9, 127.2, 126.1, 125.3, 122.1, 121.8, 110.2, 59.0, 13.4.

*Ethyl 4-chloro-2-phenyl-1H-indole-3-carboxylate (**3p'a**).*[25a] Yield, 39% (23.3 mg); white solid, mp 143-145 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.53 (br, 2H), 7.37 (br, 3H), 7.22 – 7.20 (m, 2H), 7.14 – 7.10 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 139.8, 136.6, 131.0, 129.0, 128.7, 128.1, 125.8, 124.4, 123.6, 122.4, 109.9, 106.7, 61.3, 14.0.

*Methyl 2-phenyl-1H-indole-3-carboxylate (**3ab**).*[15b] Yield, 80% (40.2 mg); white solid, mp 135-137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.24 (d, *J* = 6.9 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.47 – 7.42 (m, 3H), 7.38 (dd, *J* = 6.1, 2.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 143.7, 134.2, 131.1, 128.7, 128.4, 127.4, 126.7, 122.5, 121.4, 121.3, 110.1, 103.7, 50.1.

*Ethyl 2-(p-tolyl)-1H-indole-3-carboxylate (**3ac**).* Yield, 81% (45.2 mg); white solid, mp 148-150 ℃ (lit.[24] mp 144−146 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.31 – 8.18 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.29 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 144.9, 139.3, 135.1, 129.5, 129.0, 128.8, 127.7, 123.1, 122.1, 122.0, 111.0, 104.4, 59.7, 21.4, 14.4.

*Ethyl 2-(4-methoxyphenyl)-1H-indole-3-carboxylate (**3ad**).* Yield, 79% (46.6 mg); white solid, mp 162-165 ℃ (lit.[25a] mp 165−167 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.25 – 8.22 (m, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.30 – 7.27 (m,

2H), 7.01 – 6.92 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6, 160.3, 144.8, 135.1, 130.9, 127.7, 124.2, 122.9, 122.1, 121.9, 113.6, 110.9, 104.1, 59.7, 55.4, 14.4.

*Methyl 2-(4-methoxyphenyl)-1H-indole-3-carboxylate (**3ae**).*[15b] Yield, 75% (42.2 mg); white solid, mp 142-144 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.25 – 8.14 (m, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.37 (dd, *J* = 6.4, 2.1 Hz, 1H), 7.31 – 7.25 (m, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 160.4, 144.9, 135.1, 130.9, 127.6, 124.1, 123.0, 122.1, 122.0, 113.6, 111.0, 103.8, 55.3, 50.9.

*Ethyl 2-(4-fluorophenyl)-5-methyl-1H-indole-3-carboxylate (**3bf**).* Yield, 78% (46.3 mg); white solid, mp 160-162 ℃; IR (KBr, cm^{-1}): 3306, 1659, 1495, 1475, 1449, 1274, 1222, 1163, 841, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.04 (s, 1H), 7.65 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.18 – 7.12 (m, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 163.2 (d, $^1J_{C\text{-}F}$ = 248 Hz), 143.3, 133.4, 131.7, 131.5 (d, $^3J_{C\text{-}F}$ = 8 Hz), 128.3 (d, $^4J_{C\text{-}F}$ = 3 Hz), 127.8, 124.9, 121.9, 115.2 (d, $^2J_{C\text{-}F}$ = 22 Hz), 110.6, 104.5, 59.7, 21.8, 14.4. HRMS-ESI: $[M+H]^+$ calcd for $C_{18}H_{17}FNO_2$ *m/z* 298.1243, found *m/z* 298.1241.

*Methyl 2-(4-chlorophenyl)-1H-indole-3-carboxylate (**3ag**).*[25a] Yield, 75% (42.8 mg); white solid, mp 151-153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.28 – 8.14 (m, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.37 (m, 3H), 7.32 – 7.27 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 142.3, 134.2, 129.8, 129.2, 128.0, 127.3, 126.3, 122.4, 121.2, 121.1, 110.1, 103.6, 49.9.

*Ethyl 2-(m-tolyl)-1H-indole-3-carboxylate (**3ah**).* Yield, 74% (41.3 mg); white solid, mp 143-145 ℃ (lit.[29] mp 144–146 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.46 (m, 2H), 7.37 (t, *J* = 6.3 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.24 (d, *J* = 7.7 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 143.7, 136.6, 134.1, 130.9, 129.1, 128.8, 126.9, 126.6, 125.8, 122.0, 121.0, 120.9, 110.0, 103.4, 58.6, 20.3, 13.3.

*Ethyl 2-(3-methoxyphenyl)-1H-indole-3-carboxylate (**3ai**).* Yield, 65% (38.4 mg); white solid, mp 136-138 ℃; IR (KBr, cm^{-1}): 3261, 1651, 1603, 1475, 1461, 1438, 1379, 1280, 1234, 1206, 1145, 1054, 785, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.32 –

8.17 (m, 1H), 7.39 – 7.26 (m, 4H), 7.24 – 7.19 (m, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 159.1, 144.4, 135.2, 133.3, 129.1, 127.6, 123.2, 122.1, 122.03, 122.02, 115.4, 114.5, 111.2, 104.6, 59.8, 55.3, 14.4. HRMS-ESI: $[M+H]^+$ calcd for $C_{18}H_{18}NO_3$ *m/z* 296.1287, found *m/z* 296.1286.

*Ethyl 2-(3-fluorophenyl)-1H-indole-3-carboxylate (**3aj**).* Yield, 69% (39.1 mg); white solid, mp 160-162 ℃ (lit.[29] mp 162−164 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.25 (d, *J* = 5.4 Hz, 1H), 7.47 – 7.36 (m, 4H), 7.32 – 7.28 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 161.2 (d, $^1J_{C\text{-}F}$ = 245 Hz), 141.7, 134.2, 132.9 (d, $^3J_{C\text{-}F}$ = 8 Hz), 128.6 (d, $^3J_{C\text{-}F}$ = 8 Hz), 128.1, 126.4, 124.2 (d, $^4J_{C\text{-}F}$ = 3 Hz), 122.5, 121.2, 115.8 (d, $^2J_{C\text{-}F}$ = 23 Hz), 115.0 (d, $^2J_{C\text{-}F}$ = 21 Hz), 110.1, 104.1, 58.9, 13.2.

ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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