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Microwave-assisted synthesis of 3-substituted indoles via intramolecular arene–alkene coupling of *o*-iodoanilino enamines

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ABSTRACT

A generally applicable and high-yielding protocol for the synthesis of 3-substituted indole derivatives is described. Key features include microwave-assisted intramolecular arene–alkene coupling of *o*-iodoanilino enamines, and expedient synthesis of *o*-iodoanilino enamine substrates employing *N,O*-acetal TMS ethers, which could be conveniently derived from the corresponding amides. Our unique procedure seems quite efficient and provides an easy access to a variety of 3-substituted indoles as privileged structure for a wide range of biological targets.

1. Introduction

Indole is one of the most prevalent scaffolds in natural products, pharmaceuticals, and agrochemicals.[1] Many bioorganic materials, such as serotonin and melatonin contain indole moiety. The indole scaffold is an important privileged structure[2] in medicinal chemistry and their derivatives are observed in a large spectrum of drugs or drug candidates.[3] In particular, 3-substituted indoles are found in a wide range of synthetic and natural products, which possess diverse biological activities (Fig. 1). Among those, the 3-aryl indoles are found in, such as progesterone receptor antagonists for uterine fibroids,[4] protein tyrosine phosphatase 1B inhibitors for type 2 diabetes,[5] antidepressants including binedaline,[6] sigma 2 receptor ligands as the antipsychotic drugs,[7] and PPAR alpha agonists.[8] In addition, the 3-acyl indoles are also found in platelet-activating factor receptor (PAFR) antagonists for septic shock,[9] steroid 5α-reductase inhibitors for benign prostatic hyperplasia,[10] 5-HT3 antagonists,[11] and tachykinin NK1 antagonists as the antimigraine agents.[12] Tropisetron[13] and ramosetron hydrochloride[14] were launched as a 5-HT3 antagonist for the chemotherapy-induced emesis. The 3-alkyl indoles are found in tachykinin NK1 antagonists as bronchodilator,[15] dopamine autoreceptor agonists,[16] and 5-HT1A receptor agonists.[17] The launched drugs, eletriptan[18] and almotriptan,[19] are 5-hydroxytryptamine 1B/1D receptor agonists, which belong to this category. 3-Substituted indoles were also utilized for the syntheses of many natural products and the pharmacologically important substances.[20]

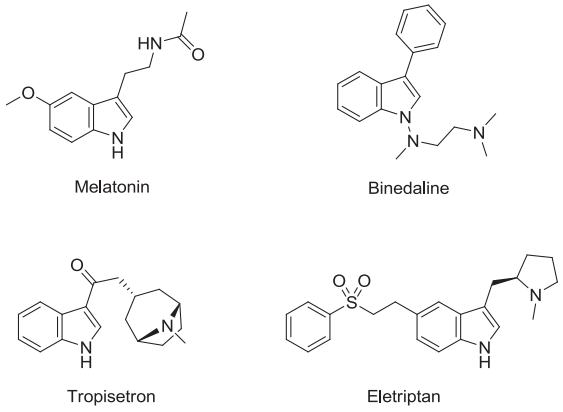

Fig. 1. Examples of bioactive 3-substituted indoles.

There have been numerous synthetic methods for indole synthesis.[21] In particular, a large number of synthetic methods for the 3-substituted indoles have been reported possibly due to the relatively feasible 2-substitution of indoles. The 3-substituted indole

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derivatives were synthesized by a variety of synthetic methods[22] and many advances were achieved by Pd-catalyzed transformation for the essential tolerability of functional groups. In these aspects, the intramolecular Heck or Heck-type reactions involving cyclization of *o*-haloanilino allylamine/double bond isomerization,[23] aminopalladation/reductive elimination domino reaction,[24] and Pd-catalyzed cyclization of *o*-haloanilino enamines[25–27] have been developed. The cyclization methods through intramolecular Heck or Heck-type reactions mainly utilize *o*-haloanilino allylamines except for a few examples. In contrast, the protocols involving *o*-haloanilino enamines were mostly limited to the enamines possessing electron-withdrawing groups, such as carbonyl, sulfonyl, nitrile, and nitro (Fig. 2, Eq. 1). Thus the intramolecular arene–alkene coupling reaction, which is usefully applicable to diverse enamine substrates (Fig. 2, Eq. 2), is yet to be explored for the synthesis of a wide range of the 3-substituted indoles, to the best of our knowledge. We herein report a microwave-assisted synthetic method for the 3-substituted indoles via intramolecular arene–alkene coupling reaction of the enamines possessing both electron withdrawing and donating groups.

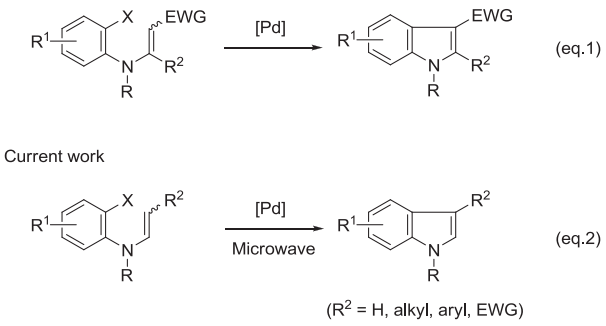


Fig. 2. Synthesis of 3-substituted indoles via intramolecular arene–alkene coupling of enamines.

2. Result and discussion

Enamines are frequently employed as an excellent substrate for the annulation reactions.[28] Thus, versatile and efficient synthetic method for enamines is importantly utilized in the indole synthesis via intramolecular arene–alkene coupling reaction. Inspired by the synthesis of *N*-vinyl-2-oxazolidinone via *N*,*O*-acetal,[29] we envisioned that *N*,*O*-acetal TMS ether (III) could be a suitable precursor for anilino enamine (II) (Fig. 3). Recently we reported the preparation of *N*,*O*-acetal TMS ether (III) from the corresponding amide (IV).[30] Taking advantage of easy access to a variety of amides using

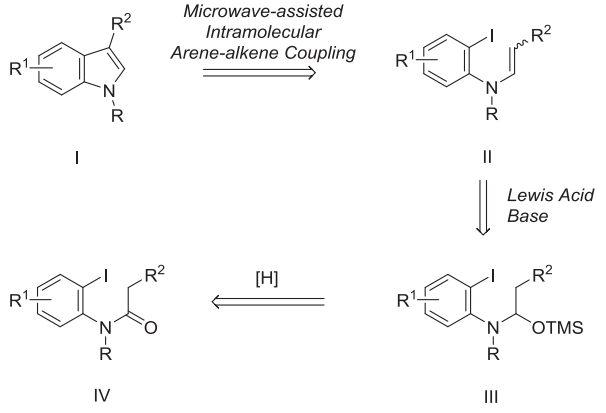
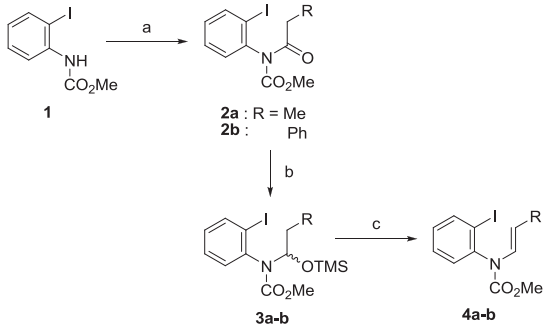


Fig. 3. Synthetic strategy for 3-substituted indoles.

conventional amidations, efficient preparation of the enamine precursors from *N*,*O*-acetal TMS ether by our strategy was anticipated. It is noteworthy that a large number of bioactive natural products consist of characteristic enamine moiety.[31]

Microwave irradiation is known to be beneficial for the intramolecular Heck reaction due to the direct and uniform input of energy into the reaction mixture.[32] Thus, we explored the microwave-assisted arene–alkene coupling reaction for indole synthesis based on the transformation of *N*-aryl β-nitroenamines into 3-nitroindoles.[27b]

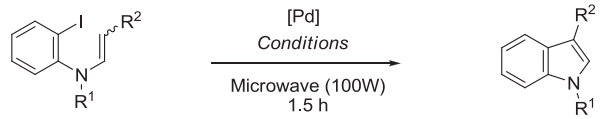
We commenced our work by the preparation of *o*-iodoanilino enamines from the corresponding amides (Scheme 1). The carbamate **1** underwent conventional amidation to give the amides **2a**,**b**. Next, the amides **2a**,**b** were reduced with DIBAL-H, and the resulting *N*,*O*-acetals were subsequently trapped with TMSOTf in situ to afford the *N*,*O*-acetal TMS ethers **3a**,**b**. Finally, the *N*,*O*-acetal TMS ethers **3a**,**b** were treated with $BF_3 \cdot OEt_2$ in the presence of Hünig base to afford the corresponding (*E*)-enamines **4a**,**b** successfully. The geometry of alkene was determined based on the coupling constants of ^{1}H NMR spectra. Encouraged by the successful transformation of *N*,*O*-acetal TMS ethers into the desired *o*-iodoanilino enamines, we turned our attention to the optimization of the microwave-assisted intramolecular arene–alkene coupling reaction.



Scheme 1. Reagents and conditions: (a) LHMDS, propionyl chloride for **2a** or phenylacetyl chloride for **2b**, THF, −78 °C to −5 °C, 93% for **2a**, 83% for **2b**; (b) DIBAL-H, pyridine, TMSOTf, CH_2Cl_2, −78 °C to −40 °C; (c) $BF_3 \cdot OEt_2$, DIPEA, CH_2Cl_2, −5 °C to rt, 65% for **4a**, 75% for **4b** (two steps).

After extensive examination of the cyclization conditions of the *o*-iodoanilino enamine **4a** under microwave irradiation (Table 1), $Pd(OAc)_2$ and PPh_3 (entry 8) were turned out to be the best combination. In addition, Jeffrey's condition[33] dramatically increased the chemical yield (entry 9). It is noteworthy that $Pd(PPh_3)_4$ was not effective at all (entry 12) for the desired cyclization, which well supported that the combination of $Pd(OAc)_2$ and PPh_3 is more effective than $Pd(PPh_3)_4$ for the generation of active zerovalent Pd catalyst in Heck-type reaction.[34] We also examined the synthesis of the 3-phenylindole. The yield for the enamine **4b** under the same cyclization conditions (entry 14) significantly decreased. However, chemical yield was recovered by the use of potassium acetate (entry 18) although the role of the acetate ion in the cyclization reaction is not understood clearly.[34] Cyclization for indole-3-carboxylate, which was attempted under the same conditions, suffered from the unexpected deprotection of carbamate (entry 19). Fortunately, carbamate protection with a bulkier protective group, such as Boc suppressed the undesirable side reaction (entry 20). The chemical yield of the cyclization under the conditions without microwave irradiation (entry 21) was quite lower compared to that of the microwave-assisted conditions in spite of the prolonged reaction time (12 h vs 1.5 h). The reaction mainly resulted in remaining of the substrate.

Table 1
Optimization of arene–alkene coupling reaction[a]



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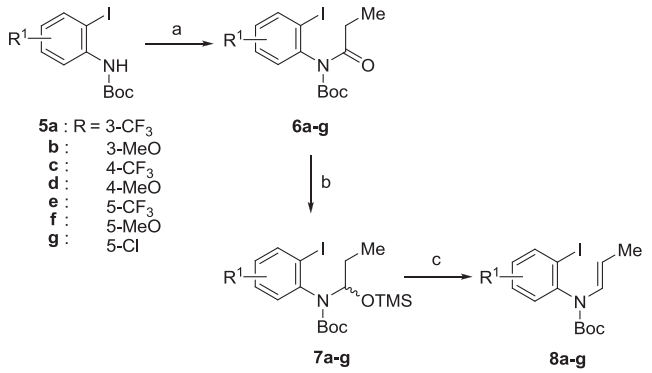
Entry	R^1	R^2	Catalyst	Ligand	Base	Additive	Solvent	Temperature (°C)	Yield[b] (%)
1	CO_2Me	Me	$Pd(PPh_3)_4$		Et_3N		DMF	100	—
2	CO_2Me	Me	$Pd(OAc)_2$		DABCO		DMF	85	—
3	CO_2Me	Me	$Pd(OAc)_2$	X-Phos	Cs_2CO_3		1,4-Dioxane	125	—
4	CO_2Me	Me	$Pd(OAc)_2$	X-Phos	Cs_2CO_3	Et_4NCl	DMF	125	—
5	CO_2Me	Me	Pd_2dba_3	$^tBu_3PHBF_4$	Cy_2NMe		NMP	100	—
6	CO_2Me	Me	Pd_2dba_3	DavePhos	KOAc	Et_4NCl	DMA	100	—
7	CO_2Me	Me	$PdCl_2$(dppf)		NaOAc	AgOAc	DMF	150	—
8	CO_2Me	Me	$Pd(OAc)_2$	PPh_3	K_2CO_3		CH_3CN	80	<10
9	CO_2Me	Me	$Pd(OAc)_2$	PPh_3	K_2CO_3	Et_4NCl	CH_3CN	80	85
10	CO_2Me	Me	$Pd(OAc)_2$	PPh_3	K_2CO_3	Et_4NCl	DMF	80	23
11	CO_2Me	Me	$Pd(OAc)_2$	P(*o*-tol)$_3$	K_2CO_3	Et_4NCl	CH_3CN	80	—
12	CO_2Me	Me	$Pd(PPh_3)_4$		K_2CO_3	Et_4NCl	CH_3CN	80	—
14	CO_2Me	Ph	$Pd(OAc)_2$	PPh_3	K_2CO_3	Et_4NCl	CH_3CN	80	15
15	CO_2Me	Ph	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Et_4NCl	CH_3CN	80	<10
16	CO_2Me	Ph	$Pd(OAc)_2$	PPh_3	K_3PO_4,	Et_4NCl	CH_3CN	80	26
17	CO_2Me	Ph	$Pd(OAc)_2$	PPh_3	NaO^{t}Bu	Et_4NCl	CH_3CN	80	—
18	CO_2Me	Ph	$Pd(OAc)_2$	PPh_3	KOAc	Et_4NCl	CH_3CN	80	91
19	CO_2Me	CO_2Me	$Pd(OAc)_2$	PPh_3	KOAc	Et_4NCl	CH_3CN	80	15[c]
20	Boc	CO_2Me	$Pd(OAc)_2$	PPh_3	KOAc	Et_4NCl	CH_3CN	80	95
21[d]	Boc	Me	$Pd(OAc)_2$	PPh_3	KOAc	Et_4NCl	CH_3CN	80	<30

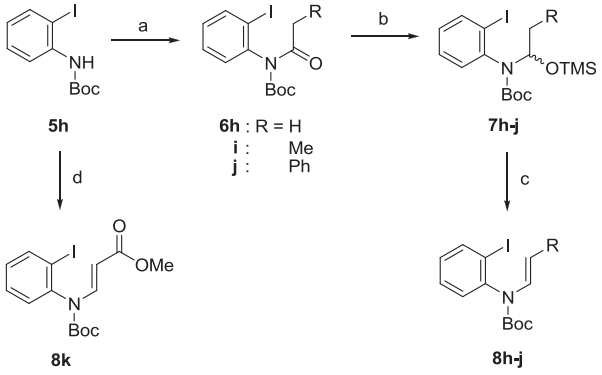
[a] Reactions were conducted with **4** (1.0 equiv), Pd catalyst (20 mol %), phosphine ligand (40 mol %), base (3.0 equiv), and additive (2.0 equiv) in solvent at given temperature for 1.5 h under microwave irradiation.
[b] Isolated yield.
[c] See text.
[d] The reaction was conducted under the conventional heating conditions and the starting material remained after 12 h. X-Phos=2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, dba=dibenzylideneacetone, dppf=1,1′-bis(diphenylphosphino)ferrocene, DavePhos=2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, *o*-tol=*o*-tolyl.

Having successfully optimized the reaction conditions, we examined the scope of the established protocol. The electronic and steric effects as well as the functional diversity of the substituents at the 3-position of indole were investigated. As shown in Scheme 2, the Boc-protected *o*-iodoanilines were acylated to provide the amides **6a**–**g**. The amides **6a**–**g** were reduced with DIBAL-H, followed by in situ silylation to afford the *N*,*O*-acetal TMS ethers **7a**–**g**, which were finally subjected to the elimination conditions to provide the *o*-iodoanilino enamines **8a**–**g**.



Scheme 2. Reagents and conditions: (a) LHMDS, propionyl chloride, THF, −78 °C to −5 °C, 85–93%; (b) DIBAL-H, pyridine, TMSOTf, CH_2Cl_2, −78 °C to −40 °C; (c) $BF_3{\cdot}OEt_2$, DIPEA, CH_2Cl_2, −5 °C to rt, 63–75% (two steps).

Likewise, the *o*-iodoanilino enamines **8h**–**j** were prepared from the Boc-protected *o*-iodoaniline **5h** using the corresponding acid chlorides. Enamine **8k** was readily prepared in 98% yield from the Boc-protected *o*-iodoaniline **5h** and methyl propiolate in the presence of catalytic amount of DABCO[35] (Scheme 3).

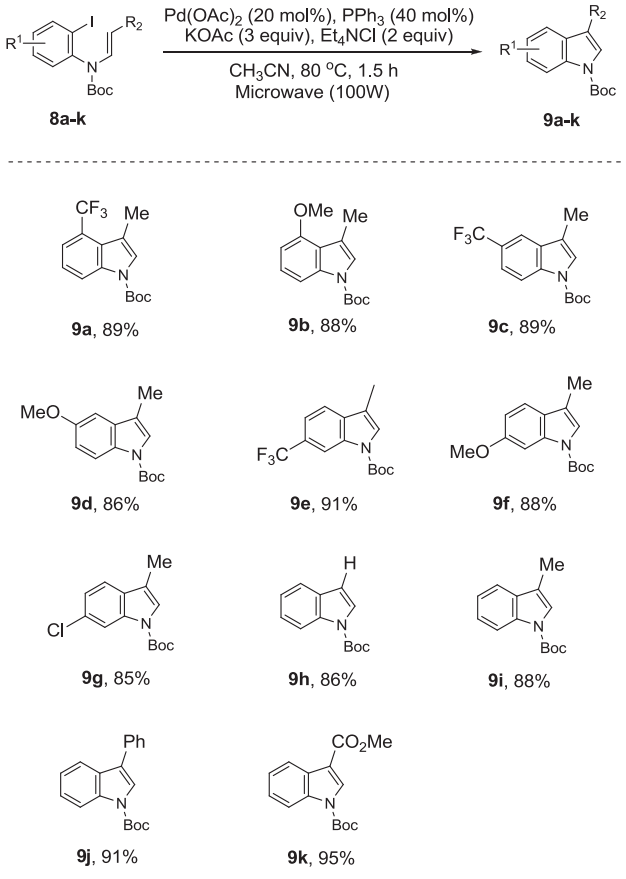


Scheme 3. Reagents and conditions: (a) LHMDS, acetyl chloride for **6h**, propionyl chloride for **6i**, phenylacetyl chloride for **6j**, THF, −78 °C to −5 °C, 95% for **6h**, 98% for **6i**, 80% for **6j**; (b) DIBAL-H, pyridine, TMSOTf, CH_2Cl_2, −78 °C to −40 °C; (c) $BF_3{\cdot}OEt_2$, DIPEA, CH_2Cl_2, −5 °C to rt, 62% for **8h**, 75% for 8**i**, 73% for **8j** (two steps); (d) DABCO, methyl propiolate, CH_2Cl_2, 0 °C to rt, 98%.

With the requisite *o*-iodoanilino enamines **8a**–**k** in our hands, cyclization using the microwave-assisted arene–alkene coupling reaction was explored.

As summarized in Scheme 4, a variety of the 3-substituted indoles were obtained in high yields from the corresponding enamines under the optimized conditions. The *o*-iodoanilino enamines possessing various substituents on the benzene ring including 3-CF_3 (**8a**), 3-MeO (**8b**), 4-CF_3 (**8c**), 4-MeO (**8d**), 5-CF_3 (**8e**),

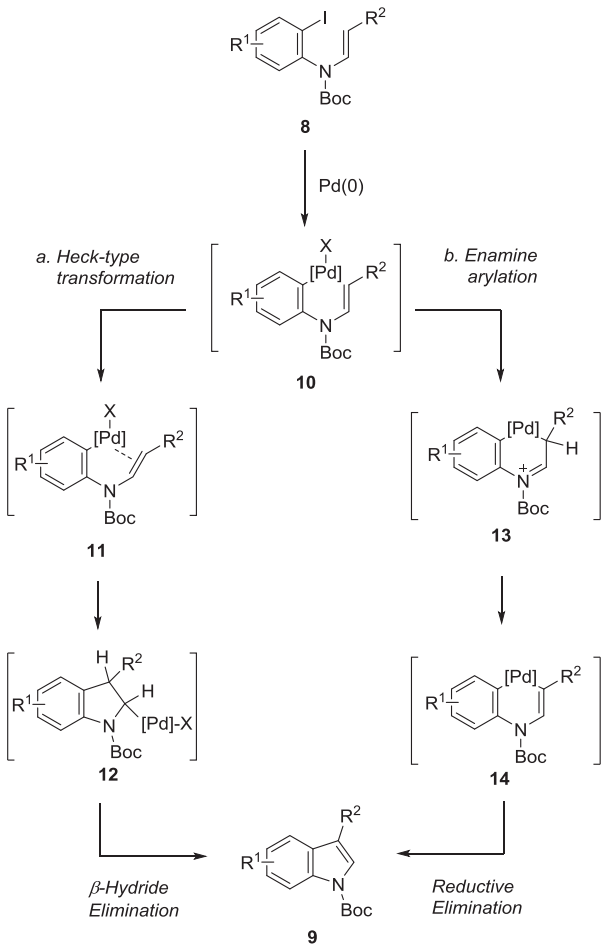
5-MeO (**8f**), and 5-Cl (**8g**) underwent facile cyclization regardless of the steric (**8a**,**b**) and electronic (**8a**–**f**) effects of the substituent as well as the substitution position. Moreover, indoles possessing the 3-alkyl (**9i**), aryl (**9j**), and carboalkoxy (**9k**) substituents as well as the non-substituted indole (**9h**) were successfully prepared. It is also noteworthy that the synthesis of indoles possessing both the electron donating, withdrawing substituents at the 3-position under the same reaction conditions has not been reported until the present report.



[a]Isolated yields.

Scheme 4. Scope of cyclization.[a]

Plausible mechanisms for the current intramolecular arene–alkene coupling are proposed in Scheme 5. The reaction is likely initiated by the oxidative addition of *o*-iodoanilino enamine **8** to Pd(0). Then, the reaction may proceed via intramolecular Heck-type reaction (pathway *a*). It is known that *trans*-alkene is mainly formed in the conventional Heck reaction by virtue of *syn*-β-elimination. But in this system, the cyclic structure of the carbopalladium complex **12** limits the bond rotation after insertion, so there is no *syn*-H and the *syn*-β-H elimination of conventional Heck mechanism cannot take place. However, it was also known that base-catalyzed *anti*-β-H elimination via the E2-like mechanism could not be completely ruled out.[32] In addition, there is a recent report that base-assisted *anti*-β-H elimination is favored in the systems that do not have *syn*-β-H from the theoretical study by DFT methods.[36] An alternative mechanism involving enamine arylation has been suggested by Latham and Stanforth[37] (pathway *b*). After oxidative addition to the Pd(0), intramolecular enamine arylation, followed by subsequent deprotonation and reductive elimination may occur to provide the corresponding indole (pathway *b*). Similar mechanisms have been reported for Pd-catalyzed intramolecular cyclizations in which palladacyles were involved.[38]



Scheme 5. Plausible mechanisms.

3. Conclusion

In conclusion, we have developed a versatile and high-yielding protocol for the preparation of 3-substituted indoles using microwave-assisted intramolecular arene–alkene coupling reaction of *o*-iodoanilino enamines. The *o*-iodoanilino enamines were readily prepared from the *N*,*O*-acetal TMS ethers, which were conveniently derived from the corresponding amides. We believe our protocol would provide a variety of 3-substituted indoles as privileged structure for a wide range of biological targets.

4. Experimental section

4.1. General

Commercially available reagents and solvents were used without additional purification. All reactions were performed under inert atmosphere of nitrogen. The microwave reactions were carried out using a CEM microwave reactor in closed vials. Melting points were taken on a BUCHI Melting Point B-540 and were uncorrected. IR spectra were obtained on Perkin–Elmer 1710 FT-IR. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Ascend™ 400 MHz or JEOL JNM ECA-600 MHz spectrometer using $CDCl_3$, DMSO-d_6 or methanol-d_4 as solvents. All chemical shifts are given in parts per

million. Data are reported as follows: chemical shift, multiplicity, coupling constants (Hertz), and integration. High-resolution mass spectra were recorded on JMS-AX 505WA or JMS-700 (JMS).

*4.1.1. Preparation of Boc-protected anilines **5a**–**g**.*[39] *General procedure for* **5a**, **5c**–**g**: To a solution of the aniline (5.40 mmol) in anhydrous THF (35 mL) was added Boc_2O (12.42 mmol) followed by DMAP (0.54 mmol). The solution was stirred at reflux for 6 h then concentrated to dryness and partitioned between 0.5 N-HCl (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2×50 mL) and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude di-Boc product. The crude material was dissolved in methanol (35 mL), treated with potassium carbonate (16.2 mmol), and stirred at reflux for 6 h. The mixture was concentrated to dryness and partitioned between 0.5 N-HCl (100 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in reduced pressure. The crude product was purified by flash silica gel column chromatography (*n*-hexane/EtOAc=9:1) to afford carbamate **5**.

*4.1.1.1. tert-Butyl 2-iodo-3-(trifluoromethyl)phenylcarbamate (**5a**).* Yield 93.2%; white solid; mp 50–52 °C; FT-IR (thin film, neat) ν_{max} 3390, 2970, 2349, 2309, 1739, 1647, 1589, 1517, 1456, 1367, 1322 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J=8.1 Hz, 1H), 7.43–7.33 (m, 2H), 7.20 (br s, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 140.7, 134.3 (q, J=30.4 Hz), 128.9, 123.4, 122.8 (q, J=273.8 Hz), 122.2 (q, J=6.0 Hz), 86.8, 81.6, 28.2; HR-MS (FAB^+) calcd for $C_{12}H_{13}F_3INO_2$ $[M]^+$ 386.9943; found 386.9948.

*4.1.1.2. tert-Butyl 2-iodo-4-(trifluoromethyl)phenylcarbamate (**5c**).* Yield 90.5%; white solid; mp 73–75 °C; FT-IR (thin film, neat) ν_{max} 3394, 3015, 2970, 1739, 1606, 1573, 1526, 1456, 1366, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J=8.7 Hz, 1H), 7.98 (d, J=1.3 Hz, 1H), 7.57 (dd, J=8.7, 2.0 Hz, 1H), 7.02 (br s, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 141.9, 135.8 (q, J=3.9 Hz), 126.4 (q, J=3.7 Hz), 126.0 (q, J=33.2 Hz), 123.0 (q, J=272.0 Hz), 118.8, 87.0, 81.9, 28.2; HR-MS (FAB^+) calcd for $C_{12}H_{13}F_3INO_2$ $[M]^+$ 386.9943; found 386.9947.

*4.1.1.3. tert-Butyl 2-iodo-4-methoxyphenylcarbamate (**5d**).* Yield 85.3%; colorless oil, FT-IR (thin film, neat) ν_{max} 3401, 2971, 2835, 2349, 2309, 1736, 1647, 1602, 1572, 1516, 1457, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J=8.6 Hz, 1H), 7.30 (d, J=2.8 Hz, 1H), 6.89 (dd, J=9.0, 2.8 Hz, 1H), 6.54 (br s, 1H), 3.76 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 153.0, 132.3, 123.7, 122.0, 114.9, 90.3, 80.7, 55.7, 28.3; HR-MS (FAB^+) calcd for $C_{12}H_{16}INO_3$ $[M]^+$ 349.0175; found 349.0171.

*4.1.1.4. tert-Butyl 2-iodo-5-(trifluoromethyl)phenylcarbamate (**5e**).* Yield 88.5%; white solid; mp 86–88 °C; FT-IR (thin film, neat) ν_{max} 3015, 2970, 2349, 2309, 1739, 1647, 1581, 1523, 1427, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.86 (d, J=8.3 Hz, 1H), 7.01 (d, J=8.2 Hz, 1H), 6.96 (br s, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 139.6, 139.3, 131.8 (q, J=32.8 Hz), 123.7 (q, J=272.6 Hz), 120.6 (q, J=3.7 Hz), 116.2 (q, J=4.0 Hz), 91.9, 81.8, 28.2; HR-MS (FAB^+) calcd for $C_{12}H_{13}F_3INO_2$ $[M]^+$ 386.9943; found 386.9933.

*4.1.1.5. tert-Butyl 2-iodo-5-methoxyphenylcarbamate (**5f**).* Yield 85.1%; colorless oil; FT-IR (thin film, neat) ν_{max} 3015, 2970, 2349, 2309, 1739, 1647, 1565, 1542, 1517, 1433, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.57 (d, J=8.8 Hz, 1H), 6.83 (br s, 1H), 6.40 (dd, J=8.8, 1.4 Hz, 1H), 3.80 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 152.4, 139.6, 138.7, 111.6, 105.1, 81.1, 55.4, 28.3; HR-MS (FAB^+) calcd for $C_{12}H_{16}INO_3$ $[M]^+$ 349.0175; found 349.0176.

*4.1.1.6. tert-Butyl 5-chloro-2-iodophenylcarbamate (**5g**).* Yield 85.4%; colorless oil; FT-IR (thin film, neat) ν_{max} 3841, 3735, 3391, 2971, 1738, 1569, 1507, 1436, 1405, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J=2.3 Hz, 1H), 7.63 (d, J=8.5 Hz, 1H), 6.85 (br s, 1H), 6.77 (dd, J=8.5, 2.5 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 139.8, 139.2, 135.4, 124.5, 119.6, 85.0, 81.6, 28.2; HR-MS (FAB^+) calcd for $C_{11}H_{13}ClINO_2$ $[M]^+$ 352.9680; found 352.9669.

*4.1.1.7. tert-Butyl 2-iodo-3-methoxyphenylcarbamate (**5b**).*[40] To a solution of *tert*-butyl 3-methoxyphenylcarbamate (995 mg, 4.456 mmol) in anhydrous ether (60 mL) was added *tert*-butyllithium (10.5 mL of 1.7 M, 17.850 mmol) at −78 °C slowly. The reaction mixture was warmed to −20 °C and stirred for 3 h. The solution was again cooled to −78 °C and quenched by the addition of a solution of iodine (1.697 g in 10 mL of ether, 6.686 mmol) via a cannula, ensuring the reaction temperature did not rise above −65 °C. After 1 h, the reaction mixture was warmed to room temperature slowly and stirred for 12 h. After addition of a saturated aqueous $Na_2S_2O_3$ solution, the mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc=30:1) to afford 1.08 g (69.4%) of **5b** as a gel-type compound; FT-IR (thin film, neat) ν_{max} 3461, 3386, 3014, 2970, 2945, 2349, 2309, 1738, 1647, 1592, 1574, 1542, 1517, 1469, 1408, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J=8.3 Hz, 1H), 7.29–7.22 (m, 1H), 7.05 (br s, 1H), 6.53 (d, J=8.2 Hz, 1H), 3.88 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 152.6, 140.2, 129.6, 112.4, 105.3, 80.9, 56.5, 28.3; HR-MS (FAB^+) calcd for $C_{12}H_{16}INO_3$ $[M]^+$ 349.0175; found 349.0185.

*4.1.2. General procedure for **2a**, **6a**–**g**.* To a stirred solution of **5** (2.5 mmol) in THF (5 mL) was added LHMDS (1.0 M solution in THF, 3.75 mmol) and stirred for 1 h. Propionyl chloride (5.0 mmol) was added at −78 °C and stirred for 10 min. The reaction mixture was allowed to −5 °C and stirred for 2 h then quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc=5:1) to afford amide **6**.

*4.1.2.1. Methyl 2-iodophenyl(propionyl)carbamate (**2a**).* Yield 93.1%; white solid; mp 83–85 °C; FT-IR (thin film, neat) ν_{max} 2970, 2952, 2310, 1753, 1698, 1469, 1439, 1363, 1300 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J=7.9 Hz, 1H), 7.41–7.35 (m, 1H), 7.16 (dd, J=7.8, 1.3 Hz, 1H), 7.08–7.02 (m, 1H), 3.69 (s, 3H), 3.13–2.96 (m, 2H), 1.20 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 153.3, 140.8, 139.2, 129.5, 129.2, 129.1, 99.5, 53.8, 31.5, 8.8; HR-MS (FAB^+) calcd for $C_{11}H_{13}INO_3$ $[M+H]^+$ 333.9940; found 333.9945.

*4.1.2.2. tert-Butyl 2-iodo-3-(trifluoromethyl)phenyl(propionyl)carbamate (**6a**).* Yield 90.2%; white solid; mp 105–107 °C; FT-IR (thin film, neat) ν_{max} 2970, 2943, 2349, 2309, 1742, 1648, 1565, 1542, 1508, 1424, 1370, 1319, 1301 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J=7.9, 1.3 Hz, 1H), 7.52–7.45 (m, 1H), 7.32 (dd, J=7.8, 1.1 Hz, 1H), 3.17–2.99 (m, 2H), 1.37 (s, 9H), 1.22 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 151.0, 144.4, 135.5 (q, J=30.9 Hz), 132.1, 129.0, 126.7 (q, J=5.8 Hz), 122.5 (q, J=274.0 Hz), 98.5, 83.7, 31.7, 27.7, 8.9; HR-MS (FAB^+) calcd for $C_{15}H_{18}F_3INO_3$ $[M+H]^+$ 444.0284; found 444.0291.

*4.1.2.3. tert-Butyl 2-iodo-3-methoxyphenyl(propionyl)carbamate (**6b**).* Yield 88.2%; white solid; mp 76–78 °C; FT-IR (thin film, neat)

ν_{max} 3015, 2970, 2944, 2349, 2309, 1739, 1648, 1581, 1542, 1508, 1433, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 1H), 6.83–6.74 (m, 2H), 3.90 (s, 3H), 3.10–2.90 (m, 2H), 1.38 (s, 9H), 1.20 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 159.2, 151.4, 143.3, 129.5, 121.6, 109.9, 92.1, 83.1, 56.6, 31.7, 27.8, 9.0; HR-MS (FAB^+) calcd for $C_{15}H_{21}INO_4$ $[M+H]^+$ 406.0515; found 406.0516.

*4.1.2.4. tert-Butyl 2-iodo-4-(trifluoromethyl)phenyl(propionyl)carbamate (**6c**).* Yield 89.6%; white solid; mp 98–100 °C; FT-IR (thin film, neat) ν_{max} 2971, 2942, 2349, 1744, 1604, 1457, 1395, 1371, 1322, 1301 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12–8.09 (m, 1H), 7.67–7.62 (m, 1H), 7.28–7.23 (m, 1H), 3.15–2.98 (m, 2H), 1.39 (s, 9H), 1.21 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 150.8, 145.3, 136.2 (q, J=3.8 Hz), 131.2 (q, J=33.2 Hz), 129.5, 126.2 (q, J=3.6 Hz), 122.6 (q, J=272.9 Hz), 99.6, 83.9, 31.6, 27.8, 8.9; HR-MS (FAB^+) calcd for $C_{15}H_{18}F_3INO_3$ $[M+H]^+$ 444.0284; found 444.0278.

*4.1.2.5. tert-Butyl 2-iodo-4-methoxyphenyl(propionyl)carbamate (**6d**).* Yield 85.3%; colorless oil; FT-IR (thin film, neat) ν_{max} 2970, 2943, 2349, 2309, 1739, 1647, 1595, 1647, 1595, 1565, 1542, 1508, 1490, 1441, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J=2.6 Hz, 1H), 7.03 (d, J=8.7 Hz, 1H), 6.91 (dd, J=8.7, 2.6 Hz, 1H), 3.80 (s, 3H), 3.06–2.88 (m, 2H), 1.40 (s, 9H), 1.20 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 158.9, 151.8, 134.7, 129.2, 124.0, 114.8, 99.6, 83.0, 55.6, 31.6, 27.8, 9.1; HR-MS (FAB^+) calcd for $C_{15}H_{21}INO_4$ $[M+H]^+$ 406.0515; found 406.0509.

*4.1.2.6. tert-Butyl 2-iodo-5-(trifluoromethyl)phenyl(propionyl)carbamate (**6e**).* Yield 88.4%; colorless viscous oil; FT-IR (thin film, neat) ν_{max} 3461, 2970, 2943, 2349, 2309, 1742, 1648, 1604, 1565, 1542, 1508, 1474, 1413, 1370, 1332 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J=8.3 Hz, 1H), 7.40 (d, J=1.9 Hz, 1H), 7.29 (dd, J=8.3, 1.9 Hz, 1H), 3.16–2.98 (m, 2H), 1.39 (s, 9H), 1.22 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 150.9, 142.7, 139.9, 131.8 (q, J=33.4 Hz), 126.1 (q, J=3.8 Hz), 125.7 (q, J=3.6 Hz), 123.4 (q, J=272.4 Hz), 104.2, 83.9, 31.6, 27.7, 8.9; HR-MS (FAB^+) calcd for $C_{15}H_{18}F_3INO_3$ $[M+H]^+$ 444.0284; found 444.0272.

*4.1.2.7. tert-Butyl 2-iodo-5-methoxyphenyl(propionyl)carbamate (**6f**).* Yield 86.7%; white solid; mp 111–113 °C; FT-IR (thin film, neat) ν_{max} 3461, 2970, 2943, 2349, 2309, 1739, 1647, 1593, 1571, 1542, 1508, 1473, 1456, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J=8.7 Hz, 1H), 6.73 (d, J=2.8 Hz, 1H), 6.66 (dd, J=8.7, 2.8 Hz, 1H), 3.78 (s, 3H), 3.08–2.92 (m, 2H), 1.40 (s, 9H), 1.20 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 160.5, 151.4, 142.5, 139.2, 115.5, 115.3, 88.1, 83.2, 55.5, 31.6, 27.8, 9.0; HR-MS (FAB^+) calcd for $C_{15}H_{21}INO_4$ $[M+H]^+$ 406.0515; found 406.0515.

*4.1.2.8. tert-Butyl 5-chloro-2-iodophenyl(propionyl)carbamate (**6g**).* Yield 88.6%; white solid; mp 69–71 °C; FT-IR (thin film, neat) ν_{max} 2970, 2349, 1740, 1457, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J=8.5 Hz, 1H), 7.17 (d, J=2.3 Hz, 1H), 7.05 (dd, J=8.5, 2.3 Hz, 1H), 3.13–2.94 (m, 2H), 1.40 (s, 9H), 1.21 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 150.9, 142.9, 139.8, 134.7, 129.5, 129.5, 97.0, 83.7, 31.6, 27.8, 8.9; HR-MS (FAB^+) calcd for $C_{14}H_{18}ClINO_3$ $[M+H]^+$ 410.0020; found 410.0019.

*4.1.2.9. Methyl 2-iodophenyl(2-phenylacetyl)carbamate (**2b**).* Compound **2b** was prepared according to the method for synthesis of **2a** except that phenylacetyl chloride was used instead of propionyl chloride: yield 83.3%; colorless viscous oil; FT-IR (thin film, neat) ν_{max} 3029, 2970, 1746, 1496, 1469, 1438, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92–7.82 (m, 1H), 7.45–7.02 (m, 8H), 4.45 (d, J=16.0 Hz, 1H), 4.34 (d, J=16.0 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 153.5, 140.8, 139.4, 134.0, 129.8, 129.4, 129.2, 128.4, 127.0, 99.5, 54.1, 44.2; HR-MS (FAB^+) calcd for $C_{16}H_{15}INO_3$ $[M+H]^+$ 396.0097; found 396.0093.

*4.1.2.10. tert-Butyl acetyl(2-iodophenyl)carbamate (**6h**).* Compound **6h** was prepared according to the method for synthesis of **6a** except for acetyl chloride instead of propionyl chloride: yield 95.1%; white solid; mp 105–107 °C; FT-IR (thin film, neat) ν_{max} 3057, 3001, 2976, 2933, 1742, 1705, 1580, 1541, 1469, 1414, 1394, 1370, 1304 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J=7.9, 1.3 Hz, 1H), 7.41–7.36 (m, 1H), 7.16 (dd, J=7.9, 1.5 Hz, 1H), 7.08–7.02 (m, 1H), 2.64 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 151.5, 141.6, 139.2, 129.4, 129.1, 129.1, 99.4, 83.4, 27.8, 26.6; HR-MS (FAB^+) calcd for $C_{13}H_{17}INO_3$ $[M+H]^+$ 362.0253; found 362.0258.

*4.1.2.11. tert-Butyl 2-iodophenyl(propionyl)carbamate (**6i**).* Compound **6i** was prepared according to the method for synthesis of **7a**: yield 98.0%; colorless gel-type compound; FT-IR (thin film, neat) ν_{max} 2980, 2942, 1726, 1579, 1469, 1367, 1331 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J=7.8 Hz, 1H), 7.38–7.31 (m, 2H), 7.02–6.93 (m, 1H), 2.44 (q, J=7.5 Hz, 2H), 1.44 (s, 9H), 1.16 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 152.1, 143.2, 139.5, 129.3, 128.9, 111.0, 99.9, 81.8, 28.1, 27.3, 9.0.

*4.1.2.12. tert-Butyl 2-iodophenyl(2-phenylacetyl)carbamate (**6j**).* Compound **6j** was prepared according to the method for synthesis of **6a** except for phenylacetyl chloride instead of propionyl chloride: yield 80.2%; white solid; mp 103–105 °C; FT-IR (thin film, neat) ν_{max} 2971, 1739, 1496, 1469, 1455, 1369 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J=7.9 Hz, 1H), 7.38–7.20 (m, 6H), 7.10 (d, J=7.8 Hz, 1H), 7.02 (t, J=7.6 Hz, 1H), 4.42 (d, J=16.1 Hz, 1H), 4.32 (d, J=16.1 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 151.4, 141.6, 139.2, 134.4, 129.9, 129.3, 129.2, 129.0, 128.3, 126.8, 99.5, 83.5, 44.2, 27.8; HR-MS (FAB^+) calcd for $C_{19}H_{21}INO_3$ $[M+H]^+$ 438.0566; found 438.0568.

*4.1.3. General procedure for **4a**, **8a**–**j**.* To a solution of **6** (1.4 mmol) in dry CH_2Cl_2 (20 mL) was added DIBAL-H (1.0 M solution in DCM, 2.8 mmol) at −78 °C. After stirring for 1 h, the reaction mixture was treated with pyridine (4.2 mmol) and then TMSOTf (3.5 mmol). The mixture was stirred at −78 °C for 10 min, and then slowly warmed to −40 °C and stirred for 1 h then quenched with 15% aqueous sodium potassium tartarate solution, and diluted with diethyl ether. The resultant mixture was warmed to room temperature and stirred vigorously until two layers were completely separated. The mixture was extracted with diethyl ether and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by amino silica gel column chromatography (*n*-hexane/EtOAc=30:1) to afford the mixture of **7** as a major product and small amount of **5** and used without further purification. This mixture was dissolved in dry CH_2Cl_2 and added *N*,*N*-diisopropylethylamine (3.67 mmol), $BF_3{\cdot}OEt_2$ (2.75 mmol) at −5 °C and stirred for 10 min then allowed to room temperature. After stirring for 2 h, the reaction mixture was quenched with Et_3N and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc=9:1) to afford enamine **8**.

*4.1.3.1. (E)-Methyl 2-iodophenyl(prop-1-enyl)carbamate (**4a**).* Yield 65.4%; colorless gel-type compound; ^1H NMR (400 MHz, $CDCl_3$): *Note: a splitting or broadening of some peaks was observed due to rotamers* δ 7.92 (dd, J=7.9, 1.1 Hz, 1H), 7.45–7.39 (m, 1H), 7.25–7.17 (m, 1H), 7.13–6.82 (m, 2H), 4.33–4.19 (m, 1H), 3.87 and 3.69 (s, 3H), 1.62 (dd, J=6.7, 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 141.0, 139.9, 129.8, 129.5, 129.4, 128.2, 106.9, 99.9, 53.4, 14.9.

*4.1.3.2. (E)-Methyl 2-iodophenyl(styryl)carbamate (**4b**).* Yield: 75.2%; colorless gel-type compound; FT-IR (thin film, neat) ν_{max} 3003, 2970, 2952, 2349, 1741, 1634, 1578, 1471, 1439, 1366, 1333 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C): *Note: a splitting or broadening of some peaks was observed due to rotamers* δ 8.03 (dd, *J*=7.9, 1.3 Hz, 1H), 7.79 (d, *J*=14.6 Hz, 1H), 7.60–7.53 (m, 1H), 7.48–7.42 (m, 1H), 7.30–7.20 (m, 5H), 7.17–7.09 (m, 1H), 5.10 (d, *J*=14.7 Hz, 1H), 3.84 and 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 152.3, 139.9, 139.3, 135.6, 129.7, 129.5, 129.3, 128.1, 127.8, 125.7, 124.7, 111.0, 99.3, 53.0; HR-MS (FAB^+) calcd for $C_{12}H_{13}INO_4$ $[M+H]^+$ 361.9889; found 361.9900.

*4.1.3.3. (E)-tert-Butyl 2-iodo-3-(trifluoromethyl)phenyl(prop-1-enyl)carbamate (**8a**).* Yield 71.5%; colorless oil; FT-IR (thin film, neat) ν_{max} 2971, 2935, 2888, 1719, 1668, 1579, 1516, 1456, 1423, 1368, 1330, 1306 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ 7.75–7.61 (m, 2H), 7.55–7.49 (m, 1H), 6.95 (d, *J*=14.2 Hz, 1H), 4.21–4.08 (m, 1H), 1.62–1.56 (m, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 150.0, 143.8, 134.1 (q, *J*=30.1 Hz), 133.0, 129.5, 127.7, 126.2 (q, *J*=5.8 Hz), 122.3 (q, *J*=274.0 Hz), 105.1, 98.9, 80.6, 27.3, 14.0; HR-MS (EI^+) calcd for $C_{15}H_{17}F_3INO_2$ $[M]^+$ 427.0256, found 427.0257.

*4.1.3.4. (E)-tert-Butyl 2-iodo-3-methoxyphenyl(prop-1-enyl)carbamate (**8b**).* Yield 64.3%; white solid; mp 80–82 °C; FT-IR (thin film, neat) ν_{max} 3005, 2970, 2349, 2309, 1739, 1715, 1669, 1648, 1581, 1572, 1542, 1508, 1469, 1456, 1430, 1366, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *Note: a splitting or broadening of some peaks was observed due to rotamers* δ 7.40–7.27 (m, 1H), 7.07–6.71 (m, 3H), 4.27–4.15 (m, 1H), 3.91 (s, 3H), 1.59 (dd, *J*=6.7, 0.9 Hz, 3H), 1.57 and 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 151.6, 143.2, 129.5, 127.8, 122.0, 109.5, 105.6, 92.2, 80.8, 56.5, 28.0, 14.9; HR-MS (FAB^+) calcd for $C_{15}H_{20}INO_3$ $[M]^+$ 389.0488; found 389.0489.

*4.1.3.5. (E)-tert-Butyl 2-iodo-4-(trifluoromethyl)phenyl(prop-1-enyl)carbamate (**8c**).* Yield 75.1%; colorless oil; FT-IR (thin film, neat) ν_{max} 2970, 2937, 2349, 2309, 1720, 1669, 1678, 1603, 1565, 1476, 1456, 1368, 1324 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ 8.26–8.19 (m, 1H), 7.87–7.75 (m, 1H), 7.52–7.43 (m, 1H), 6.93 (d, *J*=14.3 Hz, 1H), 4.25–4.11 (m, 1H), 1.62–1.55 (m, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 149.8, 145.1, 135.5 (q, *J*=3.9 Hz), 130.3, 129.3 (q, *J*=32.5 Hz), 127.5, 126.0 (q, *J*=3.7 Hz), 123.4, 122.2 (q, *J*=272.9 Hz), 105.5, 100.3, 80.7, 27.3, 13.9; HR-MS (FAB^+) calcd for $C_{15}H_{17}F_3INO_2$ $[M]^+$ 427.0256; found 427.0257.

*4.1.3.6. (E)-tert-Butyl 2-iodo-4-methoxyphenyl(prop-1-enyl)carbamate (**8d**).* Yield 68.2%; white solid; mp 115–117 °C; FT-IR (thin film, neat) ν_{max} 3004, 2970, 2936, 2349, 2309, 1738, 1715, 1669, 1648, 1590, 1570, 1542, 1507, 1475, 1457, 1424, 1366, 1352, 1322 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *Note: a splitting or broadening of some peaks was observed due to rotamers* δ 7.73 (d, *J*=8.6 Hz, 1H), 7.07–6.71 (m, 2H), 6.65 (d, *J*=8.6 Hz, 1H), 4.31–4.18 (m, 1H), 3.79 (s, 3H), 1.61 (d, *J*=6.7 Hz, 3H), 1.57 and 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 160.5, 151.4, 151.1, 142.4, 139.8, 139.5, 128.2, 127.8, 115.8, 115.5, 115.1, 105.8, 88.2, 81.8, 81.0, 55.4, 28.3, 28.0, 15.0; HR-MS (FAB^+) calcd for $C_{15}H_{20}INO_3$ $[M]^+$ 389.0488; found 389.0472.

*4.1.3.7. (E)-tert-Butyl 2-iodo-5-(trifluoromethyl)phenyl(prop-1-enyl)carbamate (**8e**).* Yield 63.2%; colorless viscous oil; ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ 8.21 (d, *J*=8.3 Hz, 1H), 7.61–7.57 (m, 1H), 7.49–7.43 (m, 1H), 6.93 (dd, *J*=14.3, 1.4 Hz, 1H), 4.23–4.12 (m, 1H), 1.61 (dd, *J*=6.7, 1.5 Hz, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 149.9, 142.2, 140.4, 130.1 (q, *J*=32.8 Hz), 127.7, 126.0 (q, *J*=3.5 Hz), 125.2 (q, *J*=3.7 Hz), 123.0 (q, *J*=272.5 Hz), 105.4, 105.3, 80.7, 27.3, 13.9.

*4.1.3.8. (E)-tert-Butyl 2-iodo-5-methoxyphenyl(prop-1-enyl)carbamate (**8f**).* Yield 70.2%; colorless viscous oil; FT-IR (thin film, neat) ν_{max} 2970, 2349, 2309, 1739, 1717, 1669, 1648, 1594, 1566, 1542, 1508, 1490, 1456, 1366, 1322 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ 7.47–7.42 (m, 1H), 7.15–7.08 (m, 1H), 7.05–6.99 (m, 1H), 6.92 (d, *J*=14.2 Hz, 1H), 4.24–4.10 (m, 1H), 3.80 (s, 3H), 1.60–1.54 (m, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 158.2, 150.5, 133.9, 129.4, 128.2, 123.8, 114.6, 104.3, 99.6, 79.9, 55.2, 27.4, 13.9; HR-MS (FAB^+) calcd for $C_{15}H_{20}INO_3$ $[M]^+$ 389.0488; found 389.0484.

*4.1.3.9. (E)-tert-Butyl 5-chloro-2-iodophenyl(prop-1-enyl)carbamate (**8g**).* Yield 65.4%; white solid; mp 113–115 °C; FT-IR (thin film, neat) ν_{max} 3015, 2970, 2349, 2309, 1739, 1670, 1647, 1571, 1542, 1508, 1434, 1366, 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J*=8.3 Hz, 1H), 7.30–6.79 (m, 3H), 4.28–4.16 (m, 1H), 1.62 (d, *J*=6.7 Hz, 3H), 1.60–1.32 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 143.0, 140.3, 134.7, 129.9, 129.3, 127.7, 106.3, 97.4, 81.6, 28.1, 15.0; HR-MS (FAB^+) calcd for $C_{14}H_{17}ClINO_2$ $[M]^+$ 392.9993; found 392.9985.

*4.1.3.10. tert-Butyl 2-iodophenyl(vinyl)carbamate (**8h**).* Yield 62.3%; white solid; mp 71–73 °C; FT-IR (thin film, neat) ν_{max} 2978, 1718, 1633, 1580, 1472, 1457, 1368, 1344, 1316 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ 7.97 (d, *J*=7.8 Hz, 1H), 7.53–7.43 (m, 1H), 7.29–7.23 (m, 1H), 7.22–7.09 (m, 2H), 4.24 (d, *J*=8.8 Hz, 1H), 3.60 (d, *J*=15.8 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 150.3, 140.0, 139.0, 132.8, 129.4, 129.1, 129.0, 99.3, 92.7, 80.6, 27.3; HR-MS (FAB^+) calcd for $C_{13}H_{17}INO_2$ $[M+H]^+$ 346.0304; found 346.0301.

*4.1.3.11. (E)-tert-Butyl 2-iodophenyl(prop-1-enyl)carbamate (**8i**).* Yield 75.2%; white solid; mp 92–94 °C; FT-IR (thin film, neat) ν_{max} 2970, 2349, 1739, 1721, 1669, 1472, 1440, 1366, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *Note: a splitting or broadening of some peaks was observed due to rotamers* δ 7.95–7.85 (m, 1H), 7.45–7.34 (m, 1H), 7.26–7.23 and 7.22–7.13 (m, 1H), 7.10–6.99 and 6.93–6.85 (m, 2H), 4.25–4.14 (m, 1H), 1.61 (dd, *J*=6.7, 1.3 Hz, 3H), 1.57 and 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 141.7, 139.6, 129.7, 129.2, 129.0, 128.0, 105.9, 99.9, 81.1, 28.1, 15.1; ^1H NMR (600 MHz, DMSO-d_6, 80 °C): δ 9.30 (d, *J*=9.9 Hz, 1H), 8.73–8.68 (m, 1H), 8.45–8.39 (m, 1H), 8.31–8.24 (m, 1H), 8.03 (d, *J*=17.8 Hz, 1H), 4.58–4.47 (m, 1H), 1.34 (d, *J*=8.3 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6, 80 °C): δ 178.1, 166.4, 164.0, 152.1, 151.5, 150.2, 121.1, 114.6, 90.5, 24.5, 7.8; HR-MS (FAB^+) calcd for $C_{14}H_{18}INO_2$ $[M+H]^+$ 359.0382; found 359.0380.

*4.1.3.12. (E)-tert-Butyl 2-iodophenyl(styryl)carbamate (**8j**).* Yield 73.2%; colorless viscous oil; FT-IR (thin film, neat) ν_{max} 2971, 1718, 1646, 1579, 1471, 1447, 1367, 1323 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ 8.04–7.98 (m, 1H), 7.73 (d, *J*=14.7 Hz, 1H), 7.58–7.50 (m, 1H), 7.40–7.33 (m, 1H), 7.28–7.16 (m, 5H), 7.16–7.07 (m, 1H), 5.14 (d, *J*=14.7 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 150.4, 140.3, 139.1, 135.9, 129.4, 129.3, 129.1, 128.0, 127.8, 125.5, 124.6, 110.1, 99.2, 81.0, 27.3; HR-MS (FAB^+) calcd for $C_{19}H_{20}INO_2$ $[M]^+$ 421.0539; found 421.0539.

*4.1.3.13. Methyl 3-(tert-butoxycarbonyl(2-iodophenyl)amino)acrylate (**8k**).* DABCO (3.690 mg, 0.033 mmol) was added to a mixture of **5h** (105 mg, 0.329 mmol) and methyl propiolate (27.660 mg, 0.329 mmol) in DCM (2 mL) with ice-cooling. The mixture was then stirred at 0 °C for 3 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography (*n*-hexane/EtOAc=20:1) to afford 139.7 mg (98.0%) of **8k** as a colorless viscous oil. FT-IR (thin film, neat) ν_{max} 2971, 1736, 1632, 1579, 1471, 1437, 1369 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J*=12.7 Hz, 1H),

7.93 (d, J=7.9 Hz, 1H), 7.48–7.39 (m, 1H), 7.19 (d, J=7.7 Hz, 1H), 7.14–7.07 (m, 1H), 4.55 (d, J=14.1 Hz, 1H), 3.68 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 150.7, 142.7, 140.1, 140.0, 130.1, 129.7, 129.1, 99.6, 98.7, 83.7, 51.2, 27.9; HR-MS (FAB$^+$) calcd for $C_{15}H_{19}INO_4$ $[M+H]^+$ 404.0359; found 404.0367.

4.1.4. General method for ***9i–l***, ***9j–l***, ***9a–k***. The mixture of **8** (0.42 mmol), $Pd(OAc)_2$ (0.084 mmol), PPh_3 (0.168 mmol), KOAc (1.26 mmol), and Et_4NCl (0.84 mmol) in acetonitrile (2.5 mL) was placed in a 10 mL vial closed with a silicon septum and containing a magnetic stirring bar. The tube was placed in the microwave cavity (Discover, CEM) and subjected to MW irradiation (100 W, 80 °C, 1.5 h). After cooling to room temperature, the reaction mixture was filtered through Celite pad and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (*n*-hexane/EtOAc=30:1) to afford desired indole **9**.

*4.1.4.1. Methyl 3-methyl-1H-indole-1-carboxylate (****9i–l****).*[41] Yield 88.1%; colorless viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (br s, 1H), 7.50 (d, J=7.7 Hz, 1H), 7.38–7.30 (m, 2H), 7.28–7.22 (m, 1H), 4.01 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 135.4, 131.4, 124.5, 122.6, 122.3, 118.9, 117.2, 115.0, 53.5, 9.6.

*4.1.4.2. Methyl 3-phenyl-1H-indole-1-carboxylate (****9j–l****).* Yield 91.3%; colorless viscous oil; FT-IR (thin film, neat) ν_{max} 3015, 2970, 2951, 1739, 1647, 1607, 1565, 1542, 1508, 1455, 1442, 1376, 1310 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4): δ 8.24 (d, J=8.0 Hz, 1H), 7.85–7.76 (m, 2H), 7.69–7.61 (m, 2H), 7.52–7.44 (m, 2H), 7.41–7.26 (m, 3H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, methanol-d_4): δ 152.9, 137.5, 134.9, 130.2, 130.0, 129.0, 128.4, 125.9, 124.4, 124.2, 123.5, 121.0, 116.3, 54.5; HR-MS (EI$^+$) calcd for $C_{16}H_{13}NO_2$ $[M]^+$ 251.0946, found 251.0945.

*4.1.4.3. tert-Butyl 3-methyl-4-(trifluoromethyl)-1H-indole-1-carboxylate (****9a****).* Yield 89.2%; colorless oil; FT-IR (thin film, neat) ν_{max} 3005, 2970, 2942, 1738, 1723, 1669, 1648, 1579, 1542, 1509, 1456, 1423, 1367, 1330, 1306 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, J=8.3 Hz, 1H), 7.57 (d, J=7.6 Hz, 1H), 7.48 (s, 1H), 7.37–7.30 (m, 1H), 2.34 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 137.0, 127.0 (q, J=1.6 Hz), 126.1, 124.4 (q, J=271.8 Hz), 123.1, 121.8 (q, J=32.6 Hz), 120.2 (q, J=6.2 Hz), 118.9, 115.3, 84.0, 28.2, 11.9 (q, J=5.3 Hz); HR-MS (EI$^+$) calcd for $C_{15}H_{16}F_3NO_2$ $[M]^+$ 299.1133, found 299.1126.

*4.1.4.4. tert-Butyl 4-methoxy-3-methyl-1H-indole-1-carboxylate (****9b****).* Yield 88.3%; colorless oil; FT-IR (thin film, neat) ν_{max} 2970, 2349, 2309, 1738, 1647, 1605, 1566, 1542, 1508, 1496, 1435, 1368, 1352, 1308 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J=7.1 Hz, 1H), 7.22–7.14 (m, 2H), 6.62 (d, J=8.0 Hz, 1H), 3.88 (s, 3H), 2.40 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 149.8, 137.1, 125.0, 121.4, 120.5, 116.7, 108.2, 103.0, 83.1, 55.2, 28.2, 12.4; HR-MS (EI$^+$) calcd for $C_{15}H_{19}NO_3$ $[M]^+$ 261.1365, found 261.1366.

*4.1.4.5. tert-Butyl 3-methyl-5-(trifluoromethyl)-1H-indole-1-carboxylate (****9c****).* Yield 89.3%; white solid; mp 78–80 °C; FT-IR (thin film, neat) ν_{max} 3014, 2970, 2945, 2349, 2309, 1739, 1625, 1542, 1508, 1448, 1370, 1315 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J=7.1 Hz, 1H), 7.76, (s, 1H), 7.55 (d, J=8.7 Hz, 1H), 7.44 (s, 1H), 2.29 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 137.0, 131.1, 124.9 (q, J=271.7 Hz), 124.6 (q, J=32.0 Hz), 124.4, 120.9 (q, J=3.6 Hz), 116.4, 116.3 (q, J=4.1 Hz), 115.3, 84.0, 28.2, 9.4; HR-MS (EI$^+$) calcd for $C_{15}H_{16}F_3NO_2$ $[M]^+$ 299.1133, found 299.1131.

*4.1.4.6. tert-Butyl 5-methoxy-3-methyl-1H-indole-1-carboxylate (****9d****).* Yield 86.1%; colorless oil; FT-IR (thin film, neat) ν_{max} 3126, 2971, 2939, 2836, 1729, 1621, 1576, 1489, 1442, 1391, 1373, 1353, 1324 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (br s, 1H), 7.35 (d, J=8.5 Hz, 1H), 7.23 (s, 1H), 6.87 (d, J=8.5 Hz, 1H), 3.88 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 149.9, 136.4, 125.2, 121.4, 119.3, 116.3, 111.6, 99.3, 83.0, 55.6, 28.2, 9.6; HR-MS (EI$^+$) calcd for $C_{15}H_{19}NO_3$ $[M]^+$ 261.1365, found 261.1361.

*4.1.4.7. tert-Butyl 3-methyl-6-(trifluoromethyl)-1H-indole-1-carboxylate (****9e****).* Yield 91.3%; white solid; mp 104–106 °C; FT-IR (thin film, neat) ν_{max} 3014, 2970, 2945, 2349, 2309, 1739, 1647, 1542, 1508, 1445, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br s, 1H), 7.57 (d, J=8.2 Hz, 1H), 7.51–7.43 (m, 2H), 2.28 (d, J=1.1 Hz, 3H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 134.6, 133.8, 126.2 (q, J=31.9 Hz), 125.2, 124.9 (q, J=271.8 Hz), 119.2, 119.0 (q, J=3.6 Hz), 116.1, 112.7 (q, J=4.5 Hz), 84.0, 28.1, 9.5; HR-MS (EI$^+$) calcd for $C_{15}H_{16}F_3NO_2$ $[M]^+$ 299.1133, found 299.1126.

*4.1.4.8. tert-Butyl 6-methoxy-3-methyl-1H-indole-1-carboxylate (****9f****).* Yield 88.4%; colorless oil; FT-IR (thin film, neat) ν_{max} 2970, 2941, 2349, 2309, 1729, 1604, 1565, 1542, 1508, 1480, 1455, 1392, 1373 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br s, 1H), 7.33 (s, 1H), 6.96–6.88 (m, 2H), 3.87 (s, 3H), 2.23 (s, 3H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 149.7, 132.2, 130.1, 123.4, 116.1, 115.8, 112.6, 101.7, 83.0, 55.7, 28.2, 9.7; HR-MS (EI$^+$) calcd for $C_{15}H_{19}NO_3$ $[M]^+$ 261.1365, found 261.1364.

*4.1.4.9. tert-Butyl 6-chloro-3-methyl-1H-indole-1-carboxylate (****9g****).* Yield 85.3%; colorless oil; FT-IR (thin film, neat) ν_{max} 3015, 2970, 2945, 1738, 1647, 1564, 1543, 1508, 1456, 1436, 1366, 1314 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.37 (d, J=8.3 Hz, 1H), 7.32 (s, 1H), 7.20 (d, J=8.3 Hz, 1H), 2.23 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 135.8, 130.2, 129.9, 123.3, 122.8, 119.6, 116.1, 115.4, 83.7, 28.1, 9.5; HR-MS (EI$^+$) calcd for $C_{14}H_{16}ClNO_2$ $[M]^+$ 265.0870, found 265.0873.

*4.1.4.10. tert-Butyl 1H-indole-1-carboxylate (****9h****).* Yield 86.2%; colorless oil; FT-IR (thin film, neat) ν_{max} 3153, 3119, 3054, 2979, 2933, 2308, 1735, 1607, 1534, 1474, 1452, 1381, 1370, 1349, 1333 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J=7.5 Hz, 1H), 7.59 (d, J=3.2 Hz, 1H), 7.56 (d, J=7.7 Hz, 1H), 7.34–7.27 (m, 1H), 7.25–7.18 (m, 1H), 6.57 (d, J=3.7 Hz, 1H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 135.1, 130.5, 125.8, 124.1, 122.6, 120.9, 115.1, 107.2, 83.6, 28.2; HR-MS (EI$^+$) calcd for $C_{13}H_{15}NO_2$ $[M]^+$ 217.1103, found 217.1105.

*4.1.4.11. tert-Butyl 3-methyl-1H-indole-1-carboxylate (****9i****).* Yield 88.4%; colorless oil; FT-IR (thin film, neat) ν_{max} 3052, 2979, 1933, 1732, 1609, 1575, 1476, 1454, 1423, 1389, 1372, 1357, 1308 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.49 (d, J=7.7 Hz, 1H), 7.40–7.19 (m, 3H), 2.27 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 135.4, 131.4, 124.2, 122.8, 122.2, 118.9, 116.3, 115.1, 83.1, 28.2, 9.6; HR-MS (EI$^+$) calcd for $C_{14}H_{17}NO_2$ $[M]^+$ 231.1259; found 231.1258.

*4.1.4.12. tert-Butyl 3-phenyl-1H-indole-1-carboxylate (****9j****).* Yield 91.2%; colorless oil; FT-IR (thin film, neat) ν_{max} 3055, 2979, 2933, 1734, 1608, 1564, 1494, 1475, 1452, 1375, 1336, 1309 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J=7.6 Hz, 1H), 7.82 (d, J=7.6 Hz, 1H), 7.71 (s. 1H), 7.67–7.61 (m, 2H), 7.50–7.43 (m, 2H), 7.40–7.33 (m, 2H), 7.32–7.26 (m, 1H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, methanol-d_4): δ 151.0, 137.3, 135.0, 130.2, 129.9, 128.9, 128.3, 125.7, 124.1, 123.7, 123.5, 120.9, 116.4, 85.1, 28.4; HR-MS (EI$^+$) calcd for $C_{19}H_{19}NO_2$ $[M]^+$ 293.1416, found 293.1416.

*4.1.4.13. 1-tert-Butyl 3-methyl-1H-indole-1,3-dicarboxylate (****9k****).* Yield 95.3%; white solid; mp 122–124 °C; FT-IR (thin film, neat)

ν_{max} 2971, 1744, 1718, 1560, 1481, 1452, 1372, 1333, 1309 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.22–8.12 (m, 2H), 7.42–7.31 (m, 2H), 3.94 (s, 3H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.9, 135.5, 132.1, 127.5, 125.1, 123.9, 121.6, 115.1, 112.2, 85.0, 51.4, 28.1; HR-MS (FAB^+) calcd for $C_{15}H_{18}NO_4$ $[M+H]^+$ 276.1236; found 276.1237.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.06.101.

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